Chronic kidney disease–mineral and bone disorder: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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In 2017, Kidney Disease: Improving Global Outcomes (KDIGO) published a Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). Since then, new lines of evidence have been published related to evaluating disordered mineral metabolism and bone quality and turnover, identifying and inhibiting vascular calcification, targeting vitamin D levels, and regulating parathyroid hormone. For an in-depth consideration of the new insights, in October 2023, KDIGO held a Controversies Conference on CKD-MBD: Progress and Knowledge Gaps Toward Personalizing Care. Participants concluded that the recommendations in the 2017 CKD-MBD guideline remained largely consistent with the available evidence. However, the framework of the 2017 Guideline, with 3 major sections—biochemical abnormalities in mineral metabolism; bone disease; and vascular calcification—may no longer best reflect currently available evidence related to diagnosis and treatment. Instead, future guideline efforts could consider mineral homeostasis and deranged endocrine systems in adults within a context of 2 clinical syndromes: CKD-associated osteoporosis, encompassing increased fracture risk in patients with CKD; and CKD-associated cardiovascular disease, including vascular calcification and structural abnormalities, such as valvular calcification and left ventricular hypertrophy. Participants emphasized that the complexity of bone and cardiovascular manifestations of CKD-MBD necessitates personalized approaches to management.

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Chronic kidney disease–mineral and bone disorder (CKD-MBD) affects the skeletal and cardiovascular systems, occurs across all CKD stages, and results from the individual and combined effects of traditional and CKD-specific risk factors for skeletal and cardiovascular diseases (Figure 1). CKD-specific risk factors encompass those resulting from the interplay of uremic toxins, disturbances in mineral metabolism, and altered activity of immune,

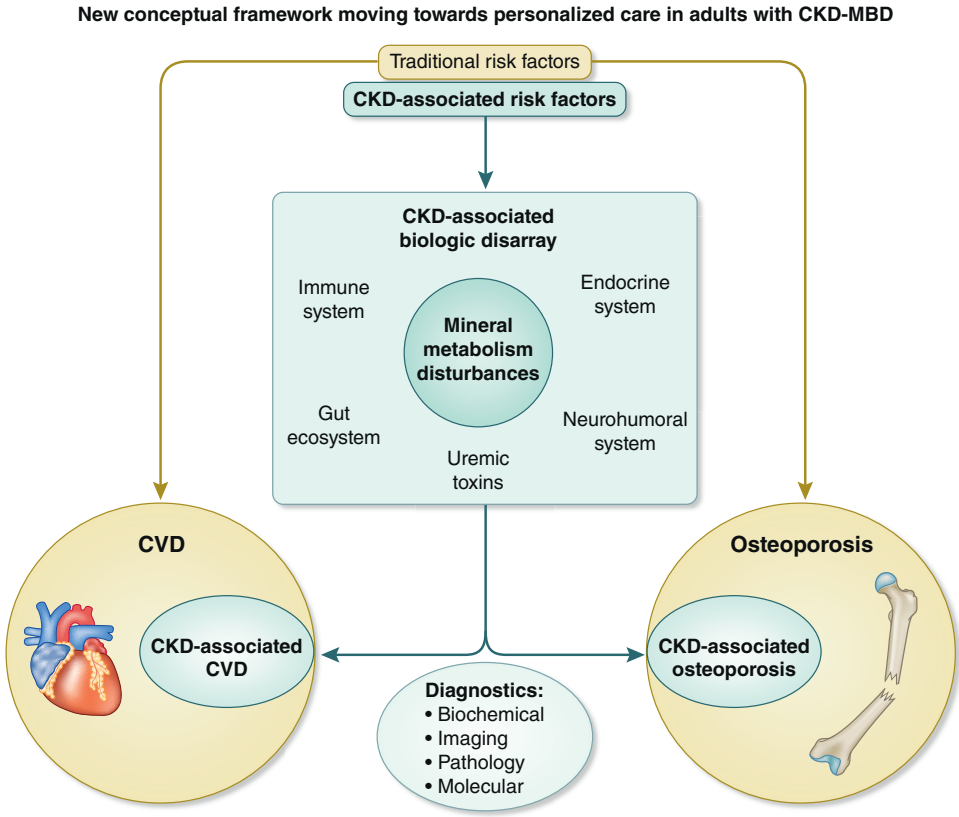

Figure 1 | Conceptual framework moving toward personalized care in adults with chronic kidney disease–mineral and bone disorder (CKD-MBD). CKD-MBD results from the individual and combined effects of traditional and CKD-specific risk factors for skeletal and cardiovascular diseases. CKD-associated risk factors include the interplay of disturbances to mineral metabolism, uremic toxins, and the immune, endocrine, neurohormonal, and gut systems. Although CKD-associated cardiovascular disease (CVD) and osteoporosis exist within the larger context of cardiovascular and skeletal systems, the extent of their overlap is not completely understood. Diagnosis of disorders associated with CKD-MBD can be based on the following: (i) biochemical assessment (calcium, phosphorus, 25-hydroxyvitamin D, parathyroid hormone, fibroblast growth factor-23, and bone formation and resorption markers); (ii) skeletal imaging (thoracic/lumbar spine films and dual-energy X-ray absorptiometry); (iii) histomorphometric assessments (bone biopsy); and/or (iv) cardiovascular imaging (vascular calcification, echocardiogram). Once the clinical manifestations of CKD-MBD have been identified, measures to mitigate disease severity and progression should be initiated to prevent negative clinical outcomes, including bone loss, fractures, major adverse cardiac events, and/or death.

endocrine, neurohormonal, and gut systems. Diagnosis of the disorders associated with CKD-MBD can be based on the following: (i) biochemical assessment (calcium, phosphorus, 25-hydroxyvitamin D [25-(OH)]D), parathyroid hormone [PTH], fibroblast grown factor-23 [FGF23], and bone formation and resorption markers); (ii) skeletal imaging (thoracic/lumbar spine films and dual-energy X-ray absorptiometry); (iii) histomorphometric assessments (by bone biopsy); and/or (iv) cardiovascular imaging (vascular calcification, echocardiogram).

Kidney Disease: Improving Global Outcomes (KDIGO) published its first clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD in 2009.[1] In 2017, a selective update of the guideline was published.[2] Since then, new lines of evidence have emerged within the field of CKD-MBD. To synthesize and evaluate the new insights for their relevance and potential impact on patient care, in October 2023, KDIGO held a Controversies Conference on CKD-MBD: Progress and Knowledge Gaps Toward Personalizing Care. Conference discussions were organized into 4 major groupings: (i) management of secondary hyperparathyroidism; (ii) osteoporosis, bone morphology, and histopathology; (iii) maintenance of phosphate and calcium homeostasis; and (iv) diagnostic tests and interventions for cardiovascular calcifications.

During conference discussions, participants emphasized the complex nature of treating bone fragility and vascular abnormalities in patients with CKD and the necessity of incorporating patient health and preferences into management (Figure 2). There was consensus that the original framework within the 2009 guideline and 2017 update may no longer best reflect currently available evidence related to diagnosis and treatment in clinical practice. A concept was put forth to move to a framework of 2 clinical syndromes in adults: CKD-associated osteoporosis and CKD-associated cardiovascular disease. Both would be included within the more general disorders of the cardiovascular and skeletal systems. This report summarizes the major themes resulting from conference discussions, identification of key research needs, and areas of important consideration in future guideline

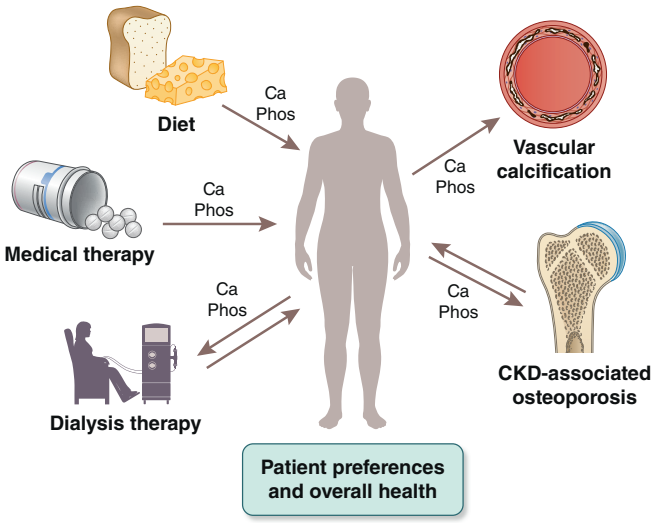

Figure 2 | Holistic approach to skeletal and vascular complications of chronic kidney disease (CKD). A personalized strategy for optimal management of calcium (Ca) and phosphate (Phos) levels in patients with CKD should consider the complete chronic kidney disease–mineral and bone disorder phenotype and overall health, priorities, and preferences of the individual patient. Sources of calcium and phosphate include diet, medications, and bone when high bone turnover is present. Phosphate is removed from circulation during dialysis, whereas calcium fluxes can be bidirectional. Both calcium and phosphate can be taken up by bone during bone remineralization (hungry bone syndrome).

development (Table 1). Conference plenary slide presentations are available on the KDIGO website: https://kdigo.org/conferences/controversies-conference-on-personalizing-ckd-mbd-care/.

CKD-ASSOCIATED OSTEOPOROSIS

Terminology

A key issue at the Controversies Conference was the concept of bone fragility and osteoporosis versus renal osteodystrophy (ROD) in patients with CKD. A main concern was that the term ROD represents a roadblock to managing fracture risk and fosters an overly PTH- and calcium-phosphate–centric approach to bone disease management, focusing solely on bone turnover while ignoring other critical abnormalities in bone tissue properties that also drive fracture risk and are not corrected by PTH- and calcium-phosphate–centered strategies. Conference participants robustly debated whether a change in terminology could recenter treatment of bone disease to the skeleton itself, meaning correcting bone quality defects that are responsible for decreased bone strength in patients with CKD.

Osteoporosis is a disorder of bone that decreases bone strength and increases risks of fracture. Bone strength is defined by both the amount and quality of bone. Bone quantity (i.e., volume) can be evaluated by imaging with either 2-dimensional dual-energy X-ray absorptiometry (DXA) or 3-dimensional computed tomography (CT). Bone quality is defined by bone properties, including bone geometry (size, shape), microarchitecture (trabecular and cortical), and tissue properties (turnover, mineralization, collagen content, and microcracks). Abnormality in any of these features of bone strength increases the risk of fractures. Clinically, osteoporosis is defined as a T-score $\leq$–2.5 measured by DXA and/or having a fragility fracture at any level of bone mineral density (BMD).

ROD is a bone disorder that is associated with global defects in bone quality and strength, increasing risk of fracture independent of BMD. Therefore, conference participants regarded ROD as part of the osteoporosis spectrum (Figure 3). Furthermore, conference participants recognized that bone disease in patients with CKD is complex and multifaceted, with overlapping features of ROD and other forms of osteoporosis (e.g., age or immobility related, postmenopausal, hypogonadal, glucocorticoid induced, or nutritional, etc.).

The term CKD-associated osteoporosis was developed to acknowledge and emphasize that ROD is a disorder of bone strength that increases fracture risk. Because CKD-associated osteoporosis is a distinct form of osteoporosis with overlapping metabolic bone diseases, management strategies must be tailored to the distinct features of bone quality that are impaired in an individual rather than algorithmized, as for postmenopausal osteoporosis. Below we describe approaches that were discussed regarding diagnosis and management.

Pathogenesis

A key issue at the Controversies Conference was the recognition that management of CKD-MBD biochemical abnormalities cannot be dissociated from the relevant clinical outcomes of bone loss and fractures.[3] Conference attendees recognized the need to better understand mechanisms by which uremia, altered gut and immune systems, inflammation, and medications affect the CKD-associated osteoporosis phenotype.

Disturbed mineral metabolism is an important driver of CKD-associated osteoporosis, with hyperparathyroidism and vitamin D deficiency playing central roles. Parameters of mineral metabolism (calcium, phosphate, 25-[OH]D, PTH, and FGF23) associate with bone disease and fracture risk, but their individual contributions are complex. For example, in CKD, there is variability in skeletal responsiveness to PTH. Skeletal PTH responsiveness has multifactorial determinants, such as hyperphosphatemia, uremic toxins, gut ecosystem disturbances, and inflammation, and the interactions of these are poorly understood. High PTH may increase bone formation and resorption, resulting in a cascade of impairments to bone quality, including cortical microarchitectural deterioration, abnormal bone mineralization, and altered crystal structure. In contrast, oversupplementation with active vitamin D derivatives may suppress PTH, resulting in adynamic or low-turnover bone, possibly propagating and worsening microcracks. In addition, older patients and those on glucocorticoids may have impaired trabecular microstructure. Patients with vitamin D deficiency may have impaired bone mineralization. The attendees also recognized

Table 1 | Consensus points, clinical guideline–related commentary, key knowledge gaps, and research priorities in CKD-MBD

Type of statement	CKD-associated osteoporosis	CKD-associated cardiovascular disease
Important clinical concepts	• In most cases, bone formation and resorption markers are sufficient to assess bone turnover. In some cases, bone biopsy may be needed to elucidate complex bone disease. • The concept of a "pleiotropic" effect for both nutritional and active vitamin D should be abandoned. However, for controlling PTH, low-dose active vitamin D could be a helpful supplement to nutritional vitamin D and dietary phosphate restriction. • PTH is not a bone turnover marker, and PTH values must be assessed in relation to values of calcium, phosphate, and 25(OH)-vitamin D.	• Recommendations for calcium intake should be personalized, considering the state of mineral metabolism, overall calcium balance, current medical therapy, and bone and vascular health. • Risks of hypocalcemia should not be ignored. It is reasonable to consider the cause of, and correct, hypocalcemia.
Commentary related to guideline recommendations	• Although the 2009 Guideline used the term "target" for PTH levels 2–9 times the ULN in CKD G5D,[1] there is uncertainty as to whether this is in fact the optimal range. • Future guidelines should distinguish between persistent and secondary hyperparathyroidism after kidney transplantation, as these differ both in biochemical presentation and in pathophysiology.	• Guidance is needed on sufficient calcium intake in patients with CKD, including the safe upper limit to avoid the risk of vascular calcification progression. • Future Work Group could consider whether to recommend measuring ionized calcium in blood. • There is a need for guidance on holistic management of calciphylaxis.
Knowledge gaps and key questions	• Whether vitamin D supplementation has any effect on important skeletal outcomes in CKD • The upper 25-(OH)D safety limit and whether vitamin D >75 nmol/l [30 ng/ml] should be aimed for in patients with CKD • Whether people with CKD not on dialysis should have a different lower limit for 25-(OH)D from the general population • Whether people with CKD not on dialysis benefit from any target PTH level • How to manage secondary hyperparathyroidism in CKD not on dialysis to improve clinically relevant outcomes, including patient-reported outcomes • How to define optimal PTH and phosphate levels in CKD-G5D (on an individual basis) • Optimal PTH targets in early and late post-transplantation periods • Long-term data on bone health and mineral metabolism beyond 12 mo post-transplant • How to appropriately manage mineral metabolism disturbances after kidney transplantation • The long-term effect on serum phosphate with measures targeting bone resorption • Optimal targets of serum calcium in all patients with CKD • Optimal protocols for bone-targeting therapy ○ Timing, choice of agents, outcome evaluation	• Methods to assess calcium balance, internal fluxes, and deposition in tissues • How to accurately measure calcium mass transfer during dialysis on an individual level • Whether there is a benefit of optimizing calcium intake in CKD • How to identify persons likely to benefit from modulation of serum magnesium • Whether modulating serum magnesium delays or prevents vascular calcification or other adverse clinical outcomes in kidney failure, or whether it affects bone turnover • In patients on hemodialysis, what do CPP levels indicate and whether changes translate to improved clinical outcomes • Validated histologic criteria for diagnosing calciphylaxis • The clinical relevance and applicability of measuring FGF23 • The clinical relevance and applicability of measuring klotho
Research and translation priorities	• Standardize the PTH assays. • Incorporate patient-centered outcomes in future CKD-MBD trials and clinical practice. • Evaluate long-term effects on phosphate within studies of bone-targeting agents. • Determine the dose–response for supplementation with different doses/formulations of vitamin D2/D3 and their influence on PTH, calcium, and phosphorous in CKD. • Determine optimal management of secondary hyperparathyroidism in CKD not on dialysis. • Compare 2 different PTH targets in CKD not on dialysis. • Conduct observational studies to determine the association between persistent hyperparathyroidism post-transplant and bone and vascular outcomes. • Determine the effects of different protocols measuring MBD profile on patient-centered outcomes, including after parathyroidectomy. • Increase participation in clinical trials of bone-targeting agents and registries for all patients with CKD-associated osteoporosis.	• Trials of treatment strategies with primary vascular endpoints should also include relevant bone endpoints and vice versa. • Solicit patient preferences on treatment of calcium and phosphate across the spectrum of CKD • Access target effect of novel therapies to lower FGF23 in CKD G3–G4 and blocking of FGF23 in CKD G5D on cardiovascular outcomes • Use novel techniques (calcium isotopes, ^{18}F-sodium fluoride positron emission tomography, and high-resolution peripheral quantitative computed tomography) to explore tissue calcium balance at different stages of CKD • Adequately powered RCTs using robust endpoints for vascular calcification should also include endpoints relating to histology, biomarkers of bone turnover, or bone fractures. • Long-term and large RCTs (e.g., SNF472, magnesium, and vitamin K) with clinically relevant endpoints (e.g.,

Table 1 | (Continued)

Type of statement	CKD-associated osteoporosis	CKD-associated cardiovascular disease
	• Harmonize bone turnover marker assays ○ Evaluate associations and dynamics with clinical outcomes (mortality, cardiovascular risk, and fractures) as well as treatment thresholds within CKD • Conduct trials on vitamin D/calcium effects on skeletal biology and outcomes to determine their optimal targets in CKD • Conduct RCTs or pragmatic trials on skeletal outcomes of antiresorptive and anabolic agents in CKD • Aid efforts to establish bone mineral density by DXA as a surrogate outcome for fracture in CKD • Explore the role of artificial intelligence in diagnosing, monitoring, and predicting skeletal outcomes • Consider how CKD-specific fracture liaison services might be introduced to improve fracture management and mitigate future risk	death or major adverse cardiovascular events) are required. • Adequate consideration of sex and gender differences in phosphate homeostasis, bone disease, and vascular calcification is required. • Unify terminology related to CPP assays. • Studies on the biological and molecular function of CPP and the impact of source of phosphate (diet vs. bone) and inflammation on phosphate buffering • Randomized clinical trials for the management of calciphylaxis

25-(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; CPP, calciprotein particle; DXA, dual-energy X-ray absorptiometry; FGF23, fibroblast growth factor 23; MBD, mineral and bone disorder; PTH, parathyroid hormone; RCT, randomized controlled trial; ULN, upper limit of normal.

that CKD-associated osteoporosis is an important clinical phenotype after kidney transplantation. While the pathogenesis of skeletal abnormalities may differ from prekidney to postkidney transplantation, abnormalities in biochemical markers of CKD-MBD are involved. For example, persistent hyperparathyroidism after kidney transplantation is an independent risk factor for fractures.[4] Glucocorticoid exposure is a major determinant of bone loss[5–7] and fractures after kidney transplantation.[3] While minimizing glucocorticoid use has been shown to protect the skeleton, each patient's individual immunologic risk must be considered to protect against transplant rejection.

Diagnostics

Laboratory assessments. The CKD-associated osteoporosis phenotype can be assessed by measuring circulating protein products of osteoblast and osteoclast cell function (Table 2).[8–14] Evaluating multiple biochemical measures (e.g., bone turnover markers + PTH + 25-[OH] vitamin D levels) may help in diagnosing and defining the severity of the clinical phenotype and provide surrogate outcome measures to both inform and monitor integrative and personalized treatment approaches.

Turnover can also be evaluated by measuring bone formation or resorption markers, or a combination thereof. Non–kidney-cleared markers of bone formation (bone-specific alkaline phosphatase, intact procollagen type I N-propeptide) and resorption (tartrate-resistant acid phosphatase isoform 5b) are recommended. Total alkaline phosphatase can be a proxy for bone-specific alkaline phosphatase, especially in a setting with normal levels of gamma-glutamyltransferase. Kidney-cleared biomarkers must be interpreted with caution, taking into account knowledge of kidney function, with trends more informative than single time point measurements. Bone turnover markers may prove useful for both guiding therapy choices and monitoring therapy response, either as stand-alone or adjunct to PTH (Supplementary Table S1).

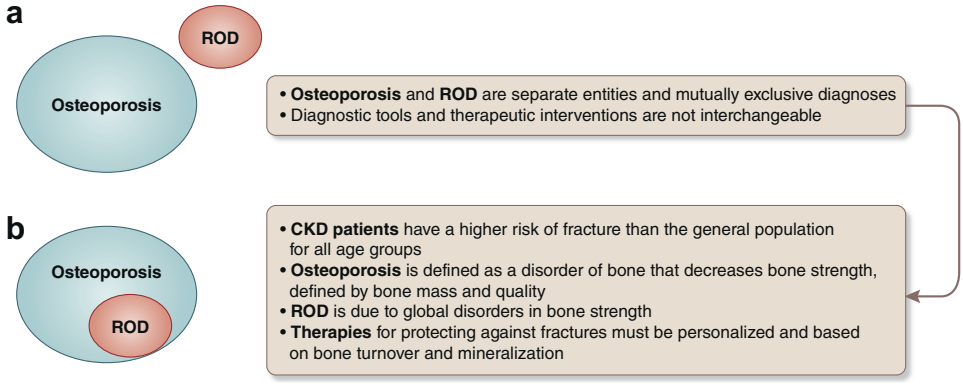

Figure 3 | Evolution of terminology for renal osteodystrophy (ROD). The approach to ROD has been evolving as we appreciate that ROD is a bone disorder that impairs bone quality and increases bone fragility. Osteoporosis is defined as a bone disorder that decreases bone strength and increases risk of fracture. Bone strength is defined by both the quantity and quality of bone. ROD is due to global disorders of bone strength that increase risk of fracture. (**a**) A mutually exclusive definition of ROD and osteoporosis may no longer be operational in the clinic and for research purposes. (**b**) Chronic kidney disease (CKD)–associated osteoporosis is an inclusive definition of ROD and osteoporosis that appreciates the global impact of kidney disease on bone strength. This definition may better serve clinical efforts to treat bone disorders associated with CKD and inform and impact research into the underlying pathogenesis of fracture risk in patients with CKD.

Table 2 | Bone turnover markers and fracture prediction in CKD

Study reference	Target group	Patients	Fracture incidence	Marker	HR or OR (95% CI)	AUC
Barrera-Baena *et al.*,[8] 2023, COSMOS study	CKD G5D, prevalent HD	6274	28.5/1000 pat. yr	PTH	HR 1.04 (1.01–1.08)	
Kashgary *et al.*,[9] 2023	CKD G5D, prevalent HD	328	20/1000 pat. yr	BALP	OR 1.004 (1.001–1.007)	0.665
				Osteoporosis	OR 1.003 (0.998–1.007)	NA
Matias *et al.*,[10] 2020	CKD G5D, prevalent HD	341	31/1000 pat. yr	Mean BALP	HR 1.21 (1.16–1.33)	
				Mean PTH <300/ >800 ng/l [>32 nmol/l/<85 nmol/l]	HR 1.24 (1.18–1.29)	
Iimori *et al.*,[11] 2012	CKD G5D, prevalent HD	485	19/1000 pat. yr	BALP	HR 1.04 (1.03–1.04)	0.766
				PTH	HR 1.00 (1.00–1.00)	NA
				DXA femoral neck	HR 0.96 (0.94–0.99)	0.610
				DXA total hip	HR 0.97 (0.94–0.99)	0.659
Chen *et al.*,[12] 2016	CKD G5D, prevalent dialysis	685 (629 HD, 56 PD)	33/1000 pat. yr	Fetuin A high vs. low	HR 0.34 (0.20–0.57)	
				PTH	HR 1.04 (1.008–1.12)	
Geng *et al.*, 2019[13]	CKD G3–G4	5108	Incidence 18%	PTH >101 ng/l [11 nmol/l] as continuous variable	HR 1.16 (0.93–1.45)	
Maruyama *et al.*,[14] 2014	CKD G5D, prevalent HD	185,277	16/1000 pat. yr	ALP	HR 1.011 (1.006–1.014)	

ALP, alkaline phosphatase; AUC, area under the curve; BALP, bone-specific alkaline phosphatase; CI, confidence interval; CKD, chronic kidney disease; COSMOS, Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study; DXA, dual-energy X-ray absorptiometry; HD, hemodialysis; HR, hazard ratio; NA, not available; pat. yr, patient year; OR, odds ratio; PD, peritoneal dialysis; PTH, parathyroid hormone.

A bone-regulating hormone, PTH is a driver of bone turnover, although if PTH levels become dissociated from turnover (e.g., after treatment with an anti-resorptive agent), it is unreliable as a marker. Furthermore, in patients with CKD G5D, there is a significant "gray zone" range in which stand-alone PTH serum levels are also unreliable (approximately between 2–9 times the upper limit of normal). Nonetheless, monitoring PTH levels and treating hyperparathyroidism is critical to overall skeletal and vascular health and is part of an integrative treatment strategy for CKD-associated osteoporosis. Other critical components of the integrative strategy include monitoring and management of serum levels of 25-(OH) vitamin D, calcium, and phosphorus.

For bone mineralization, high levels of bone-specific alkaline phosphatase can help diagnose osteomalacia in the setting of vitamin D deficiency, hypocalcemia, or hypophosphatemia,[15] although bone biopsy findings from large patient cohorts suggest that osteomalacia is rare with current CKD-MBD management practices.[16]

Imaging. Bone quantity can be assessed by areal BMD from DXA, which predicts fractures in patients with CKD with comparable accuracy as in the general population.[11,17,18] Areal BMD can also be used to monitor response to bone-targeting therapy. World Health Organization T-scores predict fracture risk similarly in patients with and without CKD, including in kidney transplant recipients.[19–21] If DXA is not available, the fracture risk assessment tool predicts fractures in patients with CKD aged ≥40 years and can be used instead, although risk may be underestimated. Furthermore, the fracture risk assessment tool has not been validated in kidney transplant recipients, and the fracture risk assessment tool cannot be used to monitor risk after bone-targeted treatment has been initiated. Patients with CKD at high risk for fracture and who thus should be targeted for fracture risk screening include postmenopausal and amenorrheic females, males aged ≥50 years, patients on prednisone equivalents ≥5 mg daily for ≥3 months, and kidney transplant recipients.[22,23]

In patients with CKD and hyperparathyroidism, cortical bone is the more affected bone compartment. The total hip is a mixture of cortical and trabecular bone and is the preferred site to measure BMD. The one-third radius site is >80% cortical bone and can also be used to assess the effects of hyperparathyroidism on the skeleton. The lumbar spine is >90% trabecular bone in intact vertebrae, and the anterior-posterior image acquisition by DXA also includes (potentially calcified) aorta in the field of interest.

Vertebral fractures are usually asymptomatic. However, they are an important risk factor for future fractures and are associated with increased mortality. Vertebral fracture assessment should be performed as part of the baseline bone fragility screening process by thoracic/lumbar spine films or lateral DXA for vertebral fracture assessment.[24] The presence of vertebral fractures is an indication to start bone-targeted treatment.

Bone histomorphometry. Bone biopsy is the gold standard method to assess the skeletal effects of metabolic bone diseases. It is primarily used in research to assess tissue- and cell-level mechanisms of bone disease and drug effects. In clinical practice, bone biopsy may detect defects in bone turnover and mineralization and effects of complex bone diseases that cannot be determined noninvasively. However, in most patients with CKD, treatment decisions are made in the absence of a bone biopsy.

Although there are clinical concerns about the adverse effects of low-turnover bone disease, there are no prospective clinical outcome data suggesting that low-turnover bone *per se* has different clinical outcomes to non–low-turnover bone.[25,26] Nonetheless, knowledge of bone turnover, determined by either bone turnover markers or bone biopsy, might influence the choice of bone-targeted therapies.

Emerging diagnostics. During recent years, additional methods to assess bone quality have emerged. These range from adapting DXA software to provide the vertebral trabecular bone score and hip structural analysis, to more sophisticated methods allowing separate analysis of cortical and trabecular compartments using high-resolution peripheral quantitative CT. Transcriptomic analyses of bone samples from biopsy have the potential for generating new insights related to pathophysiology or choice of therapy. More research is needed to confirm if any of these methods is useful for diagnosis, management, and fracture prevention in CKD-associated osteoporosis.

Treatments

CKD-associated osteoporosis should be managed with bone-targeted strategies that are tailored to the patient's fracture risk profile and ROD turnover type. While PTH derangements probably account for the major impact of CKD on bone turnover, classic PTH-lowering therapies may not suffice in preventing fractures or other negative clinical outcomes, including bone loss, major adverse cardiovascular events, and/or death. The complex nature of treating CKD-associated osteoporosis requires personalized approaches to management, based on severity of abnormalities in areal BMD, underlying bone turnover, disordered mineral metabolism, cardiovascular risk profiles, and estimated duration of treatment. Comanagement between health care providers with kidney and bone expertise is indicated.

Targeting calcium and phosphate. Data from experimental studies show that hyperphosphatemia increases bone resistance to PTH, correlates with increased PTH, and decreases osteocyte viability, which all affect bone quality. Conversely, hypophosphatemia is associated with impaired mineralization. The same rationale could be used for calcium: hypocalcemia stimulates PTH and favors mineralization deficits, whereas hypercalcemia suppresses PTH and decreases osteocyte viability. Therefore, maintaining calcium and phosphate at adequate levels is also important for bone health. However, studies focusing on the skeletal effects of different levels of calcium or phosphate are lacking, except for one study in which hypophosphatemia was identified as a risk factor for mineralization defects in the post-transplant setting.[27]

Targeting 25-(OH)D. Given the current body of evidence, it remains unclear if vitamin D supplementation has any effect on important clinical outcomes in CKD. Recent large-scale studies that included CKD subgroup analyses have been negative for any benefits of vitamin D supplementation beyond biochemical ones.[28] However, these studies were not designed with specific inclusion for vitamin D–deficient individuals, and therefore the results should not be interpreted as justification for leaving patients with low levels of vitamin D unsupplemented.[29] In the kidney transplant population, data from randomized controlled trials suggest 25-(OH)D levels ≥30 ng/ml may optimize bone health as determined by BMD and fracture events.[30,31]

Targeting PTH. The optimal PTH level in patients with CKD not on dialysis remains undefined. Although there is no evidence for a specific PTH target in such patients, observational data suggest that high and progressively increasing PTH levels warrant investigation. Increased PTH and incident secondary hyperparathyroidism are independently associated with CKD progression and cardiovascular events, mortality, and fractures.[32,33] For patients with kidney failure, increased PTH prior to initiation of dialysis predicts high PTH and the need for PTH-lowering medications during diaysis.[34]

Although the 2009 Guideline used the term "target" for PTH levels 2–9 times the upper limit of normal in CKD G5D,[1] there is uncertainty as to whether this is in fact the optimal range. Epidemiologic studies have demonstrated U- or J-shaped curves between PTH and all-cause mortality,[35–39] and a more linear relationship has been found in Japan.[39] The uncertainty regarding target PTH levels is compounded by the observed variability in skeletal and kidney responses to PTH. In some patients, bone biopsy may demonstrate low bone turnover when PTH is within normal range.[40] In addition, high bone turnover can occur with only moderately elevated PTH levels.[41] Future use of bone biomarkers may aid in accurately discriminating low versus high bone turnover.

The 2017 Guideline update made a statement against routine use of activated vitamin D in patients with CKD not on dialysis. Indeed, results from the PRIMO (Paricalcitol Capsules Benefits in Renal Failure Induced Cardiac Morbidity in Subjects With Chronic Kidney Disease Stage 3/4) and OPERA (Oral Paricalcitol in Stage 3–5 Chronic Kidney Disease) studies showed activated vitamin D was associated with an increased risk of hypercalcemia without benefit on cardiac structures. However, for controlling PTH, low-dose active vitamin D could be a helpful supplement to nutritional vitamin D and dietary phosphate restriction.

In individuals with CKD not undergoing dialysis, using extended-release calcifediol to increase 25-(OH)D to unusually high levels (>125 nmol/l) can further suppress PTH.[42–45] Clinically relevant outcome data are needed before considering availability and costs of extended-release calcifediol and to appropriately define treatment goals.

In CKD G5D, novel calcimimetics (etelcalcetide, evocalcet,[46] and upacicalcet[47]) have a similar or superior efficacy to cinacalcet for PTH reduction, although there are no data to support survival benefits with this class of agents.[48] Intravenous formulations can reduce the general pill burden and increase compliance but can have shorter half-lives.

Based on data from the PROCEED trial (Parathyroidectomy versus oral cinacalcet on cardiovascular parameters in peritoneal dialysis patients with advanced secondary hyperparathyroidism) of patients undergoing

peritoneal dialysis (PD), both medical and surgical treatments are options for secondary hyperparathyroidism.[49] Parathyroidectomy obviated titration of multiple drugs and showed a more substantial increase in BMD.[50] Observational data from the Japanese Society for Dialysis Therapy Renal Data Registry have indicated parathyroidectomy is associated with lower mortality than the use of calcimimetics.[51]

In adults with persistent hyperparathyroidism after kidney transplantation, results from a randomized, placebo-controlled trial indicated cinacalcet effectively corrects both hypercalcemia and hypophosphatemia.[52] In that study, cinacalcet showed no effect on BMD change. A small, 12-month, open-label, randomized study evaluated whether subtotal parathyroidectomy is more effective than cinacalcet for controlling hypercalcemia caused by persistent hyperparathyroidism after kidney transplant.[53] Subtotal parathyroidectomy induced greater reductions of PTH and calcium and was associated with a significant increase in femoral neck BMD. Although older studies had raised concerns about a negative impact of parathyroidectomy on allograft function, a recent meta-analysis showed no long-term differences.[54] Given that reversibility of secondary hyperparathyroidism occurs in a substantial proportion of patients in the first year after kidney transplantation, there is rationale for using calcimimetics in this period. Beyond 1 year, the optimal therapeutic approach (calcimimetics vs. parathyroidectomy) remains to be defined. Calcimimetics are off label in this indication.[53]

Targeting bone. There are no primary randomized controlled trial data on fracture prevention efficacy and safety profiles of bone-targeting agents dedicated to patients with CKD G3b–G5D. Studies of bone-targeting agents in CKD include secondary analyses of the US Food and Drug Administration fracture registration trials for novel agents and primary clinical trial data for areal BMD.

Based on secondary analyses of US Food and Drug Administration trials, anti-resorptive and anabolic agents increase BMD and lower fracture risk in patients with mild to moderate CKD.[55–57] A clinical trial of denosumab and oral alendronate in patients receiving dialysis demonstrated increased BMD at the spine in both groups.[58] A clinical trial of romosozumab in patients receiving dialysis demonstrated increased BMD at the spine and hip.[59] Romosozumab, followed by denosumab, in patients with kidney failure resulted in increased BMD at the total hip and femoral neck.[60] A clinical trial of therapy with teriparatide based on bone turnover markers reported improved BMD in patients with low bone turnover.[61]

All bone-targeting agents have possible safety concerns for patients with CKD, although in many cases the concerns are similar when these drugs are used in the general population. For many (bisphosphonates, teriparatide, and romosozumab for males), their use in patients with CKD G4–G5D is off label. Concerns for adverse effects include the following: (i) for bisphosphonates: nephrotoxicity, and as in the general population, osteonecrosis of the jaw, and atypical femoral fractures; (ii) for denosumab[62,63]: osteonecrosis of the jaw, atypical femoral fractures, hypocalcemia (as in the general population),[63,64] and rebound bone resorption[65]; (iii) for teriparatide and abaloparatide: hypercalcemia and hyperuricemia; and (iv) for romosozumab: hypocalcemia, and, as in the general population, cardiovascular risk.

In the kidney transplant population, areal BMD and changes in bone turnover markers may help to identify patients at high risk for bone loss and fractures.[21] Bisphosphonate therapy may reduce fracture risk and bone pain after kidney transplantation[66] and can be considered in high-risk patients based on areal BMD and clinical risk factors.

Nonpharmacologic interventions

Nonpharmacologic interventions to lower fracture risk have benefits in all patients with osteoporosis. In the general population, between 38%−54% of the variance in areal BMD may be explained by environmental factors.[67] Nonpharmacologic approaches include exercise, avoidance of malnutrition and vitamin D deficiency, adequate dietary calcium intake,[68] smoking cessation, limiting alcohol intake, and fall-prevention strategies. Nonpharmacologic approaches can be implemented as first-step measures and should be considered in all patients with (and without) CKD-associated osteoporosis.

CKD-ASSOCIATED CARDIOVASCULAR DISEASE

Terminology

Vascular calcification, usually referring to arterial calcification, is a complex process with numerous etiological factors, including age, diabetes, inflammation, atherosclerosis, and deficiency of protective agents. Disturbed mineral metabolism is an important driver of CKD-associated cardiovascular disease, especially vascular calcification, with hyperphosphatemia playing a central role. Significant progress has been made in understanding the pathophysiology of vascular calcification in different vascular beds; however, vascular bed pathology is not directly correlated with serum levels of calcium and phosphate, and effective therapeutic interventions have been elusive. Besides vascular calcification, left ventricular hypertrophy is another prominent feature of severe CKD. Arterial calcification and elevated FGF23 levels may be significantly involved in the development of left ventricular hypertrophy and consequent congestive heart failure in CKD. To some extent, the same pathophysiology that drives vascular calcification may contribute to valvular calcification, which, in turn, can contribute to left ventricular hypertrophy and heart failure and is associated with sudden death in CKD.

Diagnostics

Although baseline and progression of coronary artery calcium score and aortic calcification scores predict all-cause mortality,[69,70] it is not known whether slowing the progression of vascular calcification leads to improved prognosis or reduced mortality. Moreover, current clinical imaging techniques do not differentiate between calcified atherosclerotic plaques and medial calcification, a difference that may be clinically

relevant. In children, data on vascular calcification progression and potential risks are few and insufficient for understanding their implications.

Imaging. Calcification, as detected by electron-beam or multidetector CT,[71,72] echocardiogram,[73–75] and X-ray scoring systems,[76,77] is associated with adverse outcomes in CKD. There are few CKD-related data using standard chest CT or mammography. Radiology international guidelines now recommend all chest CTs be read with a coronary artery calcium score. All modalities have limitations, such as inter-operator variability, incomplete sensitivity, lack of electrocardiographic gating, or measurement variation. For clinical trial purposes, only CT scans are sensitive enough to detect changes in calcification.

Although CT scans are useful for research purposes, their value in guiding treatment decisions related to the use or type of phosphate binders or calcium exposure is not clear. The role of discriminating intimal versus medial calcification in imaging is also not clear, nor is whether progression of vascular calcification is a meaningful endpoint.

Biomarkers. In the future, together with imaging techniques, biomarkers may define risks and aid personalized decisions on therapeutic approaches. At the forefront are parameters of calciprotein metabolism, including quantity of serum calciprotein monomers and calciprotein particles (CPPs) and the calcification propensity score test. Thus far, these have been evaluated separately using different assays or technical platforms, making it difficult to compare their relative performance. Associations of shortened calcification propensity score or increased CPPs with vascular calcification progression or mortality have been noted in several studies, but this association has not been universally consistent.[78–83] It is not clear if parameters of calciprotein metabolism are markers of vascular calcification or whether changes in them impact clinical outcomes.

Treatment targets

Phosphate. Since 2017, no data have emerged that would prompt reevaluation of phosphate targets across the spectrum of CKD. Results of ongoing pragmatic trials are not expected until 2026 at the earliest. In CKD G3–G4, there are no trials demonstrating that phosphate-lowering treatments in a setting of normophosphatemia or lowering FGF23 improves meaningful clinical outcomes; results from 2 studies are anticipated (Ferric Citrate and Chronic Kidney Disease in Children [FIT4KiD] trial,[84] FRONTIER [Ferric Citrate for the Prevention of Renal Failure in Adults With Advanced Chronic Kidney Disease, ClinicalTrials.gov NCT05085275]). In patients with CKD G3b–G4 without overt hyperphosphatemia, 2 studies found no benefit of phosphate binders on serum FGF23 levels or carotid-femoral pulse wave velocity.[85,86]

In CKD G5D, the benefits of strict phosphate control are being evaluated. Pilot studies have shown feasibility of having separate phosphate-level targets in a trial setting and have also indicated decreased risk of coronary artery calcification progression in patients with lower phosphate levels.[87] PHOSPHATE, a large trial including patients undergoing either hemodialysis or PD (ClinicalTrials.gov NCT03573089) is underway, and its results could impact clinical recommendations, regardless of outcome.

Calcium. There are no trial data informing the optimal targets of serum calcium. With regard to oral calcium load for the adult general population, a calcium intake of 800−1000 mg/d is recommended for optimal skeletal health (European Food Safety Authority,[88] US Institute of Medicine guidelines[89]). In CKD, 2 formal calcium balance studies have indicated that calcium balance is neutral to negative at 800–1000 mg calcium/day, but positive at 1500−2000 mg calcium/day.[90,91] A recent European calcium consensus article expressed concern for skeletal harm with too little calcium intake and recommended a total calcium intake of at least 800−1000 mg/d in patients with CKD.[68] Observational data indicate that 40%−60% of patients with CKD G5D have a calcium intake of <800 mg/d, but intake can increase dramatically with use of calcium-containing phosphate binders. In CKD G5D, overall calcium balance also depends on dialysate calcium concentrations.[92,93]

Measurement of ionized calcium in the blood can be logistically challenging, but albumin-adjusted calcium equations do not accurately estimate ionized calcium; therefore, abnormalities in ionized calcium levels can escape detection.[94–97] Hypercalcemia consistently associates with increased all-cause mortality in most observational studies, with a J- or U-shaped relationship between serum calcium and mortality.[98–100] Hypocalcemia detected by ionized calcium determination has also been associated with increased all-cause mortality,[96] and a recent large, observational study found increased risk of cardiovascular mortality with hypocalcemic episodes, regardless of cause.[101]

During treatment with calcimimetics, severe and symptomatic hypocalcemia is not uncommon and likely underreported. Severe hypocalcemia (defined as total or albumin-corrected calcium <7.5 mg/dl or <1.87 mmol/l) is reported in 7%−9% of patients in trials and observational data sets.[102–106] In trials, the risk of hypocalcemia-related symptoms is higher with intervention versus placebo, and these include muscle spasms (11.5% vs. 6.6%), myalgia (1.6% vs. 0.2%), paresthesia (4.8% vs. 0.6%), and hypoesthesia (1.8% vs. 0.8%).[102] Previous guideline recommendations argued for permissible hypocalcemia with calcimimetic use.[2] However, given that the risks of severe hypocalcemia are well understood, most would find it reasonable to consider the cause of, and correct, hypocalcemia.

There are no new high-quality data to inform the optimal ionized calcium concentration in the dialysate. Observational studies support the current recommendation of a dialysate calcium concentration of 1.25–1.50 mmol/l. Calcium mass transfer during dialysis is not easily predictable, but the ionized calcium dialysate-plasma gradient is a major determinant.[107] Calcium mass transfer may be influenced by different dialysis techniques (standard acetate or bicarbonate, predilution or postdilution hemodiafiltration, daily or

nocturnal, continuous ambulatory PD or automated PD with/without icodextrin).[108] Currently, the calcium mass transfer is not directly measured for each patient but is estimated on the basis of study data. In general, calcium mass transfer is positive with a dialysis calcium concentration of 1.75 mmol/l, neutral with 1.25−1.50 mmol/l, and negative with 1.00 mmol/l.[109–112] A dialysate calcium concentration of 1.75 mmol/l is associated with vascular calcification and increased mortality risk,[113,114] and a dialysate calcium concentration of <1.25 mmol/l is associated with intradialytic cardiovascular instability and risk of hospitalization.[115,116]

We do not, at present, have any means of directly assessing calcium balance or internal calcium fluxes, particularly calcium deposition in tissues. A future Work Group could consider guidance for a sufficient calcium intake in patients with CKD, including the safe upper limit to avoid the risk of vascular calcification progression.

Treatments

Vascular calcification in CKD is a complex and multisystem disease for which modification of multiple parameters is often needed,[117] requiring a personalized approach.

Phosphate lowering. Early evidence indicated calcium-containing phosphate binders increase the risk of vascular calcification progression.[118,119] A subsequent trial found no excess risk of all-cause or cardiovascular mortality with calcium- versus non–calcium-containing phosphate binders, but there was a signal for harm with calcium-containing binders in persons aged >65 years.[120,121] Since 2017, several randomized controlled trials and observational and *post hoc* analyses compared lanthanum carbonate or sevelamer carbonate with calcium-containing binders or placebo, and overall there was not a consistent benefit in terms of reduced progression of vascular calcification associated with the calcium-free compounds (Table 3).[70,86,87,122–125] In IMPROVE-CKD (IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease), after 96 weeks, lanthanum carbonate did not increase likelihood of arterial stiffness or vascular calcification compared with placebo in CKD G3b and G4.[86] In IMPROVE-CKD, phosphate levels were normal at baseline, which may be indicative of a low risk for calcification progression. In the randomized LANDMARK trial (Outcome Study of Lanthanum Carbonate Compared with Calcium Carbonate on Cardiovascular Mortality and Morbidity in Patients with Chronic Kidney Disease on Hemodialysis), with participants undergoing hemodialysis with hyperphosphatemia and having at least 1 vascular calcification risk factor, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a significant difference in composite cardiovascular events or all-cause mortality.[125]

While LANDMARK was a high-quality study, the trial ultimately had reduced statistical power from not meeting the prespecified inclusion target and having a lower-than-anticipated rate of events. The study was based in Japan, where dietary calcium intake is known to be low, and the elemental calcium dose from the binder used was also low, at 600−1200 mg calcium/day. In Japan, cardiovascular risk profiles are different than in the European Union and United States, as are mineral metabolism targets. The study also excluded patients with intact PTH >240 pg/ml. Despite study limitations, the results suggest that it may be better to avoid a high cumulative calcium load than to discourage or limit use of calcium-based binders altogether, as suggested in the 2017 Guideline update.

Considering the overall phenotype of the patient allows for a distinction between different phosphate sources. For example, in states of high bone turnover, the skeleton, rather than dietary intake, may be the major source of hyperphosphatemia. Targeting hyperparathyroidism and high bone turnover (by parathyroidectomy,[126] calcimimetics,[102,106,127] or anti-resorptives[128]) results in reductions in serum phosphorus levels. The phosphate-lowering effect of targeting bone turnover could potentially be anticipated by baseline levels of PTH or bone turnover markers, including bone-specific alkaline phosphatase.[58,106,128] It is, however, not clear whether the effect is transient or could improve long-term phosphate control.

Additional novel approaches for phosphate control include adopting certain plant-based diets,[129] using tenapanor in addition to classic phosphate binders,[130–133] or adjusting intensity of dialysis. Patiromer may have phosphate-lowering effects but needs further investigation.[134] Ongoing trials (FIT4KID,[84] FRONTIER [NCT05085275]; expected study completion 2024) of phosphate-lowering therapies include patient-relevant outcomes.

Hypocalcemia and hypercalcemia. There is no new high-level evidence to guide measures for preventing iatrogenic hypocalcemia in high-risk situations. Several recent reports highlight the risks of iatrogenic hypocalcemia in situations of rapid bone (re)-mineralization after correction of hyperparathyroid bone disease (hungry bone syndrome) following parathyroidectomy, anti-resorptive therapy,[63] and potent calcimimetics.[135,136] To correct severe and/or symptomatic hypocalcemia, i.v. or oral calcium, i.v. or oral vitamin D receptor activators, and high calcium in dialysate are typically used.[126] In patients undergoing parathyroidectomy, preoperative and postoperative use of active vitamin D derivatives may reduce the incidence of severe hypocalcemia.[137,138] Data from retrospective studies and pilot trials have been used in prediction models using bone turnover markers to guide postoperative need for calcium supplementation.[64,139–141] One observational study suggested that a short-acting bisphosphonate could be used to attenuate the hungry bone syndrome after parathyroidectomy; however, there is concern that this could potentially limit bone remineralization.[138]

Transplantation. Mineral metabolism disturbances after kidney transplantation are highly common and do not often resolve spontaneously, with their severity partly depending on their management prior to transplantation.[142,143] Hypophosphatemia associates with bone mineralization defects.[144,145] Hyperparathyroidism both with and without

Table 3 | Clinical trials since 2017 pertaining to phosphate lowering

Study reference	No. of patients (population specifics)	Intervention group	Control group	Duration	Measures/outcome	Results summary
CKD G3–G5						
Toussaint *et al.*,[86] 2020 (IMPROVE-CKD)	278 (G3b–G4)	Lanthanum 500 mg TID	Placebo TID	96 wk	cfPWV AAC	No difference in cfPWV or AAC between groups
Kovesdy *et al.*,[122] 2018	120 (G3–G5)	Lanthanum	Calcium or dietary intervention	12 mo	CAC PWV	No difference in CAC or PWV between groups
CKD G5D						
Fujii *et al.*,[123] 2018	108 (G5D, incident HD)	Lanthanum (open label)	Calcium carbonate (open label)	18 mo	CAC echocardiogram	No difference in CAC change between groups Cardiac dimensions and systolic function were improved in lanthanum group compared with placebo
Ogata *et al.*,[125] 2021 (LANDMARK)	2374 (G5D, prevalent HD with 1 CV risk factor)	Lanthanum (open label)	Calcium carbonate (open label)	3.16 yr median f/u	Composite CV event	No difference in composite CV event rate
Isaka *et al.*,[87] 2021	160 (G5D, HD)	Sucroferric oxyhydroxide (open label)	Lanthanum (open label)	12 mo	CAC	No difference in % change in CAC between binder groups % change in the strict PO_4 (median of 8.52; IQR, −1.0 to 23.9) group was significantly lower than standard PO_4 group (median change of 21.8; IQR, 10.0–36.1) $P = 0.006$

AAC, abdominal aorta calcification; CAC, coronary artery calcification; CV, cardiovascular; cfPWV, carotid-femoral pulse wave velocity; f/u, follow-up; HD, hemodialysis; IMPROVE-CKD, IMpact of Phosphate Reduction On Vascular Endpoints in Chronic Kidney Disease; IQR, interquartile range; LANDMARK, Outcome Study of Lanthanum Carbonate Compared with Calcium Carbonate on Cardiovascular Mortality and Morbidity in Patients with Chronic Kidney Disease on Hemodialysis; PO_4, phosphate; PWV, pulse wave velocity; TID, 3 times per day.

hypercalcemia post-transplant has been associated with increased risk of graft failure and all-cause mortality, although the association has not been consistently found.[144,146–151] There are no trials to guide therapy of mineral metabolism disturbances after kidney transplantation. Calcimimetics correct high calcium and low phosphate levels in persistent hyperparathyroidism, but further studies are needed to establish intervention thresholds and treatment targets.[52] Future guidelines should distinguish between persistent (also called tertiary) and secondary hyperparathyroidism, as these differ both in biochemical presentation and in pathophysiology.

Pediatrics. Age-related normal ranges of serum calcium, phosphorus, and alkaline phosphatase as well as stage-dependent PTH target ranges are used for children with CKD. Practice points for managing hypocalcemia and hypercalcemia have been given in recent consensus articles.[93,152–155]

Calcification reduction

Vitamin K. In small study cohorts, vitamin K1 and MK-7 (menaquinone-7) appeared to be safe for patients with CKD. However, despite consistently and substantially decreasing serum dephosphorylated uncarboxylated matrix Gla protein in multiple studies, vitamin K compounds did not consistently attenuate calcification progression in patients with advanced CKD (Table 4).[156–171] This may relate to altered MK-7 pharmacokinetics in advanced CKD.[172] Results from the VitaVasK pilot trial supplementing vitamin K1 during hemodialysis sessions demonstrated significant reductions of thoracic aorta calcification progression in association with significant decreases in dephosphorylated uncarboxylated matrix Gla protein serum levels over 18 months.[162] However, the difference in coronary artery calcification did not reach the level of statistical significance, probably because of recruitment difficulties, high dropout rate, and small sample size.

Sodium thiosulfate. A meta-analysis of 6 randomized and nonrandomized studies suggests sodium thiosulfate may attenuate vascular calcification in patients receiving maintenance hemodialysis.[173] Dosages have varied from 12.5−25 g/session, 2−3 times/week, for 3−6 months. In one clinical trial, a significant decline in hip bone mineral density was observed,[174] with multiple dose-dependent adverse effects identified, highlighting the importance of studying both calcification and bone outcomes simultaneously.

Magnesium. In animal models, magnesium prevents phosphate-induced vascular calcification.[175] *In vitro*, the protective effects have not been dependent on increasing intracellular magnesium but rather appeared to be due to delayed extracellular formation of hydroxyapatite.[176] Also *in vitro*, magnesium delays transition of CPPs from benign primary CPPs to likely toxic secondary CPPs.[177] However, data from clinical studies using magnesium-based interventions have been contradictory. While 1 clinical trial from Japan showed that oral magnesium oxide can decrease the progression of coronary artery calcification in patients with CKD not receiving dialysis,[168] a trial from Europe in a comparable population did not find any benefit of magnesium hydroxide.[169] Gastrointestinal adverse effects are a limitation of magnesium and may reduce adherence. Dial-Mag Canada (NCT04079582), a pragmatic cluster-randomized clinical trial, will evaluate the effects of administering 2 separate concentrations of magnesium in the dialysate (0.5 or 0.75 mmol/l) in >25,000 patients on hemodialysis (estimated completion 2028).

SNF472. SNF472 is a hexaphosphate phytate usually present in wheat. This molecule possesses a pyrophosphate-like structure and is being investigated for its potential to inhibit calcification. It is minimally absorbed in human intestine, but with parenteral administration, it reaches high plasma concentrations. In the CaLIPSO (Effect of SNF472 on Progression of Cardiovascular Calcification in End-Stage-Renal-Disease Patients on Hemodialysis) trial, 2 doses (300 and 600 mg) demonstrated significant reductions in coronary, valvular, and aortic calcification progression in hemodialysis patients.[178] The 600-mg dose may have impacted bone density in a slightly negative way, whereas the 300-mg dose showed no signal in this respect. SNF472 was also used in a prospective trial in calciphylaxis patients (CALCIPHYX),[179] in which similar improvements in wound healing were seen in a placebo-controlled trial with SNF472, as measured by a modified Bates Jensen Wound Assessment Tool and Pain Visual Analogue Scale. Fewer deaths and hospitalizations were observed in the group receiving SNF472.[180]

Calciphylaxis

A special entity within the phenotype of CKD-associated cardiovascular disease, calciphylaxis is a rare and life-threatening complication of CKD-MBD. While serum calcium and phosphate levels are not predictive of outcomes and cannot be used for guiding therapy, limiting exposure to excess calcium and phosphate is regarded as important in managing this severe disorder. Calcification inducers (e.g., high doses of active vitamin D derivatives) or lack of inhibitors (e.g., vitamin K antagonism or deficiency, inflammation) have been identified as potential risk factors for the development of calciphylaxis. Use of vitamin K antagonists for anticoagulation in patients undergoing dialysis is associated with an up to 11-fold increased risk of developing calciphylaxis.[181]

For several reasons, skin biopsy is unable to reliably diagnose calciphylaxis. There are no established features or validated histologic diagnostic criteria, and when standard staining methods alone are used, biopsy findings are not specific.[182,183] Of biopsies done for suspected calciphylaxis, 30% have inadequate sampling.[184] Reported sensitivity has been variable (20%−80%).[184,185] In addition, skin biopsy traumatizes vulnerable tissue and may trigger additional nonhealing ulcers.

Table 4 | Clinical trials evaluating calcification inhibitors

Study reference	No. of patients (population specifics)	Intervention group	Control group	Duration, mo	Measures/ outcome	Results summary
CKD G5D						
Oikonomaki *et al.*,[156] 2019	102	MK-7 200 μg/d	SC	12	CAC	No difference in CAC progression
De Vriese *et al.*,[157] 2020 (Valkyrie trial)	88 (with AF)	MK-7 2 mg TPW + rivaroxaban	Placebo	18	CAC TAC AVC	No difference in CAC, TAC, or AVC progression
Levy-Schousboe *et al.*,[158] 2021 (RenaKvit trial)	48	MK-7 360 μg/d	Placebo	24	cfPWV CAC AAC	No difference in cfPWV, CAC, or AAC progression
Naiyarakseree *et al.*,[159] 2023	96 (with cfPWV ≥10 m/s)	MK-7 375 μg/d	SC	6	cfPWV	No difference in change in cfPWV
Haroon *et al.*,[160] 2023 (Trevasc-HDK trial)	178	MK-7 360 μg TPW	SC	18	CAC AVC PWV	No difference in CAC, AVC, or PWV progression
Holden *et al.*,[161] 2023 (iPACK-HD trial)	86 (CAC > 30 AUs)	K1 10 mg TPW	Placebo	12	CAC	No difference in absolute or relative change in CAC
Saritas *et al.*,[162] 2022 (VitaVasK trial)	60 (CAC > 100 mm^3)	K1 5 mg TPW	SC	18	TAC CAC	TAC: 56% less progression in K1 group ($P = 0.039$) CAC: 68% less progression in K1 group ($P = 0.072$)
Raggi *et al.*,[163] 2020	274	SNF472 300 mg or 600 mg i.v. TPW	Placebo	12	CAC AVC	CAC: 11% (94% CI, 7%–15%) increase in SNF group vs. 20% (95% CI, 5%–24%) in placebo ($P = 0.016$) AVC: 14% (95% CI, 5%–24%) increase in SNF group vs. 98% (95% CI, 77%–123%) in placebo ($P < 0.001$)
Saengpanit *et al.*,[164] 2018 (Sodium-Thiosulfate-Hemodialysis study)	50 (CAVI ≥ 8)	STS 1.25 g i.v. TPW	SC	6	CAC CAVI	Decrease in CAVI with STS (mean difference = –0.53; 95% CI, –1.00 to –0.06; $P = 0.03$)
Djuric *et al.*,[165] 2020	60 (AAC > 100 AUs)	STS 25 g/1.73 m^2	Placebo	6	AAC	Similar increase in AAC between groups
Bian *et al.*,[166] 2022	50	STS 0.18 g/kg TPW	SC	6	CAC	CAC score decreased in STS group (between group difference in progression was not reported)
CKD G3–G5						
Witham *et al.*,[167] 2020 (K4Kidneys trial)	159	MK-7 400 μg daily	Placebo	12	cfPWV AAC	No difference in PWV or AAC progression
Sakaguchi *et al.*,[168] 2019	123	Magnesium oxide 8.3 mmol/d (elemental magnesium: 198 mg)	SC		CAC	Less percentage change in CAC in magnesium oxide group (11.3% vs. 39.5%; $P < 0.001$)
Bressendorff *et al.*,[169] 2023 (MAGiCAL-CKD trial)	148	Magnesium hydroxide 30 mmol/d	Placebo	12	CAC	No difference in baseline-adjusted CAC score
Kidney transplant recipients						
Lees *et al.*,[170] 2021 (ViKTORIES trial)	90	K1 5 mg TPW	Placebo	12	Vascular stiffness CAC	No difference in progression of vascular stiffness or CAC
Eelderink *et al.*,[171] 2023	40	MK-7 360 μg/d	Placebo	3	T50 PWV	No difference in T50 Decrease in progression of PWV in MK-7 group ($P = 0.010$)

AAC, abdominal aorta calcification; AU, Agatston unit; AVC, aortic valve calcification; CAC, coronary artery calcification; CAVI, cardio-ankle vascular index; cfPWV, carotid-femoral pulse wave velocity; CI, confidence interval; iPACK, Inhibit Progression of Coronary Artery Calcification With Vitamin K in HemoDialysis Patients; K1, vitamin K1; MAGICAL-CKD, The Effect of Oral Magnesium Supplementation on Vascular Calcification in Chronic Kidney Disease—A Randomized Clinical Trial; MK-7, menaquinone-7; PWV, pulse wave velocity; SC, standard care; STS, sodium thiosulfate; T50, calcification propensity score; TAC, thoracic aorta calcification; TPW, 3 times per week; Trevasc-HDK, Treatment to Reduce Vascular Calcification in Hemodialysis Patients Using Vitamin K; ViKTORIES, Vitamin K in kidney Transplant Organ Recipients: Investigating vEssel Stiffness.

A reduced dose of the non–vitamin K oral anticoagulant apixaban may be a safe and effective alternative to warfarin in patients with kidney failure on dialysis who have atrial fibrillation with calciphylaxis.[186] Sodium thiosulfate is widely used for treating calciphylaxis; however, it has never been evaluated in a randomized controlled trial, and a recent meta-analysis did not find an association between sodium thiosulfate and wound improvement or survival.[187] A multimodal approach to managing calciphylaxis has been suggested.[188] Important management aspects include advanced care planning, pain control, shared decision-making, and dialysis treatment options.[189] Future guidelines may consider including practice points on calciphylaxis care and future studies should also consider nonpharmacotherapy interventions, such as wound care.

SUMMARY AND CONCLUSIONS

Recent evidence generally supports the recommendations in the 2017 CKD-MBD Guideline update. Future updates may consider recommendations and practice points within a framework of 2 clinical syndromes: CKD-associated osteoporosis and CKD-associated cardiovascular disease to clinically characterize CKD-MBD, which could assist clinicians in the large areas of equipoise in clinical decision-making in CKD-MBD. Other changes could include considering renal osteodystrophy as part of the osteoporosis spectrum, a more sensitive approach to calcium balance, and a more systematic incorporation of bone turnover biomarkers in guiding management of bone health. In the future, use of artificial intelligence systems could aid in predicting risks and informing management strategies in CKD-MBD. Other opportunities and priorities for future research are depicted in Table 1.

APPENDIX

Additional Conference Participants

Carlo Alfieri, Italy; Gloria Ashuntantang, Cameroon; Sunita Bavanandan, Malaysia; Antonio Bellasi, Switzerland; Jordi Bover, Spain; Rodrigo Bueno de Oliveira, Brazil; David A. Bushinsky, USA; Iain Bressendorff, Denmark; Maria Eugênia Fernandes Canziani, Brazil; Aluizio Barbosa Carvalho, Brazil; Etienne Cavalier, Belgium; Daniel Cejka, Austria; Wei Chen, USA; Valentin David, USA; Martin H. de Borst, the Netherlands; Michelle R. Denburg, USA; Grahame J. Elder, Australia; Rosilene M. Elias, Brazil; Jürgen Floege, Germany; Masafumi Fukagawa, Japan; Maria Fusaro, Italy; Daniel Gallego, Spain; Charles Ginsberg, USA; Bak-Leong Goh, Malaysia; Rafael Alberto Gomez Acevedo, Colombia; Orlando M. Gutiérrez, USA; Takayuki Hamano, Japan; Ditte Hansen, Denmark; Mathias Haarhaus, Sweden; Sharon A. Huish, UK; Joachim H. Ix, USA; Meg J. Jardine, Australia; Pascale Khairallah, USA; Young Joo Kwon, South Korea; Marie-Hélène Lafage-Proust, France; Holly Loughton, UK; Fabrice Mac-Way, Canada; Sandro Mazzaferro, Italy; Armando Luis Negri, Argentina; Sagar U. Nigwekar, USA; Irene L. Noronha, Brazil; Susan M. Ott, USA; Farzana Perwad, USA; Isidro B. Salusky, USA; Julia J. Scialla, USA; Paweena Susantitaphong, Thailand; Irma Tchokhonelidze, Georgia; Chikako Terano, Japan; Marcello Tonelli, Canada; Yusuke Tsukamoto, Japan; Michael Walsh, Canada; Angela Yee-Moon Wang, Hong Kong/Singapore; Katherine Wesseling-Perry, USA; Myles Wolf, USA; and Jiunn Wong, Singapore.

DISCLOSURES

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