

CHRONIC KIDNEY DISEASE-MINERAL AND BONE DISORDERS (CKD-MBDs): WHAT THE ENDOCRINOLOGIST NEEDS TO KNOW

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ABSTRACT

Objective: Chronic kidney disease-mineral and bone disorders (CKD-MBDs) are a spectrum of abnormalities involving skeletal hormones, minerals, and bone turnover and mineralization. This paper focuses on what the endocrinologist should know about the assessment and management of skeletal and metabolic disorders in CKD-MBDs.

Methods: Relevant literature was reviewed to (1) define disturbances of minerals and hormones in the course of CKD; (2) identify the variable radiographic and histomorphometric changes of CKD-MBDs; (3) review the association among CKD-MBDs, vascular calcification, cardiovascular disease (CVD), and mortality; and (4) clarify issues in CKD-MBDs therapy.

Results: Assessment and treatment of CKD-MBDs is complicated by progressive changes in bone minerals and skeletal regulatory hormones as kidney function declines. CKD-MBDs are associated with fracture risk, and studies demonstrate that bone mineral density can be used to assess bone loss and fracture risk in these patients. Treatment of CKD-MBDs continues to evolve. Use of calcimim, phosphate binders, vitamin D, vitamin D-receptor analogs, and drugs for osteoporosis and CKD-MBDs treatment are

discussed in the context of safety and efficacy for patients with CKD.

Conclusion: The association of CKD with bone disease, vascular calcification, CVD, and mortality mandates earlier recognition and treatment of CKD-MBDs. Osteoporosis as a distinct entity can be diagnosed and managed in CKD, although assessment of osteoporosis becomes challenging in late (stage 4 to 5) CKD. Diabetes is common in early (stage 1 to 3) CKD. In addition, 96% of all individuals identified as having CKD have early CKD. The endocrinologist is uniquely positioned to address and treat both diabetes and many of the metabolic and skeletal disorders associated with early CKD-MBDs, including osteoporosis. (*Endocr Pract.* 2014;20:500-516)

Abbreviations:

ABD = adynamic bone disease; AP = alkaline phosphatase; BAP = bone alkaline phosphatase; BCM = biochemical markers; BMD = bone mineral density; BTO = bone turnover; CaSR = calcium-sensing receptor; Ca × P = product of total serum calcium and serum phosphorus levels; CKD = chronic kidney disease; CKD-MBDs = chronic kidney disease-mineral and bone disorders; CT = computed tomography; CVD = cardiovascular disease; DXA = dual x-ray absorptiometry; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FGF-23 = fibroblast growth factor-23; FRAX[®] = fracture risk assessment tool; GFR = glomerular filtration rate; HTN = hypertension; KDIGO = Kidney Disease Improving Global Outcome; KDOQI = Kidney Disease Outcomes Quality Initiative; mGFR = measured glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey; NKF = National Kidney Foundation; PTH = parathyroid hormone; PTX = parathyroidectomy; RANKL = receptor-activator of nuclear factor-κB ligand; RCT = randomized controlled trial; SHPT = secondary hyperparathyroidism; T2DM = type 2 diabetes mellitus; vQCT = volumetric quantitative CT; VDRα = vitamin D-receptor-activator

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INTRODUCTION

Chronic kidney disease (CKD) is a serious condition associated with increased healthcare expenditures, decreased quality of life, and premature mortality. As reported by the National Health and Nutrition Examination Survey (NHANES) III, CKD affects 11% (19.2 million) of adult (aged 20 years and older) men and women in the United States (1), and its incidence is likely to further increase with increasing longevity and the rising incidence of obesity and type 2 diabetes mellitus (T2DM). NHANES is a continuous data survey of health and nutritional status of U.S. adults, and results are analyzed and released periodically by the Centers for Disease Control. The NHANES noted a 15.9% increase in the prevalence of CKD between 1988 and 1994 and between 1999 and 2004. CKD is most common in persons ≥ 60 years of age (39.4% of this population) but also presents in persons aged 40 to 59 and 20 to 39 years (12.6 and 8.5% of these age groups, respectively) (2). T2DM is the leading cause of CKD in developed countries (3) and accounts for 45% of all cases of kidney failure (4).

Kidney disease is defined as an abnormality of kidney structure or function with implications for the health of an individual (5). The National Kidney Foundation (NKF) has traditionally categorized CKD into 5 stages based upon the glomerular filtration rate (GFR, expressed as mL/min/1.73 m² and commonly reported as mL/min) (Table 1). In 2003, CKD prevalence by stage among the U.S. population was estimated at 3.3% (5.9 million) stage 1, 3.0% (5.3 million) stage 2, 4.3% (7.6 million) stage 3, and 0.2% each for stages 4 and 5 (1). The Kidney Disease Improving Global

Table 1. National Kidney Foundation (NKF) Stages of Chronic Kidney Disease (CKD)

Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney damage with normal or ↑GFR	>90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 or dialysis

CKD is defined as either kidney damage or GFR <60 for >3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, to include blood or urine tests or imaging studies. Key: GFR = glomerular filtration rate (mL/min/1.73 m²)

Outcomes (KDIGO) 2012 clinical practice guidelines recommend that CKD staging be classified not solely on GFR but also on cause of injury and albuminuria (Table 2) (5). The inclusion of cause of kidney disease in staging is fundamentally important to outcome and cause-specific treatment. Albuminuria is a marker of injury severity and is strongly associated with progression of kidney disease, independent of GFR, and can be defined as mild, moderate, or severe increase in urine albumin. The 2012 KDIGO classification also divided stage 3 CKD into G3a (45 to 59 mL/min) and G3b (30 to 44 mL/min) to acknowledge the significant differences in health outcomes and mortality between these categories (Fig. 1) (6).

Undiagnosed CKD may lead to the underrecognition of associated diseases and loss of time in treating comorbid

Table 2: Staging of CKD by Glomerular Filtration Rate (GFR) and Albuminuria Categories: KDIGO 2012 Guidelines[†]

- CKD defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.
- CKD classified as CGA based on Cause (C), GFR (G) category, and Albuminuria (A) category.
- CKD prognosis determined by GFR and Albuminuria Categories.

GFR categories (mL/min/1.73 m ²) Description and range	Persistent albuminuria categories Description and range		
	A1	A2	A3
	Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-300 mg/g 3-30 mg/mmol	Severely increased >300 mg/g >30 mg/mmol
G1 Normal or high ≥90		1	
G2 Mildly decreased 60-89		1	
G3a Mildly to moderately decreased 45-59	1		
G3b Moderately to severely decreased 30-44			
G4 Severely decreased 15-29			
G5 Kidney failure <15			

†KDIGO 2012 Clinical Practice Guidelines. *Kidney International Supplements* 2013; 3(1): 63-72. GFR (G) and albuminuria (A) grid to reflect the risk of progression by intensity of coloring (green – low risk if no other markers of CKD, yellow – moderately increased risk, orange – high risk, red – very high risk). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

Figure 1: CKD stage and outcomes

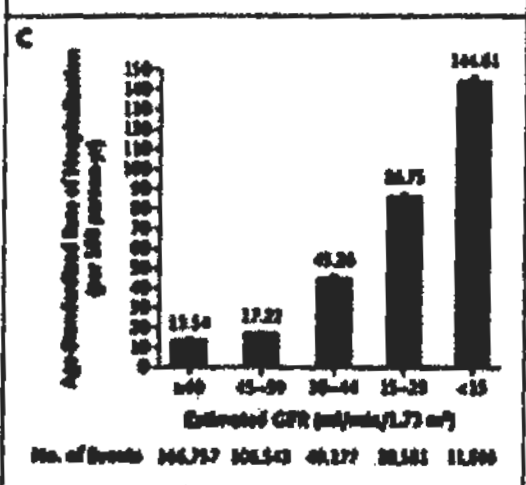
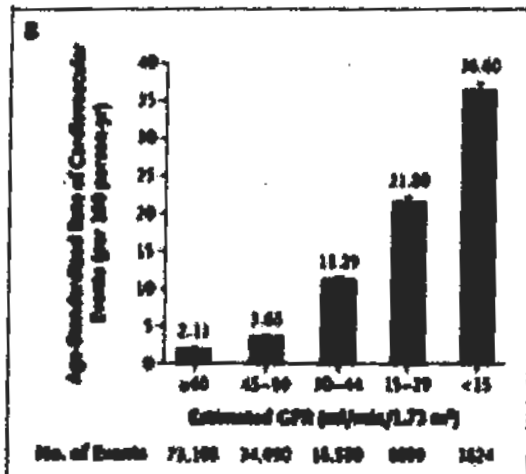
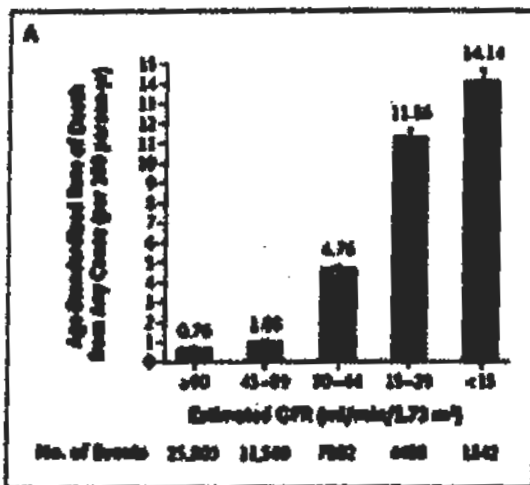
N Engl J Med 2004; 351(13):1296-1305.

Age-standardized rates of death, CVD events, and hospitalizations from any cause according to the estimated glomerular filtration rate (eGFR) among 1,120,295 ambulatory adults.

Panel A – Death

Panel B – CVD Events

Panel C – Hospitalizations



diseases at earlier stages of CKD: The CKD prevalence is greater among persons with T2DM (40.2% versus 15.4% without T2DM), cardiovascular disease (CVD) (28.2% versus 15.4% without CVD), and hypertension (HTN) (24.6% versus 12.5% without HTN). As reported by Coresh et al (1), of the 11% of adult Americans with CKD, 96% have stage 1 to 3 disease (GFR \geq 30 mL/min). Thus, a sizeable number of patients with T2DM, CVD, and HTN are at risk for CKD and should be identified and screened for comorbid diseases related to CKD, to include mineral and bone disease. In a recent abstract reporting the screening of 12 million U.S. patient records between 2008 and 2011, 44,000 patients were found to have T2DM (mean age, 64 years). Of the patients with T2DM, 51% had CKD and 22% had stage 3 to 5 disease, although 76% of stage 3 to 5 CKD patients did not have any recorded diagnosis of CKD (7). The automatic calculation of estimated GFR (eGFR) in patient laboratory reports will hopefully help increase awareness that CKD may be present.

KDIGO sponsored a conference addressing controversies in renal osteodystrophy in 2004 to (1) develop a clear, clinically relevant, and internationally acceptable

definition and classification system; (2) develop a consensus for bone biopsy evaluation and classification; and (3) evaluate laboratory and imaging markers for the clinical assessment of patients with CKD. An ideal classification system for CKD-mineral and bone disorders (CKD-MBDs) would allow categorization of patients based on readily available clinical diagnostic tools and would help guide treatment. The lack of adequate data and the nonlinearity of CKD does not allow for a classification based on severity or treatment at this time. The proposed KDIGO framework for classifying CKD-MBDs (Table 3) is based on the presence or absence of laboratory abnormalities, bone disease, and calcification of extraskeletal tissue and is meant to be a descriptive clinical model (8). KDIGO recommends that the term "renal osteodystrophy" be used exclusively to define altered bone morphology identified by bone biopsy/histomorphometry and be subsequently reported as a unified TMV classification system, which is based upon the skeletal parameters of turnover (T), mineralization (M), and volume (V). Thus, the term CKD-MBDs is used to describe a broad clinical syndrome that develops as a systemic disorder characterized by a constellation

Table 3. Classification of Chronic Kidney Disease (CKD): Position Statement from Kidney Disease Improving Global Outcomes (KDIGO)¹

Regulatory		Bone	
Low	Normal	Normal	Low
Normal	Abnormal	Normal	High
High	Abnormal	High	High
I	+		
IB	+		
IC			+
I BC			+

¹Moe S, Druska T, Cunningham J, et al. *Kidney International* 2006; 69:1945-1953.
²L: laboratory abnormalities (of calcium, phosphate, parathyroid hormone, alkaline phosphatase or vitamin D metabolism); B: bone disease (abnormalities of turnover, mineralization, volume, linear growth or strength); C: calcification of vascular or other soft tissues.

of abnormalities in regulatory hormones and bone mineral, bone turnover and mineralization, and vascular or soft tissue calcification. CKD-MBDs acknowledges the entire spectrum of disease from early hormonal and mineral disturbances to the late stages of CKD and premature mortality.

Because 96% of all CKD cases fall into stages 1 to 3 and T2DM is common in early CKD, the endocrinologist is uniquely positioned to address and treat both T2DM and many of the comorbid diseases associated with CKD, as outlined by the NKF KDOQI guidelines for management of HTN, dyslipidemia, anemia, CVD, and nutrition (2) and as outlined in the newer KDIGO guidelines for metabolic bone disease (9). This review will focus on what the endocrinologist should know about the development, assessment, and management of CKD-MBDs. For purposes of discussion, where not stated in the text, 'early CKD' refers to stage 1 to 3 disease and 'late CKD' refers to stage 4 to 5 disease. Stage 5 CKD is often referred to as end-stage renal disease (ESRD). We will not address issues associated with bone disease and kidney transplantation in ESRD.

METHODS

Preparation of this review was assisted by a library resource specialist to perform a literature search using Ovid MEDLINE, Medical Subject Headings (MeSH), and PubMed National Center for Biotechnology Information. We limited our search to the past 20 years and only

English-language articles. Literature search cross-reference terms included "chronic kidney disease," or "chronic renal disease," or "hemodialysis," or "dialysis," or "kidney failure," or "renal insufficiency" combined with "bone diseases," "metabolic," "osteodystrophy," "osteoporosis," "osteomalacia," or "bone minerals." Text words were used to search ISI Web of Science for articles and abstracts not identified in the other databases.

The relevant literature was reviewed by the authors with a focus to (1) define disturbances of minerals and hormones in the course of CKD; (2) identify the variable radiographic and histomorphometric changes of CKD-MBDs; (3) review the association among CKD-MBDs, vascular calcification, CVD, and mortality; and (4) clarify issues in CKD-MBDs therapy.

RESULTS

Bone Mineral and Regulatory Hormones in CKD-MBDs

Disturbances of bone mineral metabolism and regulatory hormones may occur early in the course of CKD, with perturbations occurring as early as stage 2 CKD and progressing as kidney function worsens (10). CKD is associated with disrupted regulation of fibroblast growth factor-23 (FGF-23) and the vitamin D parathyroid hormone (PTH) axis (11,12). Serum FGF-23 levels rise earlier than and are relatively higher than PTH levels as CKD progresses. FGF-23, which is derived from osteocytes, is a

phosphaturic hormone that also has multiple tissue effects that influence bone metabolism (13). The rise in PTH occurs before serum calcium decreases or serum phosphate increases significantly, and this eventually leads to secondary hyperparathyroidism (SHPT). As kidney function declines, a corresponding decrease in vitamin D receptors (VDRs) and calcium-sensing receptors (CaSRs) occurs in the parathyroid glands (14), making them less responsive to the actions of circulating vitamin D and calcium. All of these events worsen SHPT and its potential effect on bone. Many patients with stage 2 to 4 CKD may go unrecognized because of a reliance only on serum creatinine to assess renal status and failure to more accurately assess renal function using the GFR. The rate of glomerular filtration is generally regarded as the best overall index of renal function in health and disease (15). Normal GFR varies according to age, gender, body size, and race. The measured GFR (mGFR, as clearance of exogenous filtration markers such as iothalamate) is presently the best direct measure of renal function, and the degree of reduction in mGFR correlates with the severity of structural changes in CKD. Serum measurement of cystatin C has recently gained attention as a sensitive, noncreatinine alternative endogenous marker of filtration (16,17) for use when decisions depend on more accurate knowledge of GFR, such as confirming a diagnosis of CKD or adjusting doses of potentially toxic drugs excreted by the kidney. The 2012 KDIGO guidelines recommend measuring cystatin C in adults with an eGFR of 45 to 59 mL/min who do not have other markers of kidney damage and if confirmation of CKD is needed for treatment decisions. However, one should be aware that several factors other than renal function may affect cystatin C levels (18). Serum creatinine levels, like the mGFR, have been shown to fluctuate throughout the day; this and other determinants (such as measurement inaccuracies for creatinine and cystatin C) may account for a substantial portion of the variability in eGFR equations. Although the eGFR can be imprecise, estimating equations adjust for the effect of non-GFR determinants represented by age, sex, and race. Both the Modification of Diet in Renal Disease Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provide better estimates of GFR than the serum creatinine alone, and the 2012 KDOQI clinical practice guidelines recommend using the CKD-EPI equation as the most accurate estimate of kidney function, especially in early CKD.

Stage 3 CKD is often associated with decreased production of 1,25-dihydroxyvitamin D (calcitriol) (10) in response to a loss of functioning proximal renal tubules and reduced activity of renal 1-alpha-hydroxylase, leading to parathyroid gland hyperplasia, elevated blood levels of PTH, and SHPT. The combination of low calcitriol and elevated PTH in CKD is now recognized as a cause of bone loss (19-21) and a major contributor to bone disease commonly seen in stage 4 CKD and present in almost all

patients with stage 5 CKD (22,23). Elevated PTH levels in late CKD have also been viewed as a possible contributor to early death (24), although a recent meta-analysis did not find a significant correlation between PTH levels and mortality (25). Rather, in 4,127 patients followed for a median of 60 months, elevated phosphate levels were associated with increased coronary events and death in patients with stage 2 to 3 CKD based upon eGFR (Cockcroft-Gault equation) (26). Increased mortality has been reported with higher serum levels of both phosphate (25-28) and FGF-23 (29,30) in patients with CKD.

Clinical and experimental evidence supports the concept that integrated mechanisms are responsible for the development of SHPT and bone disease in CKD. Phosphate retention and hyperphosphatemia directly stimulate parathyroid gland function (24). However, perturbations of phosphate retention in stage 2 to 3 CKD may not be seen by measurement of serum or urine phosphate (10); and possible explanations are that compensatory increases in FGF-23 (29) and PTH lead to decreased renal tubular reabsorption of phosphate and increased urinary phosphate excretion. During stages 4 to 5 CKD, when hyperphosphatemia develops, phosphorus can affect parathyroid function both by suppressing blood calcium, contributing to hypocalcemia, and by acting directly on the parathyroid glands. Hyperphosphatemia has a direct effect on posttranscriptional increases in PTH synthesis and secretion (31) and can induce parathyroid hyperplasia independent of low blood levels of calcium or calcitriol. Phosphate retention interferes with the kidney's ability to produce calcitriol, creating a state of vitamin D deficiency and decreased intestinal absorption of calcium. The calcemic response to PTH infusion is also markedly blunted as early as stage 2 CKD. These abnormalities all contribute to SHPT.

Phosphate homeostasis is primarily regulated by the kidney. Phosphate is filtered by the renal glomerulus and 80% is then reabsorbed, mostly by the proximal nephron's brush border membrane type IIa sodium-phosphate cotransporter (NaP2a). PTH increases urinary phosphate excretion via cyclic adenosine monophosphate-dependent inhibition of NaP2a expression. However, PTH action does not account for all of phosphate homeostasis. Recent studies have shown that FGF-23 is involved in the pathophysiology of CKD (11,12) and plays a major role in various forms of osteomalacia (32). FGF-23 is a peptide hormone normally secreted by bone osteocytes and osteoblasts in response to hyperphosphatemia. The rise in FGF-23 mirrors renal phosphate retention and appears to precede the development of SHPT. Serum FGF-23 levels have been reported to be persistently increased as early as stage 3 CKD (29). This FGF-23 rise induces a decline in the number of intact nephrons and is associated with reduced expression of Klotho, the coreceptor required for FGF-23 signaling (33). Patients with CKD have high serum FGF-23 and low Klotho expression in the kidney and parathyroid glands,

suggesting that they could serve as biomarkers for progression of disease (29) and response to therapy (34-36). As CKD progresses, serum phosphate, PTH, and FGF-23 levels continue to increase, whereas responsiveness to PTH and FGF-23 decrease. In late-stage CKD, abnormally high serum FGF-23 levels can no longer reduce serum phosphate effectively. Elevated FGF-23 levels are associated with more rapid CKD progression to ESRD (29), left ventricular hypertrophy (37), and premature mortality (29,30).

Bone Turnover (BTO) and Mineralization in CKD-MBDs

The nature and type of bone disease that develops in CKD-MBDs may vary among patients. Three types of bone disease, as defined by quantitative bone histomorphometry, may be encountered in patients with CKD: (1) increased BTO and resorption due to SHPT with or without marrow fibrosis (osteitis fibrosa), (2) decreased bone turnover and formation (termed 'adynamic bone'), and (3) defective bone mineralization (osteomalacia) (38). Some patients have a mixed pattern (22,23). In order to clarify the interpretation of bone biopsy results in the evaluation of renal osteodystrophy, the TMV classification system allows for 3 key histologic descriptors to be reported in any combination (Table 3). Histomorphometry can thereby help to provide a clinically relevant description of the underlying skeletal pathology (Fig. 2) and assist in guiding therapy.

Factors that cause postmenopausal, idiopathic, or age-related bone loss may contribute to the skeletal

abnormalities of CKD. Inadequate calcium or vitamin D intake or absorption, hypogonadism, tobacco smoking, glucocorticoid steroid use, immobilization, and poor nutritional status may by themselves be a cause of bone loss. Osteoporosis, defined by the National Institutes of Health Consensus Conference on Osteoporosis, is a decrease in the quantity and/or quality of normally mineralized bone that decreases bone strength and increases the risk of skeletal fracture. Osteoporosis may coexist with CKD-MBDs and may also be present years before CKD-MBDs become evident. In a study of 421 postmenopausal women with osteoporosis and a GFR >50 mL/min, 39% had vitamin D deficiency, as defined by 25-hydroxyvitamin D levels <12 ng/dL (<30 nmol/L), and 33% had frank SHPT (serum PTH above normal laboratory values) (39). In these women, hypovitaminosis D was associated with either an elevated PTH response and increased BTO or a 'blunted' PTH response and low BTO, the latter theorized to possibly be protective against hypovitaminosis D-related bone loss. Lobao et al (40) reported on 103 patients with CKD (creatinine clearance, 10 to 78 mL/min) not receiving dialysis and found that 50 (48.5%) had low bone mineral density (BMD) (40). In this study, bone loss was found to be present in patients with both early and late CKD (median creatinine clearance, 29 mL/min), with only alkaline phosphatase (AP) and PTH levels predictive of low BMD. Bone histomorphometric analysis of the 50 patients with low BMD revealed adynamic bone disease (ABD) in 52.5% and osteomalacia in 42.5%.

Figure 2: A graphic example of the TMV system used to define and classify 'renal osteodystrophy', or CKD-MBD.

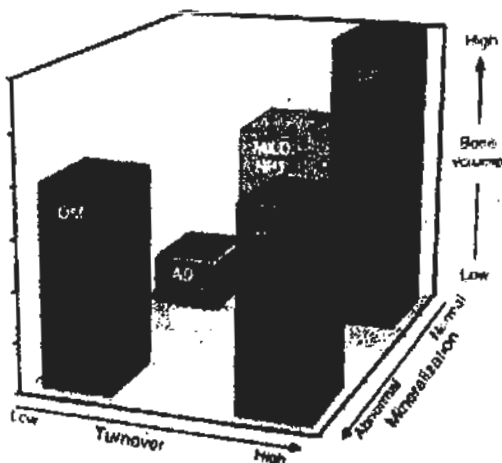
Each axis represents one of the descriptors in the TMV classification: T-turnover, M-mineralization and V-bone volume. Many patients with CKD-MBD cluster in areas shown by the bars, for example:

OM, osteomalacia, is currently described as low-BTO with abnormal M. The V may be low to medium, depending on the CKD severity and duration and other factors affecting bone.

AD, adynamic bone disease, is currently described as low-BTO with normal M, and V in this example is at the lower end of the spectrum but other patients with normal M and low-BTO will have normal V.

Mild HPT, hyperparathyroidism, and OF, osteitis fibrosa, are currently used distinct categories, but actually represent a range of abnormalities along a continuum of medium to high-BTO, and any V depending on CKD duration.

MUO, mixed uremic CKD-MBD, is variably defined internationally. In the graph example, it is depicted as high-BTO, normal V, with abnormal M.



The TMV classification system more precisely describes the range of pathologic abnormalities in CKD-MBD. [BTO, bone turnover; CKD, chronic kidney disease; MBD, metabolic bone disease.]

Moe S, et al. *Kidney International* 2006; 69:1945-1953.

Patients in early stage CKD often have mild SHPT features, putting them at risk for bone loss from high BTO, in which bone resorption exceeds bone formation. Several studies of bone histomorphometry in patients with stage 2 to 4 CKD have shown that most patients have increased rates of BTO, as defined by increased bone formation and bone resorption rates (23,41,42). There may or may not be a coexisting mineralization defect, depending on the degree of hypocalcemia, vitamin D deficiency, or aluminum deposition in bone. Bone histomorphometry in 174 patients with a GFR of 15 to 50 mL/min (stage 2 to 4 CKD) reported by Hamdy et al (23) in 1995 found that 129 patients (74%) had high BTO with osteitis fibrosa, 33 (19%) had osteitis fibrosa with osteomalacia, and 9 (5%) had low BTO 'adynamic bone,' whereas osteomalacia alone (1 patient, 0.6%) and aluminum deposition (2 patients, 1%) were rare. Paired bone biopsies in 62 of these untreated patients showed progression of CKD-MBDs in all patients within 2 years. These findings are in keeping with the hormone and mineral features of higher PTH, lower calcitriol, and higher phosphate levels seen in early CKD. Of interest, McCarthy et al (43) did not find an association between early CKD and fracture risk in 427 postmenopausal Caucasian women (median age, 68 years) in a prospective, population-based cohort study followed for up to 25 years (median, 14 years) in Rochester, Minnesota. Although univariate analysis found increased fracture risk associated with declining renal function, multivariate analysis did not find any association after adjusting for age, body weight, and BMD. Of note, the baseline creatinine clearance rate for all patients in this study was 78.7 ± 26.6 mL/min and 44.7 ± 12.7 mL/min for the 20% of subjects in the lowest quintile. Although few researchers have examined the longitudinal change in bone density in relation to BTO in CKD, high BTO from SHPT leads to bone loss (19) due to bone resorption increased out of proportion to bone formation (38).

As kidney function deteriorates to late-stage CKD, patients are at an increased risk of fracture (19-21,44-49). SHPT can result in markedly increased BTO and even marrow fibrosis (e.g., activation of precursor mesenchymal cells, which differentiate into fibroblast-like cells and form fibrous tissue adjacent to bone trabeculae). Osteitis fibrosa in CKD-MBDs is manifested by severe SHPT, excessive BTO, and marrow fibrosis, often with increased osteoid production and abnormal osteoid mineralization (Fig. 2). Coalescence of large, multinucleated osteoclasts and fibrotic marrow may result in 'brown tumors' (named for the color of these bone lesions due to hemosiderin deposits) and appear as lytic or lucent 'cysts' via radiography. Increased osteoid production may be due to increased collagen production exceeding mineralization and/or by abnormal mineralization (i.e., osteomalacia). Rapidly deposited, poorly structured, and undermineralized osteoid is often referred to as 'woven bone' and lacks the lamellar

pattern and birefringence seen histologically in normal bone.

Vitamin D is important for collagen synthesis and maturation, as well as normal mineralization of osteoid. Factors important in the development of osteomalacia in CKD-MBDs are vitamin D deficiency and/or resistance to calcitriol action. Aluminum deposition in bone can also lead to a skeletal mineralization defect in CKD. Although osteomalacia can be accurately diagnosed only by means of a tetracycline double-labeled iliac crest bone biopsy for histomorphometric analysis, hypovitaminosis D is common in both the general population (50,51) and in patients with CKD (9,10,19,39). The degree of decline in serum levels of 25-hydroxyvitamin D has been found to be related to biochemical markers of CKD-MBDs (directly with decreases in mGFR and indirectly with increases in PTH, C-telopeptide, and bone alkaline phosphatase [BAP]) (49). Low calcitriol levels are also directly related to the degree of renal insufficiency (49), and hypovitaminosis D contributes to bone loss through decreased intestinal calcium absorption (50,52), lowered bone formation (52), and increased osteoclastogenesis (53,54).

Fortunately, stage 4 to 5 CKD only accounts for 4% of reported CKD cases in the U.S. (1). Almost all patients with stage 5 CKD have abnormal bone histology. Cross-sectional studies of bone histology in dialysis patients reveal different prevalences for types of CKD-MBDs (22,23,55,56). Although high BTO and SHPT is a predominant finding in patients with stage 5 CKD, there is also a high prevalence of decreased BTO, or ABD (22,23,56). The prevalence of ABD has been reported as 30% in patients with stage 4 CKD and between 15 and 60% in patients with stage 5 CKD requiring dialysis. In patients with ESRD requiring hemodialysis, ABD is more common in Caucasians and less common in African Americans (22). ABD in CKD-MBDs is characterized histologically by low BTO with very little osteoid accumulation and thin osteoid seams (Fig. 2) (57). Both the rate of collagen synthesis by osteoblasts and the rate of bone matrix mineralization are subnormal. The latter distinguishes ABD from osteomalacia, in which defects in mineralization exceed those in bone formation and result in a relative osteoid excess and thick osteoid seams. Variability in the prevalence of ABD reported among studies may be related to differences in excess calcium loading, aluminum loading, or presence of diabetes (57-60). Aluminum bone deposition leading to ABD was a much greater problem in the era of aluminum-containing phosphate binders and unrecognized aluminum contamination in parenterally administered solutions (especially nutrition and albumin). In theory, ABD is presumed to involve impaired ability to repair skeletal microfractures due to decreased BTO and thereby result in an increased risk of fracture. However, the clinical significance of ABD remains to be determined. Barreto et al (45) identified differences in bone histology with or

without osteoporosis in 98 patients with ESRD treated with hemodialysis. In that study, the majority (56%) of patients had ABD, with 25% having significant aluminum bone deposition. Osteoporosis was associated with age, female gender, duration of amenorrhea, Caucasian ethnicity, and the serum osteoprotegerin to serum receptor-activator of nuclear factor- κ B ligand (RANKL) ratio. Neither histologic ABD findings nor serum levels of PTH, calcium, phosphate, or 25-hydroxyvitamin D were predictive of osteoporosis, although there was a trend for calcitriol use to be associated with the absence of osteoporosis ($P = .06$).

The mechanisms underlying ABD are not fully known, and it may be seen in late CKD either before or after initiating dialysis. It has been generally believed and accepted that elevated PTH levels (2 to 3 times normal) are necessary to maintain normal rates of bone formation in patients with stage 4 to 5 CKD and thereby prevent ABD from developing (9,23,59-63). Patients with ABD have lower PTH levels than those with other CKD-MBDs (22), and although oversuppression of parathyroid gland activity from excessive calcium (62) and/or calcitriol or cinacalcet administration may play a significant role, a similar 'blunting' of PTH with low BTO has been reported in postmenopausal women without CKD (39). To better understand the dynamic changes in CKD-MBDs following parathyroidectomy (PTX), paired bone biopsies taken before and after surgery were studied by Yajima et al (64) in 18 patients with SHPT and stage 5 CKD requiring hemodialysis. PTH levels, markers of BTO, bone osteoclast surfaces, and marrow fibrosis all decreased markedly 2 to 4 weeks after PTX. Significant decreases in the levels of phosphate (from 5.3 ± 1.2 mg/dL to 2.9 ± 1.6 mg/dL) and PTH (from $1,256.7 \pm 448.2$ pg/mL to 30.3 ± 61.6 pg/mL) were observed 2 to 4 weeks after PTX, and PTH fell below 30 pg/mL in all but 2 patients. A substantial increase in osteoid volume and tetracycline label was observed compared with bone biopsies in both low-PTH and high-PTH stage 5 hemodialysis control groups not having PTX, suggesting that increased mineralization was taking place. Tetracycline label in PTX subjects was observed not only at the mineralization front of trabecular surfaces but also around the osteocyte lacunar walls and canaliculi within the basic multicellular units (BMUs). The authors reported an increase in the number of empty lacunae, a reduction in lacunar volume, and a significant decline in the number of osteocytes after PTX. Whether or not these acute BMU changes after PTX were in part due to the high doses of calcium and/or vitamin D (1-alpha-hydroxyvitamin D₃ as oral alfacalcidol) administered and whether or not these bone features persist long-term after PTX is unknown. It is important to recognize the normal physiology of calcium flux into and out of bone, because there is a common misconception that bone remodeling is the major mechanism for day-to-day and minute-to-minute bodily flux of calcium. Osteocytes and bone lining cells, under stimulation by PTH and other effectors, play a much

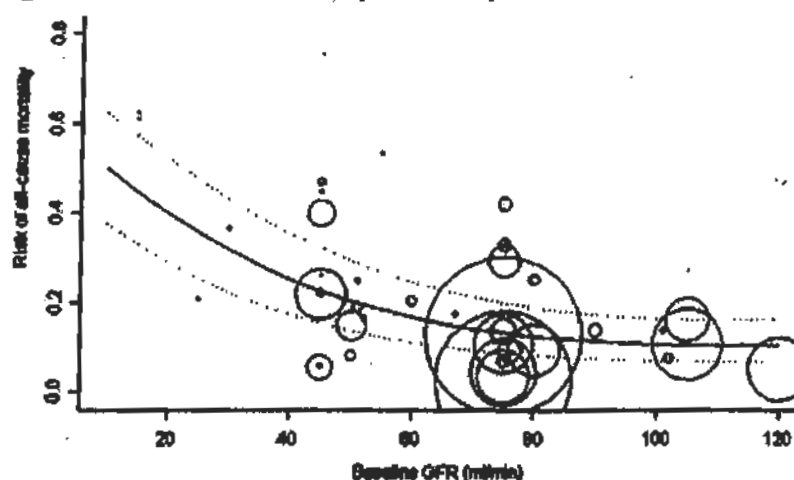
larger role in determining serum calcium concentrations than the rate of BTO, both in health and disease (41).

Malluche et al (22) studied 630 bone biopsies (obtained between 2003 and 2008 in patients with stage 5 CKD requiring hemodialysis) for the degree of trabecular (cancellous) bone volume, turnover, and mineralization. Mineralization defects were rare, being present in only 3% of patients. A total of 62% of Caucasians had predominantly low BTO, whereas 68% of African Americans had normal or high BTO. Other racial differences were also evident. Trabecular bone volume was equally distributed as low, normal, or high in Caucasians, whereas in African Americans trabecular bone volume was high in two-thirds of patients. More than 80% of all patients with low bone volume had thin trabeculae and low bone formation (i.e., ABD). In addition, PTH levels varied by race; PTH values were 499 ± 93 , 614 ± 100 , and 805 ± 99 pg/mL for Caucasians and 172 ± 12 , 343 ± 37 , and 523 ± 37 pg/mL for African Americans for low, normal, and high BTO, respectively. Thus, in more current studies in stage 5 CKD-MBDs, the presence of low bone volume with low BTO (i.e., ABD) is more frequent than previously appreciated, and defects of mineralization (i.e., osteomalacia and aluminum deposition) are rare. This study also confirmed that differences in CKD-MBDs exist within and between races, and treatment guidelines may therefore not apply similarly to all patients. The NKF 2002 KDOQI (2) and 2009 KDIGO (9) guidelines accept a wide range of elevated PTH levels (2 to 9 times the upper limit of normal) as being optimal in late-stage CKD. In 2008, Barreto and colleagues (65) compared bone histomorphometry at baseline and 1 year in 97 patients with stage 5 CKD requiring hemodialysis in order to assess the recommended KDOQI PTH range of between 150 and 300 pg/mL. They found that intact PTH levels <150 pg/mL for identifying low BTO and >300 pg/mL for identifying high BTO had positive predictive values of 83 and 62%, respectively.

Vascular or Soft Tissue Calcification in CKD-MBDs

The risk of any cardiovascular event (6), cardiovascular death (66), and death from any cause (6,66,67) increases sharply as the eGFR declines below 60 mL/min (Fig. 1 and 3). In a prospective cohort study of 382 patients with stage 3 to 5 CKD, the annual mortality rates for stages 3, 4, and 5 were 3.9, 6.3, and 9.2%, respectively (67). However, traditional CVD risk factors do not entirely account for the elevated mortality in CKD, as seen in a prospective study of 3,879 patients with stage 2 to 4 CKD followed for a median of 3.5 years (29).

Hyperphosphatemia, an elevated calcium-phosphate product ($\text{Ca} \times \text{P}$) (68), and SHPT have all been linked to increased arterial vascular calcification and/or CVD mortality. As CKD-MBDs progress, there is a physiologic change for vascular tissue to acquire bone cell characteristics, with a secondary deposition of calcium in arterial

Figure 3. All Cause Mortality in CKD by Baseline Renal Function

Risk for all-cause mortality in 42 cohorts according to baseline estimated GFR (mL/min). Risks are expressed as proportions (e.g., 0.5 = 50%). The area of each circle (i.e., data point) is proportional to the sample size of each cohort. The center line models the estimated risk for baseline GFR from the unadjusted analysis. Dotted lines represent the 95% confidence intervals. Median follow-up 4.9 years (range 0.8 to 14 years).

Towler M, et al. *Journal of the American Society of Nephrology* 2006; 17:2054-2067.

walls and on cardiac valves. One of the mechanisms of vascular calcification in CKD-MBDs is the dedifferentiation of the normal vasculature and the acquisition of an osteoblast-like phenotype. In addition, circulating stem cells originally destined to the vascular bed are recruited to an osteoblast-like phenotype within the vasculature. Thus, bone cell types contribute to arterial vascular calcification in CKD-MBDs.

The correlation between bone turnover, vascular calcification, and mortality in CKD is not well established. It is of interest that in a study of 2,348 healthy postmenopausal women, Schulz et al (44) assessed BMD and aortic calcification via lumbar computed tomography (CT) and found osteoporosis in 70% of subjects, with the degree of aortic calcium accumulation inversely related to skeletal BMD and directly related to fracture. This is in keeping with earlier (electronic beam) coronary CT findings of an association between the degree of coronary calcification and bone loss (69). Arterial vascular calcification begins as early as stage 3 CKD and is strongly linked to bone loss, CVD, and increased mortality. SHPT is associated with bone loss in patients with CKD (19), and low BMD is a risk factor for mortality in patients with ESRD needing dialysis (68). Low BMD in CKD may also accelerate CVD if circulating calcium and/or phosphorus exceed skeletal requirements and an elevated $\text{Ca} \times \text{P}$ ensues (vascular calcification may be accelerated if the tissue $\text{Ca} \times \text{P}$ exceeds 55).

Assessment and Diagnosis in CKD-MBDs

Renal Function, Minerals, and Hormones

An assessment of renal function by measurement of serum creatinine and calculation of the eGFR (http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm) should be obtained in any patient age ≥ 65 years with diabetes meli-

tus, osteoporosis, or the presence of arterial vascular calcification. NKF KDIGO guidelines suggest measurement of serum total calcium, phosphorus, 25-hydroxyvitamin D, PTH, and BAP as baseline values if patients are diagnosed with stage 3 CKD (GFR, 30 to 59 mL/min). As reported by Lobao et al (40), patients with creatine clearance between 10 and 78 mL/min and significant elevation of AP are more likely to have low dual x-ray absorptiometry (DXA) BMD and ABD or osteomalacia seen with bone biopsy histomorphometric analysis. KDIGO guidelines also exist for subsequent laboratory monitoring, but frequency of testing should be individualized as per CKD stage, CKD rate of progression, and treatment administered for CKD-MBDs (Table 4).

FRAX[®], Bone Mineral Density, and Spine Radiographs

Patients with CKD-MBDs are at risk of fracture at an earlier age than those without CKD, and use of the World Health Organization Fracture Risk Assessment Tool (FRAX[®]; <http://www.shef.ac.uk/FRAX/>) may underestimate fracture risk. In addition, FRAX[®] may be unnecessary in the presence of osteoporosis (defined as a BMD T-score ≤ -2.5 or prior spine or hip fragility fracture), as these patients may be candidates for osteoporosis therapy. At present, KDIGO guidelines do not recommend routine BMD testing in patients with stage 3 to 5 CKD. However, several studies demonstrated that DXA BMD is able to assess fracture risk and bone loss over time in patients with stage 3 to 4 CKD (70-75) and possibly in ESRD (76) and that DXA BMD is also useful in assessing changes in bone mass following PTX (74). Thus, BMD measurement is

Table 4. KDIGO Guidelines for Reasonable Serum Laboratory Monitoring in Stage 3-5 Chronic Kidney Disease (CKD)

Mo	Stage 3				Stage 4				Stage 5		
	Ca	P	PTH	AP	Ca	P	PTH	AP	Ca	P	AP
1-3									X	X	
3-6					X	X					X
6-12	X	X	X*				X				
0-12								X*			X*

Diagnosis of CKD-MBD: biochemical abnormalities. *Kidney International* 2009; 76, Suppl 113:S22-631.

Frequency of monitoring (Mo: months) of calcium (Ca), phosphorus (P), parathyroid hormone (PTH) and alkaline phosphatase (AP) based on the degree of abnormalities and CKD progression

- *Stage 3: PTH monitoring based on baseline PTH and CKD progression
- *Stage 4-5: check AP more often based on the degree of PTH elevation

*Guidelines are to measure AP at baseline in stage 3-5 CKD; the frequency of all lab monitoring should be individualized for CKD stage, CKD rate of progression, and response to treatment for CKD-MBD. Thus, AP is checked at least every 12 months in stage 4-5, but in stage 3 CKD yearly checks may or may not be needed after baseline.

indicated in stage 3 CKD (GFR, 30 to 59 mL/min), especially in patients with laboratory or other risk factors for CKD-MBDs (40), and osteoporosis may be diagnosed if the DXA BMD T-score is ≤ -2.5 or if the patient has had a prior spine or hip fragility fracture (78,79). Because men and women with stage 4 CKD (GFR, 15 to 29 mL/min) or worse are often >60 to 70 years of age (Table 5), and both age and renal failure are strong risk factors for fracture, consideration of BMD measurement also seems warranted in these patients. However, anterior-posterior lumbar spine DXA may be falsely elevated if aortic calcification is present, as it cannot be excluded from the anterior-posterior DXA measurement. Lateral DXA imaging may be useful in CKD, as it was significantly correlated with CT in identifying vascular calcification and measuring BMD in a study of 44 men and women with stage 3 to 4 CKD (80). It is important to consider thoracic and lumbar spine radiographs or a vertebral fracture assessment at the time of BMD measurement (especially in patients with significant loss of height, back pain, or ESRD) to assess for not only prior vertebral fractures but also arterial vascular calcification, both of which increase fracture risk and may demand more aggressive therapy for CKD-MBDs (81).

Neither DXA BMD nor volumetric quantitative CT (vQCT) can identify the underlying bone pathology in CKD-MBDs (e.g., SHPT, osteitis fibrosa, ABD, and osteomalacia). The DXA technique also cannot differentiate cancellous from cortical bone in the spine or elsewhere, although this limitation does not apply to vQCT scans, and vQCT of cortical lumbar bone has been shown to be predictive of vertebral fracture risk in ESRD (82). Rix et al (19)

identified the hip and radius as important locations of bone loss in patients with elevated PTH values and a GFR of 20 to 80 mL/min (stage 2 to 4 CKD), corroborating earlier reports of the catabolic effects of SHPT on cortical bone. The importance of cortical bone loss in CKD is magnified by concerns regarding its irreversibility and high rates of hip fracture documented in dialysis patients (47). Malluche et al (22) reviewed 630 iliac crest biopsies in patients with ESRD and found that three-quarters of African Americans had normal cortical thickness but high porosity, whereas there was approximately the same number of Caucasians who had low or normal cortical thickness and normal or high porosity. Cortical bone has a lower BTO rate than cancellous bone and provides a rigid outer shell to long bones that serves primarily as a structural barrier to fracture. Cancellous bone consists of an internal trabecular meshwork that provides flexibility and strength to the bone and also provides a greater surface area that undergoes more rapid BTO and bone remodeling than cortical bone. The differences between bone loss in cortical and cancellous bone, as well as differences in BTO in each of these skeletal compartments, may indeed have important clinical implications as to fracture risk.

Hip fractures are a significant complication in stage 5 CKD-MBDs (46,47,83), with a reported incidence up to 17 times greater than seen in the general population (83). In a retrospective study of 9,007 dialysis patients, a U-curve relationship between fracture risk and PTH level was detected, with fracture risk comparable at all skeletal sites for lowest and highest PTH levels (84). Of interest, in dialysis patients with SHPT, following PTX there

Table 3. Prevalence of Glomerular Filtration Rate (GFR) Categories in Adults (≥ 20 years); NHANES III, 1988-1994

Age (yr)	Total		GFR Category			
	n	%	≥ 60	45-59	30-44	< 30
All	15,600	100	64.3	31.2	4.3	0.20
20-29	7,267	47.6	65.8	30.7	3.4	0.18†
30-39	8,333	52.4	63.0	31.7	5.1	0.23†
40-49	6,263	46.1	86.0	13.7	0.21†	†
50-59	4,182	31.2	55.7	42.4	1.8	†
60-69	2,190	11.3	38.6	53.8	7.1	0.46†
70+	2,965	11.3	25.6	48.5	24.6	1.30

KDOQI Executive Summary. *American Journal of Kidney Disease* 2002; 39(2) Suppl 1:S17-S31
 †Estimate based on < 30 individuals. ‡Cells with < 10 observations.

is a significant decline in FGF-23 and the Ca \times P (36), a reported 32 and 31% decreased fracture rate for hip and any skeletal fracture, respectively (85), and 10 to 15% lower long-term mortality (24). Among patients with ESRD requiring hemodialysis, a meta-analysis of 683 patients found that lower DXA BMD measurements are related to increased fracture risk (46). However, in 52 men and women also with ESRD needing dialysis and followed for 1 year, high-resolution peripheral quantitative CT scanning of the radius was found to be predictive of nonspine fractures, whereas neither hip nor spine DXA BMD accurately predicted fractures (86). One possible explanation for these findings is that ESRD patients have a selective decline in cortical (versus trabecular) bone that may not be identified by DXA.

Biochemical Markers (BCM) and Bone Biopsy

In patients with stage 3 to 5 CKD, KDIGO guidelines recommend baseline measurement of serum PTH and BAP and suggest not to routinely measure bone-derived BCMS of collagen degradation (i.e., type I collagen cross-linked telopeptides C-TX and N-TX, pyridinoline, and deoxypyridinoline). BAP is probably the best readily available BCM for assessing bone formation in CKD, as it is not excreted by the kidney and increased levels virtually exclude the presence of ABD (57). Although BAP elevation in CKD likely reflects SHPT, it may also signify recent fracture, hypovitaminosis D, osteomalacia, or (rarely) other metabolic bone disorders. A significantly elevated PTH also excludes ABD, and marked PTH elevation (6 times above normal) is indicative of osteitis fibrosa. Normal BAP and

normal to slightly elevated PTH levels in late CKD need to be viewed with caution for possible ABD.

The 'gold standard' for the diagnosis and classification of CKD-MBDs is the tetracycline double-labeled bone biopsy. A bone biopsy requires the patient to be referred to a trained physician-surgeon and medical center that can obtain a proper 'core' iliac crest biopsy for histomorphometric analysis, the latter done at only a few centers in the U.S. In situations where it is not clear whether high or low BTO disease or osteomalacia is present, particularly in late-stage CKD with normal to mildly elevated PTH, an iliac crest bone biopsy can help distinguish between types of CKD-MBDs (Table 3 and Fig. 2) (38). Bone biopsy studies have shown an increased prevalence of low BTO during stage 5 CKD in Caucasians, with high BTO common in African Americans (22). The prevalence of CKD-MBDs has increased in the past few decades with an increase in both SHPT-related osteitis fibrosa and ABD (57). The cause of this transition is not yet clear.

Treatment of CKD-MBDs

The development of treatment options that can safely and effectively address serum phosphorus, PTH levels, bone density, CVD, and mortality in patients with CKD-MBDs continues to evolve (57,87).

Calcium

Calcium supplementation in late-stage CKD, particularly when ABD may be present, remains controversial because it may not improve BMD (88) and may accelerate vascular calcification and CVD risk by increasing the Ca

$\times P$. The NKF KDOQI and KDIGO guidelines do not give specific recommendations for calcium supplementation in stage 4 to 5 CKD. Calcium can serve as a phosphate binder, although the trend has been away from calcium use in late CKD-MBDs due to other effective phosphorus binders and concern over raising the $\text{Ca} \times P$. In a small study of 19 patients with stage 3 to 4 CKD who consumed a low-phosphate diet, administration of calcium acetate lowered elevated serum PTH levels and urinary phosphate excretion without changing serum calcium or phosphate levels (35). A larger study of 1,188 men (24% African American) having predominately stage 2 to 4 CKD (8% stage 2, 57% stage 3, 30% stage 4) reported lower mortality over 3 years when using a calcium phosphate binder (median calcium dose 780 mg/day; 507 to 1,014 mg/day at the 25th to 75th percentiles) (89). Spiegel and Brady (90) performed calcium balance studies using 800 mg versus 2,000 mg calcium diets in healthy individuals and patients with stage 3 to 4 CKD. After 9 days, negative calcium balance occurred in both groups eating an 800-mg calcium diet, whereas the 2,000-mg diet resulted in positive calcium balance that was modest in healthy persons and marked in those with CKD. The higher-calcium diet significantly decreased PTH and 1,25-dihydroxyvitamin D levels without changing the serum calcium concentration. Thus, in early CKD, ensuring a modest (1,000 to 1,200 mg) calcium intake appears to be safe and reasonable. In late CKD, some advocate using 200 mg of calcium at each meal as a phosphate binder before the use of other phosphate-binding agents (91). Others suggest prescribing calcium with caution in late CKD, as randomized controlled trials (RCTs) in patients with ESRD have shown progression of vascular calcification (92). Whether or not calcium supplementation in ESRD leads to increased CVD events has not been well studied.

Phosphate Binders

Dietary phosphate restriction and the use of phosphate binders are helpful in the treatment of hyperphosphatemia and SHPT with secondary lowering of FGF-23 (34,35,89,91). Lowering serum phosphorus also increases production of calcitriol, which has a direct effect on the parathyroid glands to decrease PTH production and secretion. Sevelamer carbonate and lanthanum carbonate are effective noncalcium phosphate binders but have been traditionally used after hyperphosphatemia occurs in stage 4 to 5 CKD. Sevelamer and calcium acetate progressively lowered urine phosphate and serum PTH in 40 patients with stage 3 CKD (creatinine clearance, 34.5 mL/min) and SHPT. Importantly, FGF-23 levels were significantly lowered only by sevelamer, an effect not mediated by (non-significant) changes in serum phosphorus or 1,25-dihydroxyvitamin D (35). The addition of lanthanum to a low-phosphate diet in 18 patients with stage 3 CKD significantly lowered urine phosphorus excretion, tubular reabsorption of phosphorus, and serum FGF-23 levels without

changing serum phosphorus or PTH levels (34). Although short- and long-term studies of the use of phosphate binders in stage 3 CKD-MBDs appear promising, long-term prospective clinical trials will be needed to determine if earlier use of phosphate binders will delay development of late-stage CKD-MBDs and reduce mortality (91).

Vitamin D

Hypovitaminosis D is common in both the general population (49,50) and in patients with CKD (9,10,19,39), and a 25-hydroxyvitamin D level should be measured in all patients at any stage of CKD. The 1,25-dihydroxyvitamin D assay is inadequate (due to poor sensitivity and wide coefficient of variation) and should not be used to either assess bodily stores of vitamin D or monitor vitamin D therapy (either by vitamin D or calcitriol). The 2010 Institutes of Medicine guidelines recommend a goal 25-hydroxyvitamin D level of 20 ng/mL for the general health of the population at large, and KDIGO guidelines only suggest that vitamin D deficiency and insufficiency be corrected in CKD using treatment strategies recommended for the general population. However, many experts in metabolic bone disease recommend a 25-hydroxyvitamin D level ≥ 30 ng/mL for bone health and treatment of osteoporosis in patients without known CKD (51). In patients with stage 3 to 4 CKD and SHPT, it is recommended to correct vitamin D deficiency with cholecalciferol (vitamin D_3) and to use calcitriol or vitamin D-receptor-activator (VDRa) analogs only if the PTH remains elevated. With the awareness of the importance of vitamin D for bodily health other than bone and kidney (93), a total 25-hydroxyvitamin D level of 20 to 30 ng/mL seems reasonable. However, it is likely best that vitamin D therapy not be used in the presence of a serum level of phosphate > 5.5 mg/dL, PTH > 150 pg/mL, or a $\text{Ca} \times P \geq 55$ (94).

VDRa Analogs

FGF-23 elevation may inhibit PTH mRNA activity, osteoblast differentiation, and bone matrix maturation. Thus, FGF-23 elevation may result in delayed increase in PTH concentrations (and therefore delayed therapy) and suppressed BTO as early as stage 2 to 3 CKD. VDRa analog therapy is expected to mitigate bone loss in CKD-MBDs by both suppressing PTH-stimulated bone resorption and by preventing low BTO due to its stimulatory effect on normal osteoblast differentiation (94). There may also be direct effects that inhibit osteoclastogenesis (47). Presently, the indication for VDRa analogs in CKD is predicated on lowering elevated serum phosphate and/or PTH levels. However, the administration of VDRa analogs in early CKD-MBDs with SHPT is often avoided because of concern that oversuppression of PTH will promote low BTO and development of ABD, as can be seen in late CKD-MBDs (57,59). In addition, there may be concerns of adverse effects to include an elevated $\text{Ca} \times P$ that

may accelerate CKD progression. However, in one study, low-dose calcitriol use in stage 5 CKD patients resulted in markedly less PTH rise than in controls and significant improvement in both spine and hip BMD (76).

RCTs have assessed the use of the VDRa analogs alfacalcidol (23,70), paricalcitol (95,96), calcitriol (96), and doxercalciferol (97) in stage 3 to 4 CKD-MBDs compared with placebo. Alfacalcidol reduced high PTH levels and prevented bone loss at the spine and hip in patients with a GFR of 20 to 60 mL/min (stage 3 to 4 CKD) (70). This is consistent with an earlier bone histomorphometric study in patients with a GFR of 15 to 50 mL/min that showed alfacalcidol reduced high BTO to more normal values, did not cause abnormally low BTO or ABD, and improved bone formation in the setting of pretreatment ABD (23). Paricalcitol treatment also significantly reduced elevated PTH levels in stage 3 to 4 CKD in 220 patients over 24 weeks (average PTH declined by 42%, with 30% suppression in 90% of patients) (95) and in 263 patients over 32 weeks (>50% PTH reduction in 62% of patients) (96). In this latter RCT, compared with placebo, calcitriol significantly reduced PTH levels (by >50%) in 54% of patients. In these RCTs, serum calcium levels increased for patients taking calcitriol and alfacalcidol, but neither paricalcitol nor doxercalciferol were different from controls as to hypercalcemia, hyperphosphatemia, Ca × P, hypercalciuria, or adverse events.

Drugs to Treat Osteoporosis

Approved therapies for osteoporosis in the U.S. include antiresorptive agents that reduce BTO and an anabolic agent that stimulates bone formation. In postmenopausal women with osteoporosis, bisphosphonates inhibit osteoclast-mediated bone resorption and decrease rates of BTO to premenopausal levels. This is usually associated with an increase in BMD, more at cancellous than cortical bone sites. Bisphosphonates are excreted by the kidney, and the U.S. Food and Drug Administration (FDA) approved labeling for currently available bisphosphonates indicates that these agents should not be used to treat osteoporosis in patients with significantly impaired renal function (GFR <35 mL/min for alendronate and zoledronate and <30 mL/min for risedronate and ibandronate). Retrospective reviews and secondary analyses of previously published RCTs with the antiresorptive drugs risedronate (71), alendronate (72), raloxifene (73), and denosumab (75) have reported both increased BMD and reduced fracture incidence without worsening renal function in patients with early CKD (few patients had an eGFR <30 mL/min in any of these studies). Because bisphosphonates may increase the risk of low BTO and ABD as CKD progresses, they are generally not recommended for the treatment of bone loss in late (stage 4 to 5) CKD. Denosumab is a human monoclonal antibody to the RANKL. Denosumab blocks the binding of RANKL to RANK and thereby decreases the

number and activity of osteoclasts, decreases bone resorption and BTO, increases BMD, and significantly decreases spine and hip fractures in postmenopausal women (98). Denosumab, unlike bisphosphonates, is not metabolized or excreted by the kidney and is not retained in bone (99,100). Jamal et al (75) studied the effects of 3 years of denosumab use compared to placebo in postmenopausal women with stage 1 to 4 CKD (73 women in stage 4, 2,817 in stage 3, and 4,911 in stage 1 to 2) and reported increased BMD and reduced fracture incidence without any adverse mineral or renal effects at any stage of CKD. Even though denosumab is not contraindicated as osteoporosis therapy in stage 4 to 5 CKD, caution should be exercised with these patients to insure adequate provision of calcium (up to 1,000 mg/day) and vitamin D (up to 800 IU/day) to avoid hypocalcemia (101). In addition, it is not yet known if denosumab over-suppresses BTO in stage 5 CKD or changes the histology of CKD-MBDs in late CKD to cause ABD. We would recommend an iliac crest bone biopsy to assess bone histology prior to denosumab use in patients with stage 5 CKD. In a 2011 study by Divers and colleagues (102) of 753 African Americans with T2DM, significant inverse correlations were found between thoracic and lumbar volumetric BMD and (coronary, carotid, and infrarenal) vascular calcification, independent of traditional CVD risk factors, supporting the hypothesis that bone metabolism and vascular calcification are related. However, the potential beneficial effects of decreasing bone remodeling by any antiresorptive agent on CDK-related vascular calcification and CVD events would be speculative only and requires further study.

The biological action of PTH on bone largely depends on pulsatile PTH secretion. This may explain the risk for ABD in patients receiving active vitamin D via suppression of PTH release, whereas dialysis patients have a constant exposure to high calcium dialysate levels, which can also suppress PTH. Teriparatide is a human recombinant hormone that contains the initial amino acid sequence (residues 1 through 34) of the complete 84-amino acid sequence of naturally occurring human PTH. Teriparatide is a skeletal anabolic agent approved for the treatment of osteoporosis. Teriparatide administration to 485 women with osteoporosis and stage 2 to 3 CKD (creatinine clearance, 30 to 79 mL/min) was shown to improve spine and hip BMD and reduce vertebral and nonvertebral fractures compared with controls (74). Transient mild 4- to 6-hour postdosing hypercalcemia was observed but without any long-term effect on renal function. Teriparatide has not been administered to patients with stage 4 to 5 CKD. Whether or not daily teriparatide injection therapy might worsen preexisting SHPT or possibly improve ABD in patients with CKD-MBDs has not been confirmed in clinical trials.

Cinacalcet is a modulator of the CaSR and reduces PTH secretion (and thereby serum calcium) by binding to

the CaSR in parathyroid cells. Cinacalcet is FDA approved in the U.S. for treatment of SHPT due to renal failure. However, the use of cinacalcet in stage 3 to 4 CKD has yet to be approved and remains controversial. Only one RCT of cinacalcet use in stage 3 to 4 CKD has been published (103). In that 32 week study of 404 patients, cinacalcet was found to significantly reduce elevated PTH levels compared with controls (43% versus 1%). In addition, serum calcium levels were significantly lower (8.9 mg/dL versus 9.9 mg/dL), and serum phosphorus levels trended higher (4.5 mg/dL versus 4.0 mg/dL) with cinacalcet use, but no adverse mineral or renal events were noted. Because cinacalcet may increase the risk of hypocalcemia, it is presently generally reserved for patient use in stage 5 CKD, although it has been safely administered in patients with stage 3 to 4 CKD who were not candidates for PTX (104). Initiating cinacalcet at low dose with gradual titration upward as needed may reduce the risk of hypocalcemia.

DISCUSSION

The focus of this article is to briefly review the pathophysiology of CKD-MBDs and to call for increased awareness of the NKF KDIGO guidelines and the early features of CKD-MBDs that can be evaluated and treated. In addition, this review discusses differentiating CKD-MBDs from traditional clinical criteria for assessment and treatment of osteoporosis. Early (stage 1 to 3) CKD comprises the majority (96%) of patients with CKD in the U.S. Treatment of CKD-MBDs is complicated by progressive changes in serum FGF-23, calcium, phosphate, PTH, and 1,25-dihydroxyvitamin D levels, with changes in bone mass and histology as kidney function declines. Management of bone loss associated with stage 2 to 4 CKD-MBDs is possible with judicious selection of calcium, vitamin D and VDRa analogs, antiresorptive agents (bisphosphonates or denosumab), or teriparatide anabolic therapy. In situations where the type of bone disease is not clinically evident and treatment choice is unclear, a tetracycline-labeled iliac crest bone biopsy can be used to help determine the presence of high or low BTO or osteomalacia. The limitation of all of the above-noted studies with bisphosphonates, denosumab, teriparatide, and cinacalcet is that effects of treatment on vascular calcification, bone histomorphometry findings, and other clinical outcomes were not all included in the various study designs.

CONCLUSION

Almost 40% of the U.S. population ≥ 60 years old have CKD, a population age group already dealing with a high prevalence of obesity, T2DM, dyslipidemia, HTN, and age-related bone loss. These diseases impact the progression of CKD-MBDs and vice versa. The close association of renal failure with vascular calcification, CVD,

and increased mortality mandates earlier recognition and treatment of CKD-MBDs. The endocrinologist is uniquely positioned to address and treat not only early CKD-MBDs but also many of the metabolic and skeletal disorders that accompany CKD-MBDs.

DISCLOSURE

Dr. Nelson Watts reports that he is the co-founder, director and a stockholder of OsteoDynamics. He has received honoraria for lectures from Amgen, Merck, Novartis and Warner Chilcott. He has received consulting fees from AbbVie, Amarin, Amgen, Bristol-Meyers Squibb, Corcept, Endo, Imagespace, Janssen, Lilly, Merck, Novartis, Novo Nordisk, Pfizer/Wyeth, Quark, Radian and sanofi-aventis. He has also received research support from Merck and NPS. Drs. Zangeneh, Clarke, Hurley and Miller have no multiplicity of interest to disclose.

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