



KDIGO Controversies Conference on Chronic Kidney Disease–Mineral and Bone Disorder: Progress and Knowledge Gaps Towards Personalizing Care

Breakout Group Discussion Questions

Breakout Group 1: Maintaining Calcium and Phosphate Homeostasis

1. Is there new evidence to guide what the phosphate target should be across the spectrum of CKD?

- a. Should the previously recommended approach to only treat persistent hyperphosphatemia in CKD persist?
 - i. Comment on ongoing research of testing an FGF23-lowering strategy for CKD.
- b. In patients on dialysis, is there new evidence to guide what the phosphate target should be? Is there evidence to suggest that phosphate targets should differ by modality or by regimen (peritoneal dialysis, hemodialysis, hemodiafiltration, or nocturnal or daily dialysis)?
 - i. Comment on ongoing research in the HiLO and PHOSPHATE trials.
- c. Given observational data indicating a risk of bone mineralization defects post-transplant, should hypophosphatemia post-transplant be corrected?
- d. Is there new evidence to guide specific recommendations for pediatric patients?

2. Is there new evidence to guide the optimal approach to phosphate control?

- a. Given that LANDMARK failed to demonstrate a benefit of lanthanum over calcium-carbonate, should the recommendation on restricting the dose of calcium-based phosphate binders be amended?
- b. Is there new evidence to recommend specific phosphate-lowering strategies over others?
 - i. Are there any updates with regards to the role of dietary recommendations?
 - ii. What is the place of iron-based binders?
 - iii. What is the role of targeting bone turnover through calcimimetics or antiresorptives?
 - iv. Comment on ongoing research with tenapanor, patiromer, and ferric citrate (FIT4KID and FRONTIER trials).

- c. Given the evidence of phosphate-lowering effect of calcimimetics, antiresorptives, and parathyroidectomy, should an approach for phosphate management consider PTH, FGF23, vascular calcification markers, and/or bone turnover markers?
- d. Is there new evidence to guide specific recommendations for pediatric patients?

3. Is there new evidence to guide what the calcium target should be across the spectrum of CKD?

- a. Current guidelines focus on the risk of calcium loading and do not specify a lower limit of calcium intake. Is there evidence to guide a minimum recommended calcium intake for patients with CKD? Is there a safe upper limit of calcium intake in CKD?
- b. Is there new evidence to suggest how calcium balance could be assessed clinically?
- c. Is there evidence to suggest the optimal calcium concentration in dialysis fluid, and does it differ based on dialysis modality or regimen (peritoneal dialysis, hemodialysis, hemodiafiltration, or nocturnal or daily dialysis)?
- d. Although calcium requirements of the growing skeleton are already included in current guidelines, is there new evidence to guide specific recommendations for pediatric patients?

4. Is there new evidence to guide management of hypo- and hypercalcemia in CKD?

- a. Previous guidelines argued for permissive hypocalcemia while on calcimimetics, but trial data show a high prevalence of severe hypocalcemia and symptoms related to hypocalcemia. Fatality related to hypocalcemia was reported in 1 trial. Given this evidence, should the recommendation persist to avoid hypercalcemia instead of maintaining serum calcium in the normal range?
- b. Is there evidence to support a specific threshold of hypocalcemia that requires treatment?
- c. Is there evidence to support specific approaches to correct hypocalcemia (dialysate calcium, calcium supplementation, active vitamin D analogues, stopping cinacalcet) that should be prioritized over others?
- d. Is there evidence to support specific strategies to prevent iatrogenic hypocalcemia? These might include active vitamin D therapy and/or calcium supplementation, increasing dialysis fluid calcium, or anti-resorptive therapy.
- e. Should concern for risk of hypercalcemia with use of active vitamin D analogues persist?

- f. Is there evidence to support the best approach for managing (mild) hypercalcemia after kidney transplantation? What should treatment thresholds be?
- g. Is there new evidence to guide specific recommendations for pediatric patients?

Breakout Group 2: Management of Secondary Hyperparathyroidism (SHPT)

1. How should SHPT and vitamin D insufficiency be managed in CKD without dialysis?
 - a. In the VITAL post hoc analysis, individuals with eGFR <60 mL/min showed no clear benefits from vitamin D. Therefore, should the role of vitamin D (ergocalciferol, cholecalciferol) be reconsidered? If so, what should the target be?
 - b. What is the role of extended-release calcifediol? Is there a need for considering availability and cost?
 - c. Is there evidence for a PTH target in CKD without dialysis? If not, when should SHPT be treated? Should it be considered in the context of (bone) alkaline phosphatase or other markers?
 - d. Is there evidence for a legacy effect with early treatment of elevated PTH (ie, better control, avoidance of need of parathyroidectomy once CKD G5D is reached)?
 - e. Is the 2017 recommendation too restrictive in use of active vitamin D? Should the recommendation be reconsidered? What is the current role of active vitamin D analogues?
2. How should SHPT be managed in CKD G5D?
 - a. What is the role of new calcimimetics (etelcalcetide, evocalcet, upacicalcet)?
 - b. What are the current roles of active vitamin D analogues and non-active supplements?
 - c. What is the position of parathyroidectomy compared to medical treatment?
 - i. Comment on PROCEED and JRDR.
 - ii. What is the optimal surgical approach for parathyroidectomy including radiofrequency ablation?
 - iii. What is the optimal imaging modality to guide the surgical approach?
 - iv. How should postoperative hypocalcemia be managed?
 - d. Should the target range for PTH for people undergoing dialysis be revised?
 - i. Should racial or regional differences be considered?

- ii. Should calcium, phosphate, (bone-) ALP, or other markers be incorporated in SHPT evaluation and management?
3. How should persistent HPT (or tertiary HPT) be managed in CKD G5T?
 - a. How should post-transplant deranged mineral homeostatis be managed?
 - b. How should tertiary HPT be defined?
 - c. What is the role of calcimimetics?
 - d. What is the role of parathyroidectomy?
 - i. Compare parathyroidectomy versus calcimimetics.
 - ii. Should parathyroidectomy be performed prior to transplantation?
 4. Other questions and research questions
 - a. Given that there are no clear advantages of using non-oxidized PTH assays, which assay should be used to measure PTH?
 - i. Do third generation assays offer benefit over second generation ones?
 - b. Should PTH (and other parameters) be measured more frequently when starting or titrating PTH-lowering therapy?
 - c. For 25 (OH)D, what are the effects of having higher levels in people with CKD versus those defined as optimal for the general population? What effect does formulation have?
 - d. Can calcimimetics be used in CKD without dialysis?
 - i. What are the risks of hyperphosphatemia and hypocalcemia?
 - e. Should quality of life be an endpoint for trials addressing SHPT?
 - f. Is oversuppression of PTH causing additional morbidity or mortality?
 - g. What is the optimal approach for early and late post-surgical hypoparathyroidism, including the hungry bone syndrome?

Breakout Group 3: Vascular Calcification – Diagnostic Tests and Interventions

1. In 2023, what is the landscape of vascular calcification in patients with kidney disease?
 - a. What are the recent trends in vascular calcification across CKD stages?
 - b. Is there new data to suggest that reducing vascular calcification translates to an all-cause mortality benefit in patients with kidney disease?

2. **What is the state of evidence to support the use of treatments (vitamin K1, vitamin K2, sodium thiosulfate, SNF472, magnesium, calcimimetics) that target vascular calcification in patients with kidney disease?**
 - a. Outcomes of interest include survival, cardiovascular events, safety, tolerability, coronary artery calcification, valvular calcification, aortic calcification, peripheral vascular disease, and calciphylaxis.
 - b. For these treatments, is there sufficient data to support special considerations for the different subgroups of CKD, including CKD 5D, CKD 3-5, kidney transplant recipients, children, or the elderly?
3. **Are there new or emerging biomarkers/diagnostic tests that may predict or diagnose vascular calcification and guide treatment?**
 - a. Are there new data regarding imaging tests used to diagnose and monitor vascular calcification?
 - b. Are there adjunct or surrogate biomarkers or diagnostic tests that can identify patients at risk for vascular calcification and progression?
 - c. Can/should these biomarkers or diagnostic tests be used to define the presence of vascular calcification, guide treatment selection, and monitor treatment?
 - d. Are these biomarkers/diagnostic tests suitable for clinical practice versus research purposes?
 - e. What are the challenges to developing and using novel or emerging biomarkers/diagnostic tests in clinical practice?
4. **Calcium-based versus calcium-free binders with respect to vascular calcification**
 - a. Is there additional evidence to support or refute the 2017 recommendations regarding the use of calcium-based versus calcium-free binders to guide the individualized care of patients with CKD 5D, CKD 3-5, and CKD5DT?
 - b. Is there new evidence that better substantiates or conflicts with current recommendations? Have large-scale studies improved the certainty or magnitude of benefit versus harm?
 - c. Is there sufficient data to support special considerations for different subgroups of CKD including CKD5D, CKD3-5, kidney transplant recipients, children, or the elderly?
5. **Calciphylaxis**
 - a. What is the role of skin biopsy in the diagnosis of calciphylaxis?
 - b. What is the evidence base regarding the interventions commonly used for the management of calciphylaxis?

- c. Is there evidence to support a best practices approach to anticoagulation in patients where calciphylaxis occurs in the setting of warfarin treatment?
- d. Is there evidence for a holistic approach to patients with calciphylaxis regarding advanced care planning, pain control, shared decision-making and dialysis treatment options?

Breakout Group 4: Osteoporosis, Bone Morphology, and Histopathology in CKD

1. What is the landscape of renal osteodystrophy (ROD) in contemporary CKD patients?

- a. Can the bone biopsy recommendations from the 2017 KDIGO guideline be clarified?
- b. What are the trends in ROD across CKD stages and across dialysis modalities?
 - i. Has the epidemiology of ROD changed?
- c. What are the opportunities and challenges of ongoing bone biopsy registries? What are the benefits of multi-center versus individual center registries? What are the economies (opportunities) of scale?
- d. What are the research challenges or opportunities related to the following?
 - i. Establishing/harmonizing reference ranges
 - ii. Establishing large-scale open-access (FAIR guideline adherent) bone biopsy repositories with healthy reference data and slide digitization
 - iii. Updating ROD epidemiology
 - iv. Using molecular diagnostics and precision medicine approaches to treat ROD and osteoporosis in CKD

2. How to assess bone health in CKD?

- a. Clarify the use of DXA as predictor of fractures in CKD
 - i. How robust is DXA as a predictor across stages of CKD and across PTH categories?
 - ii. Should screening be targeted to certain populations?
 - iii. What is the interval of follow-up scans (diagnosis vs on-treatment)?

- iv. What is the optimal site of skeletal imaging?
- v. Can DXA be used as a surrogate outcome for fracture in clinical trials?
- b. What is the role of bone biomarkers?
 - i. Are bone biomarkers adjunct, surrogates, or replacements for bone histomorphometry?
 - ii. How should turnover versus treatment selection versus treatment monitoring be defined?
 - iii. Which biomarkers should and can be used?
 - iv. Which biomarkers should be used in initial treatment versus follow-up?
 - v. What are the distinctions between clinical practice and research?
 - vi. What are the challenges to using bone biomarkers? For example, variability, insurance coverage, supportive data, kidney clearance, reference ranges
 - vii. How does the independence of PTH from bone turnover affect diagnostic utility of PTH (e.g., PTH levels in the setting of bone-targeting treatments, such as bisphosphonates)?
 - viii. When and how should BTMs be used (single use, serial use, pre-post-treatment)?
- c. When (and how: needle diameter, CT assisted, etc.) should a bone biopsy be done? What, if any, are the distinctions between clinical practice and research?
- d. Is there sufficient evidence to implement fracture risk scores (eg, FRAX) and novel imaging methods (eg, TBS) in clinical practice?
- e. Discuss novel approaches to assess bone health.
 - 1. PET imaging
 - 2. Molecular diagnostics (miRNA, transcriptomics)
 - 3. Precision medicine approaches
- f. What are considerations for standardization and harmonization of bone biomarker assays?

3. How to prevent fractures in CKD?

- a. What is the state of evidence to support the use of bone-targeting agents to prevent fractures in CKD patients?
- b. Is a bone biopsy needed before any bone-targeted treatment? If so, why? If no, why?
- c. What are the reasons to withhold pharmacological therapies approved in the general population in patients with CKD? (What are the objections to



- using pharmacological therapies approved in the general population?
How different are CKD patients?)
- d. Why is the treatment gap so wide, and how can it be narrowed?
 - e. Are there CKD-specific treatments that should be studied (e.g., etelcalcetide)?
 - f. How should bone treatment be monitored? By DXA? Bone biomarkers?
 - g. Should treatment be based on bone turnover assessment?
 - h. Are there off-target effects of bone agents that need to be considered in CKD patients, such as CKD progression or skeletal toxicity?
 - i. Are there specific considerations for post-transplant patients?
 - j. What are the research challenges and opportunities related to the following?
 - i. ROD-specific drug development for fracture prevention / bone health
 - ii. RCT of osteoporosis drugs in moderate-severe CKD for fracture prevention
 - iii. Precision medicine approaches to fracture prevention guidelines
 - iv. Trials on bone agent adverse effects on kidney and bone health