Breakout Session A: Topic Questions

Vascular Calcification

The existing KDIGO recommendations related to vascular calcification are:

3.3.1 In patients with CKD stages 3–5D, we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence o*r* absence of valvular calcification, as reasonable alternatives to computed tomography based imaging (*2C*).

3.3.2 We suggest that patients with CKD stages 3–5D with known vascular/valvular calcification be considered at highest cardiovascular risk (*2A*). It is reasonable to use this information to guide the management of CKD–MBD (*not graded*).

1. Do we need routine screening for vascular calcification in pre-dialysis CKD patients? If so,
    - What is (are) the best imaging modality for vascular calcification?
    - At what stage of CKD should screening be started?
    - At what intervals should these tests be performed?
    - Will imaging influence clinical management, and how?

2. Do we need routine screening for vascular calcification in ESRD patients? If so,
    - What is (are) the best imaging modality for vascular calcification?
    - At what intervals should these tests be performed?
    - Will imaging influence clinical management, and how?

3. Are biomarkers useful for predicting CVD development and progression in CKD?
    - If so, which biomarkers should be used?
    - Frequency of measurement?

4. At what stage of CKD should phosphate control be implemented?

5. Do we have effective methods for phosphate control and prevention of vascular calcification in pre-dialysis CKD?

6. Is there a role for non-pharmacological (dietetic) management of phosphate?
    - In CKD
    - In ESRD
    - In adults and elderly
    - In children

7. What is the evidence that non-calcium based phosphate binders (including magnesium) prevent or attenuate the progression of vascular calcification?
    - In CKD
    - In ESRD
    - In adults and elderly
    - In children

8. Should cinacalcet be implemented to prevent vascular calcification?
    - In CKD
    - In ESRD
    - In adults and elderly
    - In children

9. Does oral calcium intake (diet or binders) or dialysate calcium cause calcification? If so, is there a threshold dose?
    - In CKD
    - In ESRD
    - In adults and elderly
    - In children

10. Is vascular calcification a contributory factor:
    - In increasing cardiovascular events?
    - In increasing cardiovascular mortality?

Calcium and Phosphate

The existing KDIGO recommendations related to Ca & P are:

3.1.1. We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (*1C*). In children, we suggest such monitoring beginning in CKD stage 2 (*2D*).

3.1.2. In patients with CKD stages 3–5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (*not graded*).

Reasonable monitoring intervals would be:

- **In CKD stage 3: for serum calcium and phosphorus, every 6–12 months; and for PTH, based on baseline level and CKD progression.**
- **In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.**
- **In CKD stage 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.**
- **In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).**

In CKD patients receiving treatments for CKD–MBD, or in whom biochemical abnormalities are identified, it is reasonable to increase the frequency of measurements to monitor for trends and treatment efficacy and side-effects (*not graded*).

3.1.5 In patients with CKD stages 3–5D, we suggest that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium–- phosphorus product (Ca X P) (*2D*).

4.1.1. In patients with CKD stages 3–5, we suggest maintaining serum phosphorus in the normal range (*2C*). In patients with CKD stage 5D, we suggest lowering elevated phosphorus levels toward the normal range (*2C*).

4.1.2. In patients with CKD stages 3–5D, we suggest maintaining serum calcium in the normal range (*2D*).

4.1.3. In patients with CKD stage 5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (*2D*).

4.1.4. In patients with CKD stages 3–5 (2D) and 5D (*2B*), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD–MBD, concomitant therapies, and side-effect profile (*not graded*).

4.1.5. In patients with CKD stages 3–5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (*1B*).

In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (*2C*) and/or adynamic bone disease (*2C*) and/or if serum PTH levels are persistently low (*2C*).

4.1.6. In patients with CKD stages 3–5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (*1C).*

4.1.7. In patients with CKD stages 3–5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (*2D*).

4.1.8. In patients with CKD stage 5D, we suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia (*2C*).

5.1. In patients in the immediate post-kidney-transplant period, we recommend measuring serum calcium and phosphorus at least weekly, until stable (*1B*).

5.2. In patients after the immediate post-kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (*not graded*).

Reasonable monitoring intervals would be:

- **In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.**
- **In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.**
- **In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.**
- **In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).**

Is there any new evidence in adults, elderly, transplant recipients and children about:

1. What are the best ways to measure calcium or phosphorus status, or how frequently should this be measured? (recommendations 3.1.1, 3.1.2, 3.1.5, 5.1 and 5.2).
   Factors to consider:
   - albumin binding: tCa vs iCa vs cCa
   - variation: intraindividual (diurnal), therapy (dialysis)-induced, inter-assay
   - diagnostic properties (Sn, Sp, PPV, NPV)
   - availability/cost
   - balance vs excretion vs serum levels
   - consider for G3-G5a, HD/PD and CKD-T separately

2. What is the target range for serum phosphorus or calcium (recommendations 4.1.1 and 4.1.2)?
   Factors to consider:
   - different ranges for G3-G5a, HD/PD and Tx?
   - are there other clinical characteristics that should affect the target range?

3. What is the role of dialysis in controlling serum phosphorus and calcium (recommendations 4.1.3 and 4.1.8)?

    Factors to consider:

    - dialysate calcium concentration
    - how best to remove phosphorus with conventional HD
    - role of quotidian hemodialysis, HDF, and PD

4. What is the role of phosphorus binders/NaPi inhibitors in controlling serum phosphorus and calcium (recommendations 4.1.4, 4.1.5, 4.1.6)?

    Factors to consider:

    - calcium- vs non-calcium binders (including magnesium), including safety of aluminum
    - cost/efficacy/safety
    - maximum dose?
    - when to initiate?
    - clinical characteristics that should modify recommendations for treatment selection

5. What is the role of diet in controlling serum phosphorus and calcium (recommendation 4.1.7)?

    Factors to consider:

    - phosphorus additives + labelling
    - how to monitor adherence?
    - safe upper (and lower) limits for phosphorus and calcium intake
    - vegetarian vs animal protein
    - When to initiate?

6. How/when to treat hypophosphatemia in CKD-T?

7. How/when to treat hypercalcemia in CKD-T?

PTH and Vitamin D

The existing KDIGO recommendations related to PTH and Vitamin D are:

3.1.1. We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (*1C*). In children, we suggest such monitoring beginning in CKD stage 2 (*2D*).

3.1.2. In patients with CKD stages 3–5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (*not graded*).

Reasonable monitoring intervals would be:

- **In CKD stage 3: for serum calcium and phosphorus, every 6–12 months; and for PTH, based on baseline level and CKD progression.**
- **In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.**
- **In CKD stage 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.**
- **In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).**

3.1.3 In patients with CKD stages 3–5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions (*2C*). We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (*2C*).

4.2.1. In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH (iPTH) above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (*2C*). It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (*not graded*).

4.2.2. In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (*2C*).

4.2.3. In patients with CKD stage 5D, we suggest maintaining iPTH levels in the range of approximately two to nine times the upper normal limit for the assay (*2C*). We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range (*2C*).

4.2.4. In patients with CKD stage 5D and elevated or rising PTH, we suggest calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs be used to lower PTH (*2B*).

- **It is reasonable that the initial drug selection for the treatment of elevated PTH be based on serum calcium and phosphorus levels and other aspects of CKD–MBD (*not graded*).**

- **It is reasonable that calcium or non-calcium-based phosphate binder dosage be adjusted so that treatments to control PTH do not compromise levels of phosphorus and calcium (*not graded*).**
- **We recommend that, in patients with hypercalcemia, calcitriol or another vitamin D sterol be reduced or stopped (*1B*).**
- **We suggest that, in patients with hyperphosphatemia, calcitriol or another vitamin D sterol be reduced or stopped (*2D*).**
- **We suggest that, in patients with hypocalcemia, calcimimetics be reduced or stopped depending on severity, concomitant medications, and clinical signs and symptoms (*2D*).**
- **We suggest that, if the intact PTH levels fall below two times the upper limit of normal for the assay, calcitriol, vitamin D analogs, and/or calcimimetics be reduced or stopped (*2C*).**

Vote: 16 Acceptable; 1 Unacceptable (felt the hypocalcemia statement goes against our recommendation to keep calcium in the normal range)

4.2.5. In patients with CKD stages 3–5D with severe hyperparathyroidism (HPT) who fail to respond to medical/pharmacological therapy, we suggest parathyroidectomy (2B).

5.2. In patients after the immediate post-kidney-transplant period, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (*not graded*).

Reasonable monitoring intervals would be:
- **In CKD stages 1–3T, for serum calcium and phosphorus, every 6–12 months; and for PTH, once, with subsequent intervals depending on baseline level and CKD progression.**
- **In CKD stage 4T, for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.**
- **In CKD stage 5T, for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.**
- **In CKD stages 3–5T, measurement of alkaline phosphatases annually, or more frequently in the presence of elevated PTH (see Chapter 3.2).**

5.3. In patients with CKD stages 1–5T, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions (*2C*).

5.4. In patients with CKD stages 1–5T, we suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (*2C*).

5.6. In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73m^2 and low BMD, we suggest that treatment with vitamin D, calcitriol/alfacalcidol, or bisphosphonates be considered (*2D*).
- **We suggest that treatment choices be influenced by the presence of CKD–MBD, as indicated by abnormal levels of calcium, phosphorus, PTH, alkaline phosphatases, and 25(OH)D (*2C*).**
- **It is reasonable to consider a bone biopsy to guide treatment, specifically before the use of bisphosphonates due to the high incidence of adynamic bone disease (*not graded*).**

Nutritional vitamin D

- What are the goals of nutritional vitamin D therapy?

Physiology

- How should optimal values be determined; is there proof of benefit for levels >50 nmol/L (>20 ng/ml)?
- Should general community and CKD 3-5 and 5D targets be the same?
- Should thresholds differ with race?

Measurement, treatment regimens

- Which assays reliably measure Total 25OHD?
- In CKD 3-5 and 5D, what doses and dose regimens achieve adequate /optimal 25OHD levels?
- Should high dose vitamin D treatments be used?
- Do some patient groups need closer monitoring?

Application

- Can the efficacy of vitamin D treatment be monitored in CKD 3-5 and 5D; e.g. reciprocal relationship to PTH/bone markers/other?
- Is there a need to monitor 25OHD or should routine supplements be used?

Calcitriol and its analogs

- What are the goals of therapy with calcitriol or its analogs?

Physiology

- Should patients receive physiological $1,25(OH)_2D$ replacement in CKD 3-5 and 5D?
- If so, how would this be achieved?

Measurement, treatment regimens

- Are assays reliable?
- In which (if any) patients should we measure $1,25(OH)_2D$?

Application

- What ***evidence*** supports calcitriol/analog use for mortality /CVD/bone/other outcomes? Do these data apply to particular patient groups?
- When should pharmacological doses be used / avoided?
- In which circumstances do calcitriol/analogs and calcimimetic combinations have proven value?

PTH

Physiology

- Based on evidence, what can we achieve by pharmacological manipulation of PTH?

Measurement

- Biointact / iPTH assays; does any newer data better inform this area?
- Should bone turnover markers be assayed in addition to PTH in CKD 3-5D? If so, which markers and when are they useful?

Application

- What PTH range should be targeted in CKD 3-5? Should thresholds differ by race? What are the effects of PTH 'suppression' to normal in CKD 3-5?
- What PTH range should be targeted in CKD 5D; is the 2-9 fold assay upper range applicable?
- Should KDIGO suggestions for the use of calcimimetics, calcitriol/analogs and combinations to maintain PTH within target range be revised?
- What advice can be provided on non calcium vs. calcium-based binders for achieving PTH targets?

Bone Quality

The existing KDIGO recommendations related to bone quality are:

3.2.1. In patients with CKD stages 3–5D, it is reasonable to perform a bone biopsy in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to therapy with bisphosphonates in patients with CKD–MBD (*not graded*).

3.2.2. In patients with CKD stages 3–5D with evidence of CKD–MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (*2B*).

3.2.3. In patients with CKD stages 3–5D, we suggest that measurements of serum PTH or bone-specific alkaline phosphatase can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover (*2B*).

3.2.4. In patients with CKD stages 3–5D, we suggest not to routinely measure bone-derived turnover markers of collagen synthesis (such as procollagen type I C-terminal propeptide) and breakdown (such as type I collagen cross-linked telopeptide, cross-laps, pyridinoline, or deoxypyridinoline) (*2C*).

3.2.5. We recommend that infants with CKD stages 2–5D should have their length measured at least quarterly, while children with CKD stages 2–5D should be assessed for linear growth at least annually (*1B*).

4.3.1. In patients with CKD stages 1–2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we recommend management as for the general population (*1A*).

4.3.2. In patients with CKD stage 3 with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, we suggest treatment as for the general population (2B).

4.3.3. In patients with CKD stage 3 with biochemical abnormalities of CKD–MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (*2D*).

4.3.4. In patients with CKD stages 4–5D having biochemical abnormalities of CKD–MBD, and low BMD and/or fragility fractures, we suggest additional investigation with bone biopsy prior to therapy with antiresorptive agents (*2C*).

4.3.5. In children and adolescents with CKD stages 2–5D and related height deficits, we recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD–MBD (*1A*).

5.5. In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73m^2, we suggest measuring BMD in the first 3 months after kidney transplant if they receive corticosteroids, or have risk factors for osteoporosis as in the general population (*2D*).

5.7. In patients with CKD stages 4–5T, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population and BMD does not predict the type of kidney transplant bone disease (*2B*).

5.8. In patients with CKD stages 4–5T with known low BMD, we suggest management as for patients with CKD stages 4–5 not on dialysis, as detailed in Chapters 4.1 and 4.2 (*2C*).

This group will focus on one aspect of CKD-MBD namely abnormalities in bone turnover, mineralization, volume, linear growth, or strength in adults (elderly included), children and transplant recipients.

The clinical outcome that we will focus on is fracture.

1. Epidemiology
    a. What is the incidence / prevalence of fractures among those with CKD? We could consider examining this by stage of CKD separately or by grouping stages: predialysis and dialysis
    b. What are the associated comorbidities, incidence of mortality and economic burden of fractures? We could consider a comparison to postmenopausal women

2. Etiology
    a. What are the risk factors for impaired bone strength/altered bone quality? I think we should separate out the alternations in bone quality/bone strength: Osteoporosis, osteomalacia, low turnover bone disease, high turnover bone disease and consider etiologies separately – this is because diagnosis and treatment may vary by cause

3. Diagnosis
    a. What is the role of BMD by DXA to assess/determine fracture risk in children and adults? Does the ability of DXA to assess fracture risk vary by site used (radius vs hip) and/or by stage of CKD? Is there a role for FRAX in fracture risk assessment for CKD?
    b. What is the role of other, non invasive imaging to assess and determine fracture risk?
    c. Are there laboratory tests that can be used to assess fracture risk?
    d. Under what circumstances are bone biopsies required?
    e. Do we want to address screening?

4. Treatments
    a. What treatments can be used to reduce fracture risk in adults and children with CKD?
    b. Can antiresorptives (bisphosphonates and Denosumab) or anabolic agents (parathyroid hormone) be used in adults with CKD?
    c. How do treatment choices vary by stage of CKD and underlying etiology of disease?
    d. Duration of treatment?
    e. How do we evaluate treatment success- BMD, fracture, etc?

Breakout Session B: Revisiting 2009 CKD-MBD Guideline

When determining if revisions to guideline statements are warranted, questions denoted in red below should be addressed for all recommendations under review and those in green should be discussed as appropriate. One should bear in mind the goal of these breakouts is not to wordsmith the potential changes or reappraise the specific quality level of the evidence. Rather the objective here is to provide a suggested roadmap as to what general revisions or additions to the recommendations that the guideline update (if deemed necessary) should entail.

- **Has there been new evidence since 2009 that better substantiates or conflicts with current recommendations? Are there large-scale studies that may improve the certainty or magnitude of net benefit/harm?**
- **Should any of the guideline statements be modified/created or removed because of new data, or availability of new interventions, strategies or techniques not previously considered?**
- **Should any of the guideline statements be modified/created to address certain CKD stages separately or CKD populations not previously addressed? Any specific considerations concerning the elderly CKD population?**
- **Should any of the guideline statements be modified/removed because they are difficult to implement?**

- **Which laboratory and imaging outcomes are appropriate surrogate endpoints for CKD-MBD? Are there new surrogate endpoints to consider?**
- **What are desirable patient-level outcomes in CKD-MBD?**
- **What new topic areas should the next guideline update include (e.g., calcific uremic arteriolopathy)?**
- **What are the existing controversial questions and how can future research or improved trial design better resolve them?**

Strength of KDIGO Recommendations: Level 1 vs Level 2

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy**
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Quality of Evidence Underlying a Recommendation

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.