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

Running title: CKD-MBD and Endocrinologists

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ABSTRACT

Objective: Chronic kidney disease mineral and bone disorders (CKD-MBD) are a spectrum of abnormalities in 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-MBD.

Methods: A literature search was reviewed to a) define disturbances of minerals and hormones in the course of CKD; b) identify the variable radiographic and histomorphometric changes of CKD-MBD; c) review the association among CKD-MBD, vascular calcification, cardiovascular disease (CVD), and mortality; and d) clarify issues in CKD-MBD therapy.

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

Conclusions: The association of CKD with bone disease, vascular calcification, CVD, and mortality mandates earlier recognition and treatment of CKD-MBD. Osteoporosis as a distinct entity can be diagnosed and managed in CKD, though assessment of osteoporosis becomes challenging in late (stage 4-5) CKD. Diabetes is common in early (stage 1-3) 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-MBD, including osteoporosis.

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Abbreviations:

ABD = Adynamic Bone Disease; **AMP** = Adenosine Mono-Phosphate; **AP** = Alkaline Phosphatase; **BAP** = Bone Alkaline Phosphatase; **BMD** = Bone Mineral Density; **BTO** = Bone Turnover; **Ca** = Calcium; **CaSR** = Calcium-sensing Receptor; **Ca X P** = Product of Total Serum Calcium and Serum Phosphorus Levels; **CDC** = Center for Disease Control; **CDK** = Chronic Kidney Disease; **CKD-MBD** = Chronic Kidney Disease – Mineral and Bone Disorders; **CT** = Computed Tomography; **C-telopeptide** = Carboxy-terminal Telopeptide; **C-TX** = Carboxy-terminal Cross-linked Teloeptides of Type 1 Collagen; **C.V.** = Coefficient of Variability; **CVD** = Cardiovascular Disease; **DXA** = Dual X-ray Absorptiometry; **eGFR** = estimated Glomerular Filtration Rate; **ESRD** = End Stage Renal Disease; **FDA** = Food and Drug Administration; **FGF-23** = Fibroblast Growth Factor-23; **FRAX** = Fracture Risk Assessment Tool; **GFR** = Glomerular Filtration Rate; **HTN** = Hypertension; **HR-pQCT** = High Resolution peripheral quantitative CT; **K/DIGO** = Kidney Disease Improving Global Outcome; **K/DOQI** = Kidney Disease Outcomes Quality Initiative; **MDRD** = Modification of Diet in Renal Disease; **mGFR** = measured Glomerular Filtration Rate; **Mo** = Month; **mRNA** = messenger Ribonucleotide Nucleic Acid; **NaP2a** = Sodium-Phosphate Co-transporter, type IIa; **NHANES** = National Health and Nutrition Examination Survey; cardiovascular disease National Kidney Foundation; **Nl** = Normal; **No** = Number ; **N-TX** = Amin--terminal Cross-linked Teloeptides of Type 1 Collagen; **OPG** = Osteoprotegerin; **P** = Phosphorus; **Pop** = Population; **PTH** = Parathyroid Hormone; **PTX** = Parathyroidectomy; **Q** = Every; **RANK** = Receptor Activator of Nuclear Factor kappa-B; **RANKL** = Receptor Activator of Nuclear Factor kappa-B Ligand; **RCT** = Randomized Controlled Trial; **SHPT** = Secondary Hyperparathyroidism; **T2DM** = Type 2 Diabetes

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Mellitus; **U.S.** = United States; **vCT** = volumetric CT; **vQCT** = volumetric Quantitative CT; **VDRa** = Vitamin D Receptor activator; **WHO** = World Health Organization

INTRODUCTION

Chronic kidney disease (CKD) is a serious condition associated with increased health-care 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 (U.S.) (1), and is likely to further increase with increasing longevity and the increasing incidence of obesity and type 2 diabetes mellitus (T_2DM). NHANES is a continuous data survey of health and nutritional status of U.S. adults, and results are analyzed and released periodically by the Center for Disease Control (CDC). NHANES has noted a 15.9% increase in the prevalence of CKD between 1988-1994 and 1999-2004 data bases (cdc.gov). CKD is most common in persons $\geq$60 years of age (39.4% of this population), but also is present in persons aged 40-59 years and 20-39 years (12.6% and 8.5% of these age groups, respectively). (2) T_2DM 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 five stages based upon the glomerular filtration rate (GFR, expressed as mL/min/1.73 m^2), and commonly reported as mL/min (Table 1). In 2003, CKD prevalence by stage among the U.S. population was estimated as 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 stage 4 and stage 5. (1)

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Kidney Disease Improving Global Outcomes (KDIGO) recently published 2012 clinical practice guidelines recommend that CKD staging be classified not solely on GFR (G), but also include cause (C) of injury and albuminuria (A) (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 is defined as mildly, moderately, or severely increased. The 2012 KDIGO classification also divides stage 3 CKD into G3a (45-59 mL/min) and G3b (30-44 mL/min) to acknowledge the significant differences in health outcomes and mortality between these categories (Figure1). (6)

Undiagnosed CKD may lead to the under recognition of associated diseases and lost time in treating co-morbid diseases at earlier stages of CKD. CKD prevalence is greater among persons with T_2DM (40.2% versus 15.4% without T_2DM), 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., of the 11% of adult Americans with CKD, 96% have stage 1-3 CKD (GFR $\geq$30 mL/min). Thus, a sizeable number of patients with T_2DM, CVD, and HTN are at risk for CKD, and should be identified and screened for co-morbid diseases related to CKD, to include mineral and bone disease. In a recently reported abstract of 12 million U.S. patients screened from 2008-2011 by electronic medical records, 44 thousand were found to have T2DM (mean age 64 years). Of patients with T2DM, 51% had CKD and 22% had stage 3-5 disease, although 76% of stage 3-5 CKD patients did not have any recorded diagnosis of CKD. (7) The automatic calculation of estimated GFR (eGFR) on patient laboratory reports will hopefully help to increase awareness that CKD may be present.

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KDIGO sponsored a controversies conference on renal osteodystrophy in 2004 to a) develop a clear, clinically relevant, and internationally acceptable definition and classification system, b) develop a consensus for bone biopsy evaluation and classification, and c) evaluate laboratory and imaging markers for the clinical assessment of patients with CKD. An ideal classification system for CKD-Mineral and Bone Disorders (CKD-MBD) would allow categorization of patients based on readily available clinical diagnostic tools and would help guide treatment. The lack of adequate data and the non-linearity of CKD does not allow for a classification based on severity or treatment at this time. The proposed KDIGO framework for classifying CKD-MBD (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 based upon the skeletal parameters of turnover (T), mineralization (M), and volume (V). Thus, the term CKD-MBD is used to describe a broad clinical syndrome that develops as a systemic disorder characterized by a constellation of abnormalities in regulatory hormones and bone mineral, bone turnover and mineralization, and vascular or soft tissue calcification. CKD-MBD 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 is found in stage 1-3 CKD, and T_2DM is common in early CKD, the endocrinologist is uniquely positioned to address and treat both T_2DM and many of the co-morbid 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

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endocrinologist should know about the development, assessment, and management of CKD-MBD. For purpose of discussion, where not stated in the text, 'early CKD' refers to stage 1-3 disease and 'late CKD' refers to stage 4-5 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.

Bone Mineral and Regulatory Hormones in CKD-MBD

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, 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 (VDR) and calcium-sensing receptors (CaSR) occurs in the parathyroid glands (14) making them less responsive to the actions of circulating vitamin D and calcium. All these events worsen SHPT and its potential effect on bone. Many patients with stage 2-4 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

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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, non-creatinine 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 eGFR 45-59 mL/min who do not have other makers 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. While 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 (MDRD) 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

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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 4127 patients followed for a median of 60 months, elevated phosphate levels were associated with increased coronary events and death in patients with stage 2-3 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 integrated mechanisms responsible for SHPT and bone disease in CKD patients. Phosphate retention and hyperphosphatemia directly stimulate parathyroid gland function. (24) However, perturbations of phosphate retention in stage 2-3 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 4-5 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 post-transcriptional 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 co-transporter (NaP2a). PTH increases urinary phosphate

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excretion via cyclic-AMP 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 co-receptor required for FGF-23 signaling. (33) Patients with CKD have high serum FGF-23 and low Klotho expression in the kidney and parathyroid glands, raising the concept 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, while 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-MBD

The nature and type of bone disease that develops in CKD-MBD may vary among patients. Three types of bone disease, as defined by quantitative bone histomorphometry, may be encountered in patients with CKD: a) increased bone turnover (BTO) and resorption due to SHPT with or without marrow fibrosis (osteitis fibrosa), b) decreased bone turnover and formation (termed ‘adynamic bone’), and c) defective bone mineralization (osteomalacia). (38) Some patients have a mixed pattern. (22-23) In order to clarify the interpretation of bone biopsy

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results in the evaluation of renal osteodystrophy, the TMV classification system allows for three 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 (Figure 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-MBD, and may also be present years before CKD-MBD becomes evident. In a study of 421 postmenopausal women with osteoporosis and GFR >50 mL/min, 39% of women had vitamin D deficiency as defined by 25-hydroxyvitamin D levels <12 ng/dL (<30 nmol/L) and 33% frank SHPT (serum PTH above normal lab 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. reported on 103 patients with CKD (creatinine clearance 10-78 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 and PTH levels predictive of low BMD. Bone histomorphometric analysis on the fifty patients with low BMD revealed adynamic bone disease in 52.5% and osteomalacia in 42.5%.

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Patients in early stage CKD often have mild SHPT features putting them at risk for bone loss from high BTO where bone resorption exceeds bone formation. Several studies of bone histomorphometry in patients with stage 2-4 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 co-existing mineralization defect depending on the degree of hypocalcemia, vitamin D deficiency, or aluminum deposition in bone. Bone histomorphometry in 174 patients with GFR 15-50 mL/min (stage 2-4 CKD) reported by Hamdy et al. 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', while osteomalacia alone (1 patient, 0.6%) and aluminum deposition (2 patients, 1%) were rare. (23) Paired bone biopsies in 62 of these untreated patients showed progression of CKD-MBD in all patients within two 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. did not find an association of 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, MN. (43) Although univariant analysis found increased fracture risk associated with declining renal function, multivariant 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 $\pm$ 26.6 mL/min, and 44.7 + 12.7 mL/min for the 20% of subjects in the lowest quintile. While few 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).

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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 is a CKD-MBD manifested by severe SHPT, excessive BTO, and marrow fibrosis, often with increased osteoid production and abnormal osteoid mineralization (Figure 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 radiographs. Increased osteoid may be due to increased collagen production that exceeds mineralization, and/or abnormal mineralization (i.e., osteomalacia). Rapidly deposited, poorly structured, and under-mineralized 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-MBD 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-MBD (directly with decreases in mGFR, and indirectly with increases in PTH, C-telopeptide, and bone alkaline phosphatase). (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

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calcium absorption (50, 52), lowered bone formation (52), and increased osteoclastogenesis (53-54).

Fortunately, stage 4-5 CKD only accounts for 4% of reported CKD 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-MBD. (22-23, 55-56) While high BTO and SHPT is a predominant finding in patients with stage 5 CKD, there is also a high prevalence of decreased BTO, or 'adynamic bone disease' (ABD). (22-23, 56) The prevalence of ABD has been found to be 30% in patients with stage 4 CKD, and between 15-60% 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 is a CKD-MBD disease characterized histologically by low BTO with very little osteoid accumulation and thin osteoid seams (Figure 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, where 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 have an impaired ability to repair skeletal micro-fractures 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. identified differences in bone histology with or without osteoporosis in 98 patients with ESRD treated with hemodialysis.

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(45) In this 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 OPG/sRANKL 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=0.06).

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 (2-3 times normal) are necessary to maintain normal rates of bone formation in patients with stage 4-5 CKD, and thereby prevent ABD from developing. (9, 23, 59-63) Patients with ABD have lower PTH levels than those with other forms of CKD-MBD (22), and although over-suppression 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-MBD following parathyroidectomy (PTX), paired bone biopsies taken before and after surgery were studied by Yajima et al. in 18 patients with SHPT and stage 5 CKD requiring hemodialysis. (64) PTH levels, markers of BTO, bone osteoclast surfaces, and marrow fibrosis all decreased markedly 2-4 weeks after PTX. Phosphate (from 5.3 $\pm$ 1.2 to 2.9 $\pm$ 1.6 mg/dL) and PTH levels (from 1256.7 $\pm$ 448.2 to 30.3 $\pm$ 61.6 pg/mL) decreased significantly at 2-4 weeks after PTX, and PTH fell below 30 pg/mL in all but two 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

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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 of lacunar volume, and significant decline in osteocyte number after PTX. Whether or not these acute BMU changes after PTX were in part due to 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 in 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. studied 630 bone biopsies (obtained from 2003-2008) in patients with stage 5 CKD requiring hemodialysis for degree of trabecular (cancellous) bone volume, turnover, and mineralization. (22) Mineralization defects were rare, and present in only 3% of patients. A total of 62% of Caucasians had predominately low BTO whereas 68% of African Americans had normal or high BTO (Figure 3). 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 499 $\pm$ 93, 614 $\pm$ 100, 805 $\pm$ 99 for Caucasians and 172 $\pm$ 12, 343 $\pm$ 37, 523 $\pm$ 37 for African Americans, respectively for low, normal, and high BTO. Thus, in more current studies in stage 5 CKD-MBD the presence of low bone volume with low BTO (i.e., ABD) is more frequent than previously appreciated, and defects of mineralization

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(i.e., osteomalacia and aluminum deposition) are rare. This study also confirms that CKD-MBD differences 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 (2-9 times the upper limit of normal) as being optimal in late stage CKD. In 2008, Barreto and colleagues studied bone histomorphometric change at baseline and one year to assess the recommended KDOQI PTH range of between 150-300 pg/mL in 97 patients with stage 5 CKD requiring hemodialysis. (65) 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-MBD

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. (Figures 1 and 4). In a prospective cohort study of 382 patients with stage 3-5 CKD, the annual mortality rates for stages 3, 4, and 5 CKD 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 3879 patients with stage 2-4 CKD followed for a median of 3.5 years. (29) Hyperphosphatemia, an elevated calcium-phosphate (Ca X P) product (68), and SHPT have all been linked to increased arterial vascular calcification and/or CVD mortality. As CKD-MBD progresses, there is a physiologic change for vascular tissue to acquire bone cell characteristics, with a secondary deposition of calcium in arterial walls and on cardiac valves. One of the mechanisms of vascular calcification in CKD-MBD 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

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the vasculature. Thus, both bone cell types contribute to arterial vascular calcification in CKD-MBD.

The correlation of bone turnover, vascular calcification, and mortality in CKD is not well established. It is of interest that in a study of 2348 healthy postmenopausal women, Schulz et al. 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 bone BMD and directly related to fracture. (44) 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. As CKD-MBD progresses, calcium is less avidly incorporated into the skeleton during bone remodeling. 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 BTO in CKD may also accelerate CVD if circulating calcium and/or phosphorus exceed skeletal requirements and an elevated Ca X P product ensues (vascular calcification may be accelerated if the tissue Ca X P product exceeds 55).

Assessment and Diagnosis in CKD-MBD

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 with age ≥65, diabetes mellitus, osteoporosis, or presence of arterial vascular calcification. NKF KDIGO guidelines suggest measurement of serum total calcium, phosphorus, 25-hydroxyvitamin D, PTH, and bone alkaline phosphatase as baseline values if patients are diagnosed with stage 3 CKD (GFR 30-59 mL/min). As reported by Lobao et al. (40), patients

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with creatine clearance between 10-78 ml/min and significant elevation of alkaline phosphatase were more likely to have low dual x-ray absorptiometry (DXA) BMD, and ABD or osteomalacia seen on 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-MBD (Table 4).

FRAX®, Bone Mineral Density, and Spine Radiographs. Patients with CKD-MBD are at risk of fracture at an earlier age than those without CKD, and use of the World Health Organization (WHO) 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 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 3-5 CKD. However, several studies demonstrate that DXA BMD is able to assess fracture risk and bone loss over time in patients with stage 3-4 CKD (70-75) and possibly in ESRD (76), and is also useful in assessing changes in bone mass following PTX (74). Thus, BMD measurement is indicated in stage 3 CKD (GFR 30-59 mL/min), especially in patients with laboratory or other risk factors for CKD-MBD (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 15-29 mL/min) or worse are often >60-70 years of age (Table 5), and both age and renal failure are strong risk factors for fracture, consideration for BMD measurement also seems warranted in these patients. However, anterior-posterior (AP) lumbar spine DXA may be falsely elevated if aortic calcification is present as it cannot be excluded from the AP DXA measurement. Lateral DXA imaging may be useful in CKD, as it significantly correlated with CT in identifying

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vascular calcification and measuring BMD in 44 men and women with stage 3-4 CKD. (80) It is important to consider thoracic and lumbar spine radiographs or a vertebral fracture assessment (VFA) 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-MBD. (81)

Neither DXA BMD nor volumetric quantitative CT (vQCT) can identify the underlying bone pathology in CKD-MBD (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. have identified the hip and radius as important locations of bone loss in patients with elevated PTH values and GFR 20-80 mL/min (stage 2-4 CKD) (19) 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 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

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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-MBD (46-47, 83), with a reported incidence up to 17 times greater than seen in the general population (83). In a retrospective study in 9007 dialysis patients, a U-curve relationship between fracture risk and PTH levels 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 is a significant decline in FGF-23 and Ca X P product (36), a reported 32% and 31% decreased fracture rate respectively for hip and any skeletal fracture (85), and 10-15% lower long-term mortality (24). Among patients with ESRD requiring hemodialysis, a meta-analysis of 683 patients found lower DXA BMD measurements related to increased fracture risk. (46) However, in 52 men and women also with ESRD needing dialysis and followed for one year, high resolution peripheral quantitative CT (HR-pQCT) scanning of the radius was found to be predictive of non-spine 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 3-5 CKD-MBD, KDIGO guidelines recommend baseline measurement of serum PTH and bone specific alkaline phosphatase (BAP) and suggest not to routinely measure bone-derived biochemical markers (BCM) 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

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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-MBD 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 CKD-MBD types (Table 3 and Figure 2). (38) Bone biopsy studies have shown increased prevalence of low BTO during stage 5 CKD in Caucasians, with high BTO common in African Americans. (22) The prevalence of CKD-MBD 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 in CKD-MBD

The development of treatment options that can safely and effectively address serum phosphorus, PTH levels, bone density, CVD, and mortality in patients with CKD-MBD 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 X P product. The NKF KDOQI and KDIGO guidelines do not give specific recommendations for calcium supplementation in stage

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4-5 CKD. Calcium can serve as a phosphate binder, although the trend has been away from calcium use in late CKD-MBD due to other effective phosphorus binders and the concern of raising the Ca X P product. In a small study of 19 patients with stage 3-4 CKD and consuming a low phospate diet, administration of calcium acetate lowered elevated serum PTH levels and urinary phosphate excretion without changes in serum calcium or phosphate. (35) A larger study of 1188 men (24% African American) having predominately stage 2-4 CKD (8% stage 2, 57% stage 3, 30% stage 4) reported lower mortality over three years when using a calcium phosphate binder (median calcium dose 780 mg/day; 507-1014 mg/day at the 25^{th}-75^{th} percentiles). (89) Spiegel and Brady performed calcium balance studies using 800 mg versus 2000 mg calcium diets in healthy individuals and patients with stage 3-4 CKD. (90) After 9 days, negative calcium balance occurred in both groups eating an 800 mg calcium diet, whereas the 2000 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 change in the serum calcium concentration. Thus, in early CKD, ensuring a modest (1000-1200 mg) calcium intake appears to be safe and reasonable. In late CKD, some advocate using 200 mg 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 is not 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

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direct effect on the parathyroid glands to decrease PTH production and secretion. Sevelamer carbonate and lanthanum carbonate are effective non-calcium phosphate binders, but have been traditionally used after hyperphosphatemia occurs in stage 4-5 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 changes in serum phosphorus or PTH. (34) Although short and long-term studies with use of phosphate binders in stage 3 CKD-MBD 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-MBD 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 C.V.) 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 recommends 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 $\geq$30 ng/mL for bone health and treatment of osteoporosis in patients without known

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CKD. (51) In patients with stage 3-4 CKD and SHPT, it is recommended to correct vitamin D deficiency with cholecalciferol (vitamin D3), and to use calcitriol or vitamin D receptor activator 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 20-30 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 Ca X P product ≥55. (94)

Vitamin D Receptor Activator 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 bone turnover as early as stage 2-3 CKD. Vitamin D receptor activator (VDRa) analog therapy is expected to mitigate bone loss in CKD-MBD 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-MBD with SHPT is often avoided because of concern that over-suppression of PTH will promote low BTO and development of ABD, as can be seen in late CKD-MBD. (57, 59) In addition, there may be concerns of adverse effects to include an elevated Ca X P product that may accelerate CKD progression. However, low dose calcitriol use in stage 5 CKD patients resulted in markedly less PTH rise than controls, and significant improvement in both spine and hip BMD. (76) RCTs have assessed the use of VDRa analogs alfacalcidol (23, 70), paricalcitol (95-96), calcitriol (96), and doxercalciferol (97) in stage 3-4 CKD-MBD compared with placebo. Alfacalcidol reduced high PTH levels and prevented bone loss at the spine and hip in patients with GFR 20-60

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mL/min (stage 3-4 CKD). (70) This is consistent with an earlier bone histomorphometric study in patients with GFR 15-50 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 pre-treatment ABD. (23) Paricalcitol treatment also significantly reduced elevated PTH levels in stage 3-4 CKD in 220 patients over 24 weeks (average PTH decline by 42%, and 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, calcitriol significantly reduced PTH levels >50% in 54% of patients compared with placebo. 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 X P product, hypercalciuria, or adverse events.

Drugs to Treat Osteoporosis. Approved therapies for osteoporosis in the U.S. include anti-resorptive 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 analysis of previously published RCTs with the anti-resorptive 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

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patients had 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 4-5) CKD. Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-kB ligand (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. studied the effects of three years denosumab use compared to placebo in postmenopausal women with stage 1-4 CKD (73 women in stage 4, 2817 in stage 3, 4911 in stage 1-2) and reported increased BMD and reduced fracture incidence without any adverse mineral or renal effects at any stage of CKD. (75) Even though denosumab is not contraindicated as osteoporosis therapy in stage 4-5 CKD, caution should be applied in these patients to insure adequate provision of calcium (up to 1000 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 CKD-MBD histology 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 of 753 African Americans with T_2DM, 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. (102) However, the potential beneficial effects of decreasing bone remodeling by any anti-resorptive agent on CDK-MBD vascular calcification and CVD events would be speculative only and requires further study.

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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 1-34 amino acid human recombinant PTH hormone approved for treatment of osteoporosis. Teriparatide administration to 485 women with osteoporosis and stage 2-3 CKD (creatinine clearance 30-79 mL/min) was shown to improve spine and hip BMD and reduce vertebral and non-vertebral fractures compared with controls. (74) Transient mild 4-6 hour post-dosing hypercalcemia was observed, but without any long-term effect on renal function. Teriparatide has not been administered to patients with stage 4-5 CKD. Whether or not daily teriparatide injection therapy might worsen pre-existing SHPT or possibly improve ABD in patients with CKD-MBD has not been confirmed in clinical trials.

Cinacalcet is a modulator of the calcium sensing receptor (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 3-4 CKD has yet to be approved and remains controversial. Only one RCT of cinacalcet use in stage 3-4 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 versus 9.9 mg/dL) and serum phosphorus levels trended higher (4.5 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 3-4 CKD who were not candidates for

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parathyroidectomy. (104) Initiating cinacalcet at low dose with gradual titration upward as needed may reduce the risk of hypocalcemia.

Management of bone loss associated with stage 2-4 CKD-MBD is possible with judicious selection of the calcium, vitamin D and VDRa analogs, anti-resorptive 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

Early (stage 1-3) CKD comprises the majority (96%) of patients with CKD in the U.S. Treatment of CKD-MBD 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. The focus of this article is to briefly review the pathophysiology of CKD-MBD, and to call for an increased awareness of the NKF KDIGO guidelines and the early features of CKD-MBD that can be evaluated and treated. In addition, this review discusses differentiating CKD-MBD from traditional clinical criteria for assessment and treatment of osteoporosis. Almost 40% of the U.S. population $\geq$60 years old have CKD, a population age group already dealing with a high prevalence of obesity, T_2DM, dyslipidemia, HTN, and age-related bone loss. These diseases impact on the progression of CKD-MBD, and vice versa. The close association of renal failure with vascular calcification, CVD, and increased mortality mandates earlier recognition and treatment of CKD-MBD. The endocrinologist is uniquely

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positioned to address and treat not only early CKD-MBD, but also many of the metabolic and skeletal disorders that accompany CKD-MBD.

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

Stage	Description	GFR
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)

Table 2: Staging of CKD by Glomerular Filtration Rate (GFR) and Albuminuria Categories: KDIGO 2012 Guidelines[1]

- 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 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

[1]KDIGO 2012 Clinical Practice Guideline. Kidney International Supplements Vol. 3, Issue 1, January 2013. 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).

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

TMV Classification For Renal Osteodystrophy – Based on Bone Biopsy/Morphology		
Turnover (T)	Mineralization (M)	Volume (V)
Low		Low
	Normal	
Normal		Normal
	Abnormal	
High		High

Clinical Framework For Classification of CKD-Mineral and Bone Disease			
Type[2]	Laboratory (+)	Bone Disease	Vascular-Soft Tissue Calcification
L	+	-	-
LB	+	+	-
LC	+	-	+
LBC	+	+	+

[1]Kidney International 2006; vol.69: pg 1945–1953.
[2]L: 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.

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	PTH	AP*
1-3									X	X		
3-6					X	X					X	
6-12	X	X	X[1]				X					
Q12								X[2]				X[2]

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

- [1]Stage 3: PTH monitoring based on baseline PTH and CKD progression
- [2]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.

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Table 5. Prevalence of Glomerular Filtration Rate (GFR) Categories in Adults (≥20 years); NHANES III, 1988-1994

	Overall		Prevalence of CKD Stage (GFR as mL/min/1.73m²)			
	Subjects (No.)	Subjects (%)	Normal (90+)	Stage 2 (60-89)	Stage 3 (30-59)	Stage 4 (15-29)
Total	15,600	100	64.3	31.2	4.3	0.20
Men	7,267	46.6	65.8	30.7	3.4	0.18
Women	8,333	53.4	63.0	31.7	5.1	0.23
Age (yrs)						
20-39	6,263	40.1	86.0	13.7	0.21†	‡
40-59	4,182	26.8	55.7	42.7	1.8	‡
60-69	2,190	14.0	38.5	53.8	7.1	0.46
70+	2,965	19.0	25.5	48.5	24.6	1.30

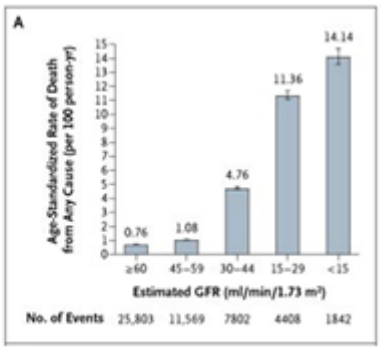
†Estimate based on <30 individuals. ‡Cells with <10 observations.

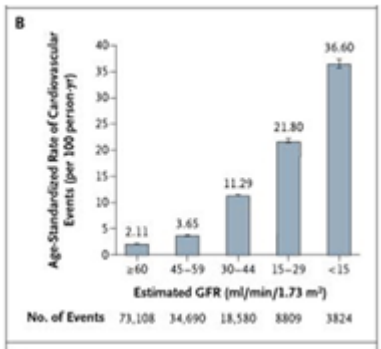
Figure 1: CKD stage and outcomes

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





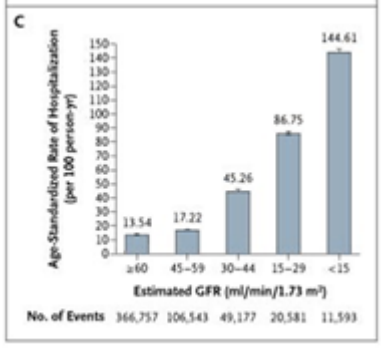


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Figure 2: Bone Turnover (BTO) and CKD-MBD

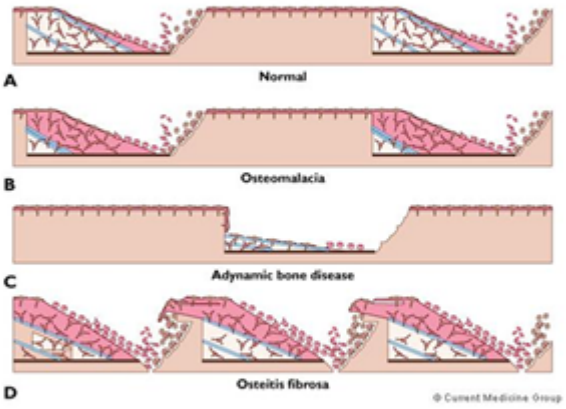
Normal BTO (A), Low BTO due to Osteomalacia (B), Very Low BTO due to Adynamic Bone Disease (C), and High BTO with osteitis fibrosa due to Hyperparathyroidism (D)

(A) In normal BTO (2 BMUs shown), osteoblast bone formation equals osteoclast bone resorption.

(B) In osteomalacia (2 BMUs shown), osteoid accumulates on most bone surfaces due to a defect in mineralization (i.e., calcification). Potential etiologies include chronic metabolic acidosis, vitamin D deficiency, and excess FGF-23.

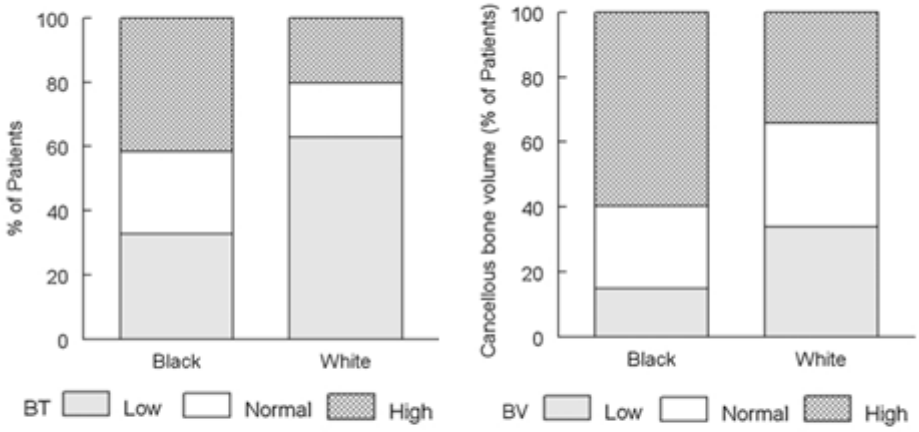
(C) Adynamic bone disease is a form of very low BTO (only 1 BMU shown) with little osteoid formed.

(D) High BTO (3 BMUs) is often related to hyperparathyroidism, with disease severity highly correlated to the degree of PTH elevation.



CKD: chronic kidney disease; MBD: mineral and bone disorders; BMU: basic multicellular unit (activity of osteoclasts and osteoblasts within a discrete bone remodeling unit); FGF-23: fibroblast growth factor 23; PTH: parathyroid hormone. In: Atlas of Osteoporosis. Orwoll, Eric S (Ed.) 3rd ed. 2009, VIII (Springer). http://extras.springer.com/2009/978-1-57340-296-5/01/0112/0112002LA.html

Figure 3: Prevalence of degree of bone turnover and amount of cancellous bone volume in patients with stage 5 CKD on hemodialysis.



Bone Turnover (Left): % of Black and White patients with low, normal, and high bone turnover (BT).
Cancellous Bone Volume (Right): % of Black and White patients with low, normal, and high cancellous bone volume (BV); equally distributed in Whites and high cancellous BV predominate in Blacks.
Data from 630 bone biopsies of adult patients with stage 5 CKD requiring dialysis, and evaluated by histomorphometry and analyzed using the turnover (T), mineralization (M), and volume (V) NKF-KDIGO classification system. Malluche HH, et al. J Bone Miner Res 2011; 26(6);1368-1376.

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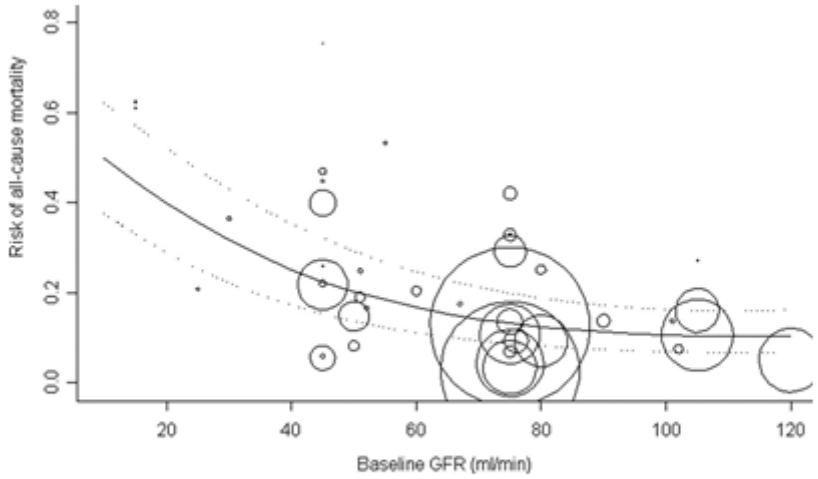
Figure 4. All Cause Mortality in CKD by Baseline Renal Function



Risk for all-cause mortality in 42 cohorts according to baseline estimated GFR (mL/min.). Risks are expressed as proportions (e.g., 0.6 = 60%). 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). Journal of the American Society of Nephrology 2006: vol.17: pg 2034-2047.

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