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In Practice

Bone Disease in CKD: A Focus on Osteoporosis Diagnosis and Management

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Osteoporosis is defined as a condition of impairment in bone strength due to low bone mineral density and poor bone quality and predisposes individuals to an increased risk of fractures. Osteoporosis may coexist with chronic kidney disease−mineral and bone disorder (CKD-MBD) and osteoporotic fractures occur in all stages of CKD. Management of osteoporosis in CKD should consider the pathophysiology of both disorders. Diagnosis and management of osteoporosis in patients with stages 1-3 CKD and patients without CKD are similar, but diagnosis and management decisions differ greatly once patients have stages 4-5 CKD. Discriminating between osteoporosis and CKD-MBD is best accomplished with quantitative bone histomorphometry. Biochemical markers, especially intact parathyroid hormone and bone-specific alkaline phosphatase, also may be helpful. When the diagnosis of osteoporosis is established, management in stages 4-5 CKD may include antiresorptive or anabolic agents, though evidence for efficacy is marginal in advanced CKD.
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INDEX WORDS: Chronic kidney disease−mineral and bone disorder (CKD-MBD); osteoporosis; renal failure; bone histomorphometry; parathyroid hormone (PTH); bone-specific alkaline phosphatase.

CASE PRESENTATION

A 54-year-old white man with end-stage renal disease (ESRD) on peritoneal dialysis therapy for 5 years experienced a right hip fracture from a fall at home. His ESRD is related to kidney biopsy–documented idiopathic focal glomerulosclerosis. He also has had type 2 diabetes mellitus for 12 years, controlled by diet and exercise and oral antidiabetic therapy. After surgery and rehabilitation for hip surgery, he was referred for evaluation and management of metabolic bone disease.

The patient had no history of glucocorticoid exposure. He was not taking agents that could suppress parathyroid hormone (PTH) production. He had no history of weight loss or gastrointestinal diseases and no family history of osteoporosis. He did not smoke and consumed less than 2 ounces of alcohol weekly. There was no history of kidney stone formation.

On examination, the patient was 68″ tall, weighed 154 lb, and had a good energy level and good proximal muscular strength, though his balance (tested by standing on 1 leg) was diminished. He had good peripheral vision and no neurologic, pulmonary, or cardiac findings.

The patient's laboratory data showed a normal biochemical profile. Specifically, total serum calcium level was 9.3 mg/dL; serum albumin, 4.1 g/dL; serum phosphorus, 4.5 mg/dL; total alkaline phosphatase (ALP), 85 (reference range, 10-120) IU/L; bone-specific ALP, 8 (reference range, 10-42) IU/L; and intact PTH, 154 (reference range, 15-65) pg/mL. Levels of biochemical markers of bone turnover, specifically serum CTX (carboxy-terminal crosslinking telopeptides of type I collagen) and PINP (procollagen type I amino-terminal propeptide), were 186 (reference range, 150-650) ng/mL and 54 (reference range, 20-108) μg/L, respectively. His 25-hydroxyvitamin D level was 30 (reference range, 0-100) ng/mL, and hemoglobin A_{1c} consistently was 7.8-8.8%. Femoral neck bone mineral density (BMD) classification by the World Health Organization (WHO) was T score of −3.8, defined as osteoporosis.

INTRODUCTION

Osteoporosis is defined by a consensus conference of the National Institutes of Health (NIH) as a condition of impairment in bone strength due to low BMD and poor bone quality (see Box 1 for a glossary of key terms).[1] Because bone quality cannot be measured in clinical practice, the operational definitions of osteoporosis are the occurrence of a low-trauma (fragility) fracture in women or men 50 years or older after other causes of bone fragility have been excluded (eg, osteomalacia and osteogenesis imperfecta).[2] In 1994, a second diagnostic criteria for osteoporosis was established. A working group of the WHO published their criteria for the diagnosis of osteoporosis by BMD criteria in individuals who have not yet had a fragility fracture.[3] The osteoporotic label was called the T score (the number of standard deviations a person's BMD is below the mean BMD for the young healthy population) and the cutoff for the diagnosis was T score of −2.5 or lower. This cutoff was chosen based on the relationship between the lifetime risk of hip fracture in white women and the average T score from age 50-85 years is −2.5 at the hip. In other words, because the lifetime risk is 20% and assuming those 20% have the lowest T scores, the cutoff for osteoporosis was set at the threshold of the lowest T score quintile (ie, −2.5).[4]

The initial purpose of the BMD dual-energy photon densitometry (DEXA) WHO-derived classification

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Box 1. Glossary of Terms

- *Bone-specific alkaline phosphatase (bone ALP):* An osteoblast-derived bone formation marker; however, bone-specific alkaline phosphatase may be elevated in other diseases in which bone formation is not increased or normal (eg, osteomalacia, Paget disease, cancer in bone).
- *Procollagen type I amino-terminal propeptide (PINP):* A more specific osteoblast-derived bone formation marker.
- *Renal osteodystrophy:* A quantitative histomorphometric classification of the bone diseases accompanying CKD.
- *Chronic kidney disease–mineral and bone disorder (CKD-MBD):* A term that embraces the systemic nature of the interactions between the metabolic bone diseases that accompany CKD linked to the pathophysiologic processes of vascular/soft tissue calcification.
- *Adynamic bone disease:* A quantitative histomorphometric-defined bone disease characterized by absent or very low bone turnover.
- *Bone turnover markers:* Serum or plasma biochemical markers that reflect the systemic levels of bone turnover (formation/resorption).
- *Mixed renal bone disease:* A quantitative histomorphometric classification of bone histomorphometry in CKD; mixed renal bone disease is a combination of defects in bone mineralization with features of high bone turnover.
- *Osteitis fibrosa cystica:* A histologic feature of hyperparathyroid bone disease characterized by increased bone resorptive cavities, increased osteoclast number, marrow fibrosis, and increased cortical porosity.
- *Osteomalacia:* A quantitative histomorphometric metabolic bone disease of diverse etiologies characterized by an increase in osteoid (matrix) surface (>80%), wide osteoid seams (>10 μm), and delay in mineralization lag time (>100 d).
- *Osteoporosis:* A systemic metabolic bone disease of diverse causes characterized by impaired bone strength and increase in fragility fracture risk. The impairment in bone strength is due to a combination of reduced bone mineral density and altered bone quality. Clinically, osteoporosis can be diagnosed by the occurrence of a fragility fracture, or in patients without fracture, by the World Health Organization dual energy x-ray absorptiometry diagnosis (T score) of −2.5 or lower at the spine, femoral neck, total hip, or forearm.
- *Parathyroid hormone (PTH):* The peptide hormone in the blood stream that regulates multiple end-organ functions, most importantly, serum calcium concentration.
- *Fibroblast growth factor 23 (FGF-23):* A peptide that is secreted by osteocytes whose most important biological function is regulation of serum phosphorus concentration by inducing phosphaturia. FGF-23 also has recognized functions to affect kidney production of 1,25 dihydroxyvitamin D synthesis, PTH production, vascular calcification, and bone turnover.
- *Sclerostin:* A glycoprotein released by osteocytes that regulates osteoblast activity and influences bone remodeling.
- *Tartrate-resistant acid phosphatase (TRAP5b):* An osteoclast cellular product that influences bone remodeling. TRAP5b serum or plasma concentration is a measure not of bone resorption as much as it is a measure of osteoclast number.

was to determine the prevalence of osteoporosis in the world's population in order to aid in health-economic planning. Soon after 1994, the T score made its way into clinical use and also was included in the *International Classification of Diseases, Ninth Revision* (*ICD-9*) as a second means of diagnosing osteoporosis in individuals who had not yet had a fragility fracture. The clinical utility of the T score lies in its use as a risk factor for osteoporotic fracture. Fracture risk approximately doubles for each standard deviation the BMD is below −2.5 in untreated postmenopausal women compared to the same population of the same age with a T score of zero.

One limitation of the T score is that it does not define the cause of low BMD, and it should not be used as a stand-alone risk factor for making management decisions.[5] Because low BMD captures ∼50% of bone strength and at the present time, bone quality (the contributing factor for the other 50% of bone strength) cannot be measured clinically,[6,7] the T score must be applied along with other validated risk factors for fracture that are independent of BMD level.[8-13] Thus, the WHO also funded the development of the largest and most robust validated risk model to predict 10-year risk for major (colles, humerus, vertebrae, hip, and tibia) and/or hip fracture in untreated postmenopausal women. Nine validated risk factors, each an independent risk factor for fracture, were identified and statistically validated in FRAX (fracture risk assessment modeling; Box 2).[3] The FRAX calculator can be accessed at the University of Sheffield WHO Collaborating Centre for Metabolic Bone Diseases (www.shef.ac.uk/FRAX/tool.jsp) and also by the International Society for Clinical Densitometry (www.iscd.org) or the National Osteoporosis Foundation (www.nof.org) websites.

Glomerular filtration rate (GFR) or estimated GFR (eGFR) is not included in the FRAX model. Because the sample size was not large enough, the WHO working groups could not validate the threshold level of GFR/eGFR related to the lifetime risk of hip fracture (analogous to the T score threshold of −2.5 used to relate BMD to hip fracture risk). However, it is important to stress that since FRAX data were completed and implemented, additional independent risk factors for fracture have been identified, such that in clinical practice, adding fracture risk to the risk calculated by FRAX alone is an important adjunct in management decisions.[14] Included in this additional risk-factor group are the magnitude of bone remodeling (turnover), fall frequency, number and/or severity of morphometric vertebral fractures, T score at the lumbar spine, and glucocorticoid dose. Newer measurements of bone strength, by quantitative computed tomography (CT)-derived finite element analysis or by DEXA-derived trabecular bone score, were not included because these technologies postdated FRAX.[15-17]

Despite the exclusion of GFR/eGFR from FRAX, there is extensive literature that supports chronic