TREATMENT OF BONE with Biphosphonates, Other Osteoporosis Medications, and Growth Hormone

CHAPTER 4.3

Guideline Recommendation Statements:

In patients with CKD G1-G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization (WHO) criteria:

- (4.3.1) Recommend management as for the general population. (1A)

In patients with CKD G3a-G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, as identified by WHO criteria:

- (4.3.2) Suggest treatment as for the general population. (2B)

In patients with CKD G3a-G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures:

NEW (4.3.3) 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)

KIDNEY TRANSPLANT BONE DISEASE

CHAPTER 5

Guideline Recommendation Statements about Evaluation:

In patients in the immediate post-kidney-transplant period:

- (5.1) Recommend measuring serum calcium and phosphate at least weekly, until stable. (1B)

In patients after the immediate post-kidney-transplant period:

- (5.2) It is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD. (Not Graded)

In patients with CKD G1T-G5T:

- (5.3) Suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and interventions. (2C)

NEW **(5.5) In those with risk factors for osteoporosis, suggest that BMD testing be used to assess fracture risk if results will alter therapy. (2C)**

Guideline Recommendation Statements about Treatment:

- (5.4) In patients with CKD G1T-G5T, suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population. (2C)

NEW **(5.6) In patients in the first 12 months after kidney transplant with an estimated GFR greater than approximately 30 ml/min per 1.73 m2 and low BMD, suggest that treatment with vitamin D, calcitriol/alfacalcidol, and/or antiresorptive agents be considered. (2D)**

- Suggest that treatment choices be influenced by the presence of CKD-MBD, as indicated by abnormal levels of calcium, phosphate, PTH, alkaline phosphatases, and 25(OH)D. (2C)
- It is reasonable to consider a bone biopsy to guide treatment. (Not Graded)

  There are insufficient data to guide treatment after the first 12 months.
- (5.7) In patients with CKD G4T-G5T with known low BMD, suggest management as for patients with CKD G4-G5 not on dialysis, as detailed in Chapters 4.1 and 4.2. (2C)

PEDIATRIC CKD-MBD

Expert Q&A

1. When should assessment and monitoring for children with CKD-MBD start?
In children, biochemical monitoring should begin in CKD G2.

2. Should children with CKD G2-G5D be assessed for linear growth at least annually?
Children with CKD G2-G5D should be assessed for linear growth at least annually and infants' length checked quarterly.

3. Should children and adolescents with CKD G2-G5D and related height deficits be treated with recombinant human growth hormone when additional growth is desired?
After addressing malnutrition and biochemical abnormalities treatment with recombinant growth hormone is recommended.

4. Is it reasonable to base the choice of phosphate-lowering treatment on serum calcium levels in children with CKD G3a-G5D?
Children and adolescents with CKD G3a-G5D should maintain serum calcium in age-appropriate normal range.

5. Is it reasonable to base the choice of phosphate-lowering treatment on serum calcium levels in children with CKD G3a-G5D?
The choice of phosphate-lowering treatments should be based on serum calcium levels, given the higher calcium requirements of the growing skeleton in children and adolescents with CKD.

6. Which therapies may be considered to maintain serum calcium levels in the age-appropriate normal range in children with CKD-MBD?
In children, calcitriol and vitamin D analogs can be used to maintain serum calcium levels in the age-appropriate normal range.

Guideline Recommendation Statements:

Diagnosis of CKD-MBD: Biochemical Abnormalities

- (3.1.1) In children, suggest monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G2. (2D)

Diagnosis of CKD-MBD: Bone

- (3.2.5) Recommend that infants with CKD G2-G5D have their length measured at least quarterly, while children with CKD G2-G5D should be assessed for linear growth at least annually. (1B)

Treatment of CKD-MBD: Serum Phosphate and Calcium

NEW **(4.1.3) In children with CKD G3a-G5D, suggest maintaining serum calcium in the age-appropriate normal range. (2C)**

NEW **(4.1.6) In children with CKD G3a-G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels. (Not Graded)**

Treatment of CKD-MBD: Serum PTH

NEW **(4.2.2) In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range. (Not Graded)**

Treatment of CKD-MBD: Bone Disease

- (4.3.4) In children and adolescents with CKD G2-G5D and related height deficits, recommend treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD-MBD. (1A)

CKD-MBD Guideline Update Highlights

- **BMD testing is now suggested in patients with CKD-MBD and/or osteoporosis risk factors, if the results will impact future treatment. Multiple new prospective studies have documented that lower DXA BMD predicts incident fractures in patients with CKD G3a-G5D.**
- **Trends—rather than single values of serum phosphate, calcium, and PTH—should be considered together to make treatment decisions for CKD-MBD.**
- **Phosphate-lowering therapies (e.g., diet, binders, dialysis) should be based on progressive or persistent elevated serum phosphate. Elevated serum phosphate levels should be lowered towards the normal range.**
- **Avoid hypercalcemia in adults, since new evidence links higher calcium concentrations to increased mortality and nonfatal cardiovascular events in adults with CKD.**
- **Restrict the dose of calcium-based phosphate binders across all severities of CKD. New evidence suggests that excess exposure to exogenous calcium in adults may be harmful in all severities of CKD, regardless of other risk markers.**
- **When limiting dietary phosphate intake, the source of phosphate (e.g., animal, vegetable, additives) should be considered, since restricting dietary phosphate must not compromise adequate protein intake.**
- **Patients with intact PTH levels that are progressively rising or persistently above the upper normal limit for the assay should be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency. It is felt that modest increases in PTH may represent an appropriate adaptive response to declining kidney function.**
- **Routine use of calcitriol or its analogs in CKD G3a–G5 is no longer recommended. It is reasonable to reserve the use of calcitriol and its analogs for patients with CKD G4-G5 with severe and progressive hyperparathyroidism. Recent studies failed to demonstrate improvements in clinically relevant outcomes (cardiovascular) but did demonstrate increased risk of hypercalcemia.**
- **Calcimimetics, calcitriol, or vitamin D analogs or a combination of these agents, are all acceptable first-line treatment approaches for lowering PTH in patients with CKD G5D.**
- **Treatment choices should take into account the magnitude and reversibility of biochemical abnormalities and CKD progression, with consideration of a bone biopsy in patients with CKD G3a-G5D with CKD-MBD and low BMD and/or fragility fractures.**

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SANOFI

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KDIGO CKD-MBD Guide

Q&A with the Experts

This guide presents the NEW recommendation statements from the KDIGO 2017 *Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD)* with those that remained unchanged from the 2009 KDIGO *Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD.*

kdigo.org

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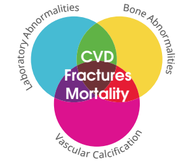
Chronic Kidney Disease-Mineral & Bone Disorder (CKD-MBD)



This figure illustrates the interrelated nature of biochemical abnormalities, bone disease, and extraskeletal calcification in CKD-MBD. It is important to recognize that treatment of one parameter could also affect the other.

DIAGNOSIS OF CKD-MBD: Biochemical Abnormalities

CHAPTER 3.1

Expert Q&A

1. When should assessment and monitoring for adults with CKD-MBD start?
Assessment and monitoring for CKD-MBD [e.g., calcium, phosphate, PTH, alkaline phosphatases and 25 (OH) D] should start as early as CKD G3a.

2. How would you account for variation in laboratory values when assessing for CKD-MBD?
It is important to take into account trends, rather than single values, to evaluate the changes in the degree and severity of laboratory abnormalities of CKD-MBD. The presence of abnormal values, the rate of change, and the severity of the abnormalities are highly variable among patients.

3. Should the presence and duration of identified abnormalities and the severity of abnormalities be taken into account for the frequency of assessment?
The frequency of assessment should take into account the presence and duration of identified abnormalities and in the context of the degree and rate of change in kidney function and the concomitant use of medications.

Frequency of Monitoring: CKD G3a-G5D

	Frequency of Monitoring	CKD G3a-G3b	CKD G4	CKD G5-G5D
Serum Calcium and Phosphate	Every 1-3 Months			✔
	Every 3-6 Months		✔	
	Every 6-12 Months	✔		
PTH	Every 3-6 Months			✔
	Every 6-12 Months		✔	
	Based on baseline level and CKD progression	✔		
Alkaline Phosphatases	Every 12 Months or more frequently in presence of ↑PTH	Obtain baseline value		✔ (CKD G4-G5D)

Guideline Recommendation Statements:

In patients with CKD G3a-G5D:

- (3.1.1) We recommend monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G3a. (1C)
- (3.1.2) It is reasonable to base the frequency of monitoring serum calcium, phosphate, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD. (Not Graded)
- (3.1.3) Suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions. (2C) Suggest that vitamin D deficiency and insufficiency[a] be corrected using treatment strategies recommended for the general population. (2C)
- (3.1.4) Recommend that therapeutic decisions be based on trends rather than on a single laboratory value, taking into account all available CKD-MBD assessments. (1C)
- (3.1.5) Suggest that individual values of serum calcium and phosphate, evaluated together, be used to guide clinical practice rather than the mathematical construct of calcium-phosphate product (Ca × P). (2D)[b]

a. Most studies define deficiency as serum 25(OH)D <10 ng/ml and insufficiency ≥10 but <20-32 ng/ml. There is no consensus on what defines 'adequate' or toxic vitamin D levels.

b. To facilitate appropriate interpretation of data, clinical laboratories should report to clinicians assay method used, any changes in methods, sample source (e.g., plasma, serum), and handling specifications.

DIAGNOSIS OF CKD-MBD: Bone

CHAPTER 3.2

Expert Q&A

1. Should DXA-based bone mineral density testing be performed routinely in patients with CKD3a-G5D?
Patients with CKD G3a-G5D have more increased fracture rates than the general population. Incident hip fractures are associated with substantial morbidity and mortality. New prospective studies have documented that dual-energy x-ray absorptiometry bone mineral density (DXA BMD) predicts incident fractures in patients with CKD G3a-G5D. Use DXA-based BMD testing to assess fracture risk if the results will impact future treatment.

2. Would it be reasonable to perform a bone biopsy in patients with CKD3a-G5D to determine the type of osteodystrophy?
Since antiresorptive therapies are effective in patients with CKD, the guideline no longer suggests that a bone biopsy must be performed prior to the initiation of these medications. However, bone biopsies should be considered in patients in whom the etiology of clinical symptoms and biochemical abnormalities is in question, and the results may lead to changes in therapy.

Guideline Recommendation Statements:

In patients with CKD G3a-G5D:

NEW (3.2.1) With evidence of CKD-MBD and/or risk factors for osteoporosis, suggest BMD testing to assess fracture risk if results will impact treatment decisions. (2B)

NEW (3.2.2) It is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions. (Not Graded)

- (3.2.3) Suggest that measurements of serum PTH or b-ALP can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover. (2B)
- (3.2.4) Suggest not to routinely measure bone-derived turnover markers of collagen synthesis and breakdown. (2C)

DIAGNOSIS OF CKD-MBD: Vascular Calcification

CHAPTER 3.3

Expert Q&A

1. Why should patients with known vascular/valvular calcification be considered at highest cardiovascular risk?
In the CKD population, coronary artery and generalized vascular calcification is exceedingly more prevalent and severe with an accelerated disease course. The presence and severity of cardiovascular calcification strongly predict cardiovascular morbidity and mortality in patients with CKD.

2. How should we test for vascular/valvular calcification?
Lateral abdominal radiograph and an echocardiogram are alternatives to computed tomography-based imaging. Lateral abdominal radiograph – detects presence or absence of vascular calcification
Echocardiogram – detects presence or absence of valvular calcification.

Guideline Recommendation Statements:

In patients with CKD G3a-G5D:

- (3.3.1) 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 or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging. (2C)
- (3.3.2) Suggest that patients 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)

DIAGNOSIS OF CKD-MBD: Serum Phosphate and Calcium

CHAPTER 4.1

Expert Q&A

1. Should serum calcium, phosphate and PTH be considered together for the treatment of CKD-MBD?
Clinical decisions should be based on serial trends of calcium, phosphate and PTH since therapeutic maneuvers at improving one parameter often have unintentional effects on another. As such it is important to emphasize the interdependency of these parameters for decision making.

2. Should the treatment be aimed at overt hyperphosphatemia?
Treatment should be aimed at overt hyperphosphatemia rather than the prevention of hyperphosphatemia given the absence of data to support that efforts to maintain phosphate in the normal range are of benefit to CKD G3a-G4 patients, including some safety concerns. Phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate and all phosphate-lowering therapies (e.g., binders, diet, dialysis) can be considered. Restrictions on the dose of calcium-based phosphate binders are advised to avoid excess exposure to calcium in adults.

3. Should treatment of hypocalcaemia be individualised?
Individualised treatment of hypocalcaemia should be considered in patients with CKD G3a-G5D. Mild and asymptomatic hypocalcaemia, especially in the context of calcimimetics treatment, may be tolerated in order to avoid a positive calcium balance.

4. Should limiting dietary phosphate intake be considered in the treatment of hyperphosphatemia?
Limiting dietary phosphate intake can be considered along with other treatments but it is also important to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations.

Guideline Recommendation Statements:

In patients with CKD G3a-G5D:

NEW **(4.1.1) Treatments of CKD-MBD should be based on serial assessments of phosphate, calcium and PTH levels, considered together. (Not Graded)**

NEW **(4.1.2) Suggest lowering elevated serum phosphate levels towards the normal range. (2C)**

NEW **(4.1.3) Suggest avoiding hypercalcemia in adult patients. (2C)**

- (4.1.4) In patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l) (2C).

NEW **(4.1.5) Decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. (Not Graded)**

NEW **(4.1.6) In adult patients receiving phosphate-lowering treatment, suggest restricting the dose of calcium-based phosphate binders. (2B)**

- (4.1.7) Recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients on dialysis, recommend avoiding dialysate aluminum contamination to prevent aluminum intoxication. (1C)

NEW **(4.1.8) Suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments. (2D) It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations. (Not Graded)**

- (4.1.9) In patients on dialysis, suggest increasing dialytic phosphate removal in the treatment of persistent hyperphosphatemia. (2C)

TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

CHAPTER 4.2

Expert Q&A

1. When should PTH-lowering therapies be considered in CKD G3a-G5 patients not yet on dialysis?
The optimal PTH level is not known and the guideline suggests that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency. Calcitriol and active vitamin D analogues should not be routinely used except in patients with severe and progressive hyperparathyroidism.

2. What PTH-lowering therapies can be considered in dialysis patients?
The Work Group had considered PTH-lowering treatments including calcimimetics, calcitriol, or vitamin D analogs as all acceptable first-line options in dialysis patients. The individual choice sould continued by guided by considerations about concomitant therapies and the present calcium and phosphate levels Choice of dialysate calcium concentrations (rec 4.1.4) should also be considered and parathyroidectomy remains a valid treatment option especially when other PTH-lowering therapies fail.

Guideline Recommendation Statements:

In patients with CKD G3a-G5 not on dialysis:

NEW **(4.2.1) The optimal PTH level is not known. However, suggest that patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency. (2C)**

NEW **(4.2.2) In adult patients, suggest calcitriol and vitamin D analogs not be routinely used. (2C) It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4-G5 with severe and progressive hyperparathyroidism. (Not Graded)**

In patients on dialysis:

- (4.2.3) Suggest maintaining intact PTH levels in the range of approximately two to nine times the upper normal limit for the assay. (2C) 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)

NEW **(4.2.4) For those requiring PTH-lowering therapy, suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs. (2B)**

- (4.2.5) In patients with CKD G3a-G5D with severe hyperparathyroidism who fail to respond to medical/pharmacological therapy, suggest parathyroidectomy. (2B)