Review Article CME

Current Concepts and Management Strategies in Chronic Kidney Disease-Mineral and Bone Disorder

Veeraish Chauhan, MD, Ellie Kelepouris, MD, Nishtha Chauhan, BDS, and Megha Vaid, MPH

Abstract: The term renal osteodystrophy describes the pathological changes in bone structure in chronic kidney disease (CKD); however, this term fails to describe adequately the adverse changes in mineral and hormonal metabolism in CKD that have grave consequences for patient survival. CKD-mineral and bone disorder (CKD-MBD) is a broader, newly defined term that should be used instead of renal osteodystrophy to define the mineral, bone, hormonal, and calcific cardiovascular abnormalities that are seen in CKD. The new paradigm in the management of renal bone disease is to "think beyond the bones" and strive to improve cardiovascular outcomes and survival. This means treating other aspects of the disease process that go beyond merely controlling parathyroid hormone levels. Primary physicians need to take a proactive approach to the management of CKD-MBD because the disorder begins early in the course of CKD, well before a patient is referred to a nephrologist. This review outlines the evidence behind the understanding of CKD-MBD, its implications for overall mortality, and the latest recommendations for management of CKD-MBD in patients with predialysis CKD.

Key Words: chronic kidney disease mineral and bone disorder, renal osteodystrophy, renal bone disease, Kidney Disease: Improving Global Outcomes guidelines, vascular calcification, osteitis fibrosa, adynamic bone disease

Progressive chronic kidney disease (CKD) is associated with adverse changes in bone-mineral metabolism. These changes begin in early CKD, although symptoms such as fractures may not occur until patients are placed on dialysis.[1] Serum parathyroid hormone (PTH) level, an indicator of bone disease in CKD, can begin to increase when the glomerular filtration rate (GFR) falls below 70 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^2.[2] At this level of renal function, a patient could be years from seeking care by a nephrologist. It could become incumbent on the primary physician to manage this care because studies suggest that abnormal mineral and hormonal homeostasis in CKD is associated with an adverse effect on mortality resulting from vascular calcification, particularly in the coronary vasculature.[3,4] It is ironic that coronary artery calcification has thus far been the least emphasized yet the most damaging consequence of bone-mineral disease in CKD.

The term renal osteodystrophy is sometimes used erroneously to describe the mineral and bone disease seen in CKD. A 2006 National Kidney Foundation position statement directed that this term be used exclusively to describe the bone morphology alterations observed in CKD.[5] The new proposed term CKD-mineral and bone disorder (CKD-MBD) instead defines a broader syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities seen as a complication of CKD. The paradigm now is to "think beyond the bones"

Key Points
- Chronic kidney disease-mineral and bone disorder should be the term used to describe the abnormalities in bone-mineral metabolism and calcific cardiovascular abnormalities seen in chronic kidney disease.
- It is important to appreciate that when untreated, abnormalities of mineral metabolism lead to cardiovascular calcifications, which are a major cause of morbidity and mortality in patients with chronic kidney disease.
- Primary care physicians need to take a proactive approach to the management of chronic kidney disease-mineral and bone disorder because the disorder begins early in the course of chronic kidney disease, well before a patient is referred to a nephrologist.

and improve patient survival, which means treating all aspects of the disease process, not just PTH levels.

This review outlines the evidence behind the understanding of CKD-MBD, its implications for overall mortality, and the latest recommendations for the management of CKD-MBD in patients with predialysis CKD. A PubMed search was conducted for English-language references published as of October 2011, using combinations of the following terms: "chronic kidney disease mineral and bone disorder," "bone disease," "fractures," "osteoporosis," "osteonecrosis," "renal osteodystrophy," "renal bone disease," "vascular calcification," "osteitis fibrosa cystic," "adynamic bone disease," "osteomalacia," "bisphosphonates," "1,25-dihydroxyvitamin D," "vitamin D," "parathyroid hormone," "cardiovascular mortality," "KDIGO guidelines," "prevention," "treatment," and "epidemiology." The bibliographies of the articles thus obtained and those of relevant review articles also were reviewed for inclusion of publications.

CKD and Mortality

As per the 2011 US Renal Data System Annual Data Report, 15.1% of the US adult population has CKD.[6] Both early CKD and end-stage renal disease (ESRD) are associated with high morbidity and mortality. A retrospective analysis reported that hypertension, diabetes, cardiovascular disease, and peripheral vascular disease were present in 87%, 35%, 40%, and 14%, respectively, of patients with predialysis CKD. Hospital days per patient-year at risk were 6.6.[7] These rates are comparable to the prevalence of these conditions in the population on dialysis.[6] Thus, comorbidities associated with ESRD also manifest themselves in early CKD.

Adjusted mortality among patients with predialysis CKD in 2009 was 56% greater than among patients without CKD and worsens with the decline in GFR. Among patients aged 65 years and older on dialysis, mortality is twice as high as for patients in the general population who have diabetes, cancer, or congestive heart failure. Adjusted rates of all-cause mortality are 6.5 to 7.4 times greater for patients on dialysis than for the general population.[6] Cardiovascular disease is the single greatest cause of mortality in CKD/ESRD, and to a large extent is attributable to abnormal mineral metabolism.[6]

Limited data exist regarding the exact prevalence of CKD-MBD. Abnormal mineral metabolism is believed to start as early as stage II CKD. The implication is that >10% of the adult US population could be at risk or already have established CKD-MBD.

CKD-MBD and Mortality

Studies have described the association between abnormal mineral metabolism and adverse cardiovascular outcomes in CKD. A study of 202 patients on dialysis described arterial medial calcification and its impact on survival in CKD.[3] Arterial intimal calcification was usually observed in older patients with a clinical history of atherosclerosis before

starting dialysis and typical risk factors for atherosclerosis. Medial calcification was observed in young and middle-aged patients without conventional atherosclerotic risk factors. Medial calcification was closely associated with dialysis duration and with dose of calcium prescribed as phosphate binder. Compared with patients with intimal calcification, patients with medial calcification had a longer survival time, but their survival time was significantly shorter than that of patients without calcifications. Medial calcification could therefore be a strong prognostic marker of all-cause and cardiovascular mortality in patients on dialysis. Another study included patients on dialysis, and stage IV CKD, and showed that rapid progression of calcification was associated with mortality.[4]

Pathophysiology

As kidney function declines, there is progressive deterioration in bone-mineral homeostasis and changes in levels of PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and fibroblast growth factor-23 (FGF-23). The spectrum of bone disease ranges from low-turnover adynamic disease to high-turnover osteitis fibrosa. More than one type can coexist in the same patient. Dialysis-related amyloidosis is another form of bone disease that is seen in patients on long-term dialysis. It is thought to occur because of the accumulation of β2-micro-globulin, and its incidence appears to be decreasing, likely because of the increased use of high-flux dialyzers with enhanced clearance of β2-microglobulin.

Osteitis Fibrosa Cystica

Osteitis fibrosa cystica is characterized by increased bone turnover caused by secondary hyperparathyroidism. PTH levels begin to rise in early CKD when the GFR decreases below 70 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^2.[2] The increase in PTH secretion occurs in response to a series of abnormalities (Fig.):

1. Phosphate retention: Decrease in the filtered phosphate load resulting from a fall in GFR causes phosphate retention. This can start in CKD stage II (GFR 60–89 mL $\cdot$ min $\cdot$ 1.73 m^2) and causes an adaptive increase in the PTH secretion that in turn increases phosphate excretion.[8] Thus, phosphate levels in the serum may not increase until the GFR falls to approximately 20 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^2.[9] Hence, increased PTH levels are considered a more accurate marker of phosphate retention in early CKD. Phosphate retention can then trigger a cascade of events that lead to secondary hyperparathyroidism by overlapping mechanisms. A decrease in free serum calcium occurs because of increased binding with the retained phosphate. A decrease in the formation of 1,25-dihydroxyvitamin D resulting from a reduction in renal mass and decreased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is seen.[10,11] The role of a novel biomarker FGF-23 in this activity has come under scrutiny. FGF-23 is a phosphaturic hormone produced by osteocytes in response to elevated phosphate and decreases the synthesis of 1,25-dihydroxyvitamin D by suppressing the activity of 1-α-hydroxylase.[12] Elevated FGF-23 has been shown to be an independent risk factor for cardiovascular events and mortality in both the general population and advanced CKD.[13,14] Alterations in 1,25-dihydroxyvitamin D

metabolism lead to increased PTH secretion because of the decreased intestinal absorption of calcium and the removal of the inhibitory effect of 1,25-dihydroxyvitamin D on the parathyroid.[10] Finally, hyperphosphatemia also directly increases PTH gene expression. An in vitro study found increased preproPTH mRNA synthesis from hyperplastic parathyroid tissue obtained from patients with CKD when it was exposed to high phosphate concentrations.[15]

2. Role of calcium-sensing receptor: Calcium exerts negative feedback on PTH secretion through the calcium-sensing receptor on the parathyroid. Decrease in serum calcium during the course of CKD caused by phosphate retention and decreased 1,25-dihydroxyvitamin D attenuates this feedback and leads to increased PTH mRNA levels and proliferation of parathyroid cells.[16] The number of calcium-sensing receptors also may decrease in hypertrophied parathyroid tissue and lead to inadequate suppression of PTH secretion even in the setting of normal or high calcium levels.[17]

3. Skeletal resistance to calcemic action of PTH: A high level of PTH can lead to downregulation of the PTH receptor on the bone as an adaptive response. This causes increased resistance to the calcemic action of PTH on bone and eventually higher PTH levels.[18]

4. Tertiary hyperparathyroidism: An unusual mechanism of PTH increase occurs because of severe parathyroid hyperplasia that no longer responds to calcium. This represents a state of autonomous oversecretion.[19] Prolonged stimulation of parathyroid cell growth results in nodular hyperplasia. These hyperplastic glands do not undergo involution even when the triggering mechanism resolves, leading to tertiary hyperparathyroidism.

Increased PTH eventually leads to increased bone resorption and turnover. This can cause extraosseous calcification (calciphylaxis) in arteries, joints, and viscera.[20] Metabolic acidosis seen in CKD also exacerbates bone disease by promoting osteoclast activity and bone dissolution.[21] The increased
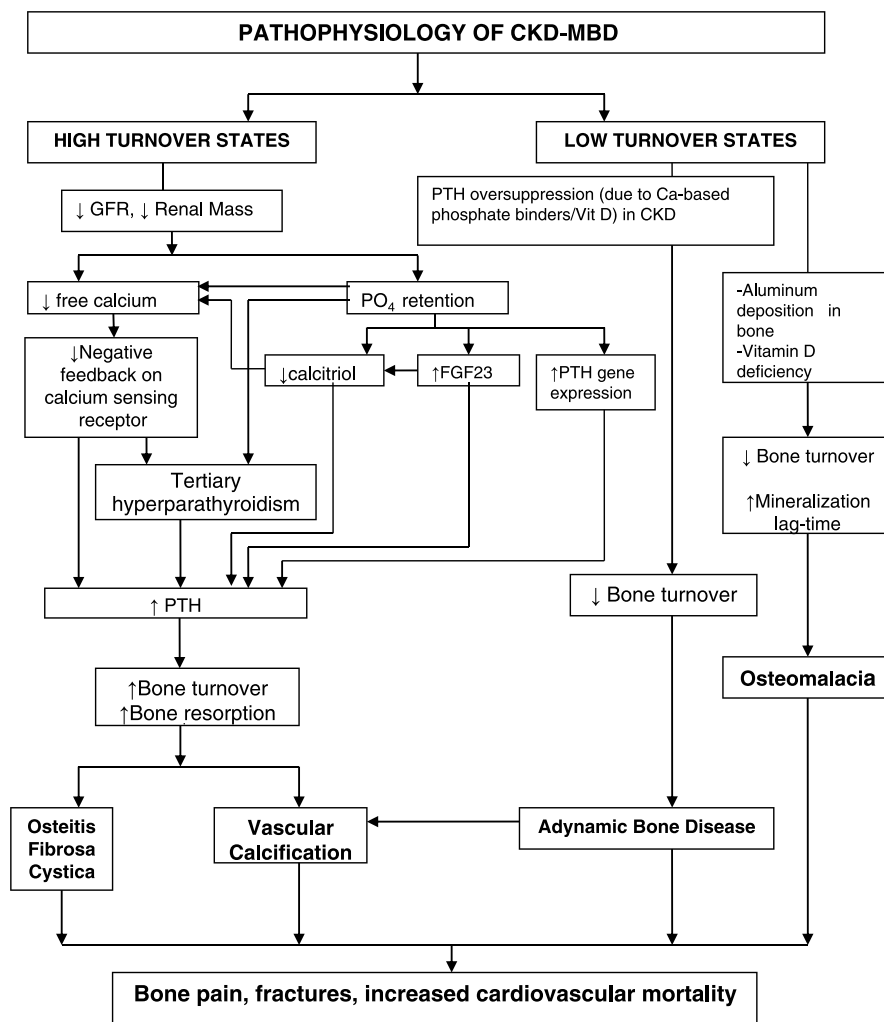

Fig. Pathophysiology of chronic kidney disease-mineral and bone disorder (CKD-MBD). FGF23 indicates fibroblast growth factor-23; GFR, glomerular filtration rate; PO_4, phosphate; PTH, parathyroid hormone.

Table 1. Factors that may influence mineral and bone metabolism

Factors prevalent in patients with chronic kidney disease
    Prolonged aluminum exposure
    Glucocorticoid therapy as in patients with parenchymatous kidney diseases and in kidney transplant recipients
    Previous parathyroidectomy
    Vitamin D treatment
    Diabetes mellitus
    β-2-microglobulinemia amyloidosis
    Metabolic acidosis
    Hypophophatemia secondary to aggressive dietary phosphate restriction or excessive use of phosphate binders
Nonchronic kidney disease–related factors
    Old age
    Postmenopausal status
    Race
    Nutritional vitamin D deficiency
    Medications that interfere with vitamin D metabolism
    Malignancy with or without bone metastasis
    Prolonged immobilization

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PTH eventually becomes maladaptive and continues to cause phosphate release from bone. The net effect is that PTH, at this stage, exacerbates the hyperphosphatemia, setting off a vicious cycle.[22]

Adynamic Bone Disease

Adynamic bone disease represents a state of reduced turnover. The rate of collagen synthesis and mineralization are subnormal. Adynamic bone disease is the principal form of bone lesion both in patients with predialysis CKD and in the population on dialysis. It is particularly common among people with diabetes.[23,24] The underlying mechanism is oversuppression of PTH, which could result from the use of calcium-based phosphate binders or vitamin D analogs. Other risk factors include advanced age, diabetes, and aluminum deposition.[25,26]

Although patients with adynamic bone disease can be asymptomatic, fractures and hypercalcemia can occur.[27] Mortality is increased because of enhanced cardiovascular calcification. A review of the risk of hip fracture in patients on dialysis revealed that PTH values <195 pg/dL (a value likely to be associated with the adynamic state) were a significant predictor of fracture risk.[28] Similarly, the Kidney Disease Outcomes Quality Initiative (K/DOQI) reports a fourfold increase in hip fracture risk in the population on dialysis.[29] The hypercalcemia and vascular calcification seen are a repercussion of decreased bone uptake of calcium because calcium is neither released from nor taken up by bone. Hence, minimal calcium loading causes hypercalcemia.[29]

Osteomalacia

Osteomalacia also is a state of low bone turnover; however, it is characterized by an increase in the volume of unmineralized bone caused by prolonged mineralization lag time.[1] Aluminum toxicity from the use of aluminum-containing antacids (to bind phosphate) was a common cause of osteomalacia in patients on dialysis. This incidence has decreased with the abandonment of aluminum-based binders and efficient treatment of water used to prepare dialysate.[29]

Other Factors Influencing Bone Abnormalities

Vitamin K deficiency has been postulated to be a reversible cause of fractures in CKD. Vitamin K is required for the carboxylation of bone matrix proteins. Low vitamin K levels can be associated with a history of fractures in patients on hemodialysis.[30]

The role of bone morphogenic protein-7 (BMP-7), a protein expressed by the kidney that induces osteoblast differentiation, has been studied to explain peritrabecular fibrosis seen in osteitis fibrosa. Low BMP-7 levels in CKD may explain the abnormal development of osteoblasts in fibroblast-like cells. Gonzalez et al demonstrated the induction of normal osteoblast development and prevention of fibrosis after administration of exogenous BMP-7 in rats.[31] Other factors that influence bone-mineral metabolism are summarized in Table 1.

Assessment and Monitoring

CKD-MBD begins in early-stage CKD and influences mortality; hence, patients with CKD require monitoring for abnormal mineral homeostasis.[2,29,32] In 2003, K/DOQI formulated guidelines to manage bone-mineral abnormalities in CKD. Later, the focus shifted from managing bone disease to improving survival. In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) foundation coined the term CKD-MBD and formulated guidelines that have superseded K/DOQI guidelines.[32] Despite these advances, high-quality evidence in the field of CKD-MBD is lacking. Therefore, the point needs to be emphasized that the majority of KDIGO

Table 2. Frequency of measurement of serum calcium, phosphorus, and PTH by stage of CKD, per the 2009 KDIGO guidelines[27]

CKD stage	GFR range (mL · min^{-1} · 1.73 m^2)	Measurement of calcium/ phosphorus	Measurement of PTH
III	30–59	Every 6–12 mo	Based on baseline level
IV	15–29	Every 3–6 mo	Every 6–12 mo
V	<15 or dialysis	Every 1–3 mo	Every 3–6 mo

CKD indicates chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

guidelines are based on expert opinion rather than good solid evidence.

Biochemical Abnormalities

KDIGO guidelines recommend monitoring serum calcium, phosphate, and PTH at regular intervals based on CKD stage (Table 2). The K/DOQI guidelines had suggested particular target levels of intact PTH at different stages of CKD; however, these targets were derived based on a second-generation assay that is no longer available. Hence, KDIGO recommends against targets based on absolute PTH levels. Instead, they suggest initiating therapy when PTH is progressively rising and remaining persistently elevated above the upper limit of normal for the assay; this, despite the fact that there is no clear evidence showing an association between elevated PTH and adverse outcomes in predialysis CKD.

In addition, there is little evidence concerning outcomes in patients with predialysis CKD with abnormal calcium levels; however, both hypocalcemia and hypercalcemia are associated with increased mortality in patients on dialysis.[33] KDIGO suggests that serum calcium and phosphate be maintained in the normal range for patients with predialysis CKD stage III to V. The key change in the new guidelines is the recommendation that calcium and phosphate levels be evaluated individually, not based on the old mathematical construct of the calcium-phosphate product (recommended to be maintained at <55 mg^2/dL^2).[30] 25-Hydroxyvitamin D levels also should be measured at least annually. Therapeutic decisions should be based on trends, not on single laboratory values.

Bone Abnormalities

The ability to diagnose the exact type of osteodystrophy without the pathological description enabled by a bone biopsy does not exist. Hence, the gold standard test to determine the type of CKD bone disease is an iliac crest bone biopsy with double tetracycline labeling and histomorphometric analysis. In clinical practice, it is not necessary to perform a bone biopsy in most clinical situations; however it may be warranted in a few scenarios.

Short of a bone biopsy, biochemical tests such as bone-specific alkaline phosphatase or intact PTH can be used to evaluate bone disease because markedly high or low values do predict underlying bone turnover.[32] Imaging tests such as radiographs and BMD calculation are not recommended for the assessment of bone disease in CKD. Even though radiography can reliably detect bone erosion, it has a sensitivity of 60% and a specificity of 75% for the identification of osteitis fibrosa, and thus is an inadequate test.[29] The rationale for not performing BMD assessment routinely in this population is the fact that BMD does not predict fracture risk in patients with CKD as it does in the general population, nor does it predict the type of osteodystrophy.[32] Current data being insufficient, there

is no recommendation for the routine use of markers of bone turnover such as hydroxyproline.[32]

Vascular Calcification

KDIGO guidelines do not recommend routinely screening patients for vascular calcifications; however, if patients are assessed for this, the recommended screening tests are a lateral x-ray of the lumbar spine (for vascular calcifications) and echocardiography (for valvular calcifications). Computed tomography–based tests are needed if quantification of vascular calcifications is required. Patients with CKD with known vascular/valvular calcifications should be considered at highest risk for cardiovascular events.[32]

Treatment of CKD-MBD in Patients with Predialysis CKD

There is a paucity of high-quality evidence evaluating the clinical benefit of various treatments provided to patients with CKD-MBD. The current approach seeks to maintain calcium and phosphate in the normal range for patients with predialysis CKD. The optimal PTH level for such patients is not known; however, patients with levels of intact PTH above the upper limit of normal for the assay should be evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency.[32]

High-Turnover Osteodystrophy

Prevention of a positive phosphate balance is the initial focus of management in high-turnover states. Intervention is required when intact PTH is rising and remaining above the upper limit of normal for the assay or when the phosphate levels are greater than the target range. There is a lack of evidence from randomized trials demonstrating that lowering phosphate level affects clinical outcomes. Given its role in the disease pathogenesis, however, it is considered reasonable to lower phosphate.[32] Lowering phosphate is done initially by dietary restriction of phosphate intake to 800 to 1000 mg/day.[29] Protein sources with the least amount of phosphate, such as meats and eggs, should be prescribed. Calcium, phosphate, and PTH levels should be monitored at regular intervals (Table 2). Calcium and phosphate should be maintained in the normal range. If phosphate levels remain persistently high after 2 to 4 months of dietary restriction, then either calcium-based (when initial serum calcium level is <9.5 mg/dL, or <2.37 mmol/L) or noncalcium-based (when initial serum calcium is >9.5 mg/dL, or >2.37 mmol/L) phosphate binders can be administered.[32] If nutritional vitamin D deficiency exists, as demonstrated by the serum 25-hydroxyvitamin D level of <30 ng/mL, then treatment with ergocalciferol can be added as long as serum calcium does not exceed 10.2 mg/dL (2.54 mmol/L).

If the PTH level remains elevated despite dietary phosphate restriction, phosphate binders, and ergocalciferol therapy after a 6-month period, then an orally active vitamin D analog

or 1,25-dihydroxyvitamin D can be added to the regimen.[32] These should not be given if the serum calcium is >9.5 mg/dL (2.37 mmol/L) or when the serum phosphate levels are elevated. Follow-up is essential to avert hypercalcemia. If the PTH levels remain refractory to the above combination, then a calcimimetic-like cinacalcet may be considered.[32] Close monitoring is required because of the risk of hypocalcemia and hyperphosphatemia; however, because of the paucity of data, cinacalcet is not approved for use in patients with predialysis CKD. Finally, severe hyperparathyroidism that fails to respond to medical therapy may require parathyroidectomy.[32]

Adynamic Bone Disease

No controlled trials have been undertaken on the treatment of adynamic bone disease. Accumulating data suggest that adynamic histology is not benign. Low levels of intact PTH, usually <100 pg/mL (11 pmol/L), may be a surrogate marker for adynamic disease. The adynamic state can be confirmed by bone biopsy, but it is usually treated empirically by letting the PTH levels increase, which allows for an increase in bone turnover. This can be accomplished by either decreasing the dose or eliminating agents that suppress PTH secretion, such as calcium-based phosphate binders or vitamin D. It is interesting that low bone turnover also is seen in the majority of patients with osteoporosis even when they do not have CKD. Recent advances in the treatment of osteoporosis have used PTH administration to stimulate bone formation.[29]

Vascular Calcification

Treatment of vascular calcification involves the management of coexisting biochemical abnormalities. Based on the KDIGO guidelines, this would mean optimal control of the PTH, calcium, phosphate, and vitamin D levels to the normal range, if possible. The role of calcimimetics such as cinacalcet in the prevention and management of vascular calcifications has come under scrutiny. Cinacalcet permits optimum control of calcium, phosphate, and PTH in patients whose disease is not adequately controlled with phosphate binders and vitamin D analogs. The potential of cinacalcet to reduce vascular calcifications and improve all-cause/cardiovascular mortality, hospitalizations, and peripheral vascular disease is being investigated in the EVOLVE (Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events) trial.[34] Other interventions that may lead to a favorable outcome on vascular calcification include statins, bisphosphonates, calcium-channel blockers, and subtotal parathyroidectomy.[35–38]

Conclusions

CKD-MBD is a major cause of mortality and morbidity in patients with CKD.[2,29,32] Management protocols for CKD-MBD derive from weak evidence.[2,3,32] The KDIGO guidelines recommend monitoring calcium, phosphate, and PTH at regular intervals and maintaining levels within the normal range.[32] X-rays of the lumbar spine and echocardiography can screen for vascular calcifications.[29,32]

The prevention of a positive phosphate balance is the mainstay of treatment of high-turnover bone disease. Allowing PTH levels to increase by eliminating agents that suppress PTH is the treatment for adynamic bone disease. The treatment of vascular calcification rests on the optimum control of PTH, calcium, phosphate, and vitamin D levels. The role of cinacalcet in the management of CKD-MBD–related mortality is being studied.[29,32,34]

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