KDIGO CKD-MBD
Quick Reference Guide

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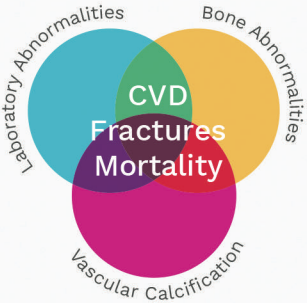
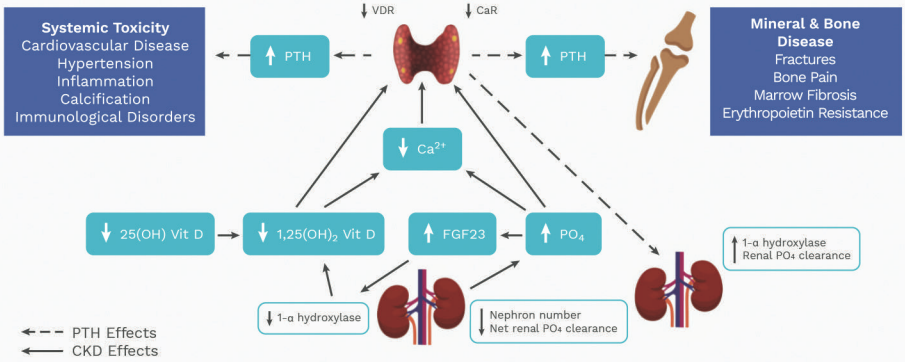
This guide presents the new recommendation statements (quoted in **bold and starred ★**) from the KDIGO 2017 *Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD)* with those that remained unchanged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

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.

Pathophysiology of Secondary Hyperparathyroidism in CKD



As kidney function declines in CKD, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphate (PO_4) and calcium (Ca), and changes in circulating levels of hormones. These include parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH) Vit D], 1,25 dihydroxyvitamin D [1,25 $(OH)_2$ Vit D], and fibroblast growth factor-23 (FGF-23). CaR, parathyroid calcium-sensing receptor; VDR, parathyroid vitamin D receptor

GFR Categories (ml/min/1.73 m^2)
Description and Range
Suffix "T" is added when referring to kidney transplant recipients

G1	Normal or high	≥90	G3b	Moderately to severely decreased	30-44
G2	Mildly decreased	60-89	G4	Severely decreased	15-29
G3a	Mildly to moderately decreased	45-59	G5	Kidney failure	<15

CHAPTER
3.1 DIAGNOSIS OF CKD-MBD: Biochemical Abnormalities

KEY CONCEPTS

- Assessment and monitoring for CKD-MBD [e.g., calcium, phosphate, PTH, alkaline phosphatases and 25(OH)D] should start as early as CKD G3a.
- It is important to take into account trends, rather than single values, to evaluate the changes in the degree of 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.
- The frequency of assessment should take into account the presence and duration of the identified abnormalities, the severity of the abnormalities, all in the context of the degree and rate of change in kidney function and the concomitant use of medications.

Frequency of Monitoring

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)	

What the Guideline Statements Say

In patients with CKD G3a-G5D:

- (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.

CHAPTER 3.2

DIAGNOSIS OF CKD-MBD: Bone

KEY CONCEPTS

- It is well established that patients with CKD G3a-G5D have increased fracture rates, compared with the general population; moreover, incident hip fractures are associated with substantial morbidity and mortality.
- Multiple new prospective studies have documented that lower 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.
- Bone biopsy remains an option to diagnose the type of renal osteodystrophy.
- Serum measurements of PTH and bone-specific alkaline phosphatase (b-ALP) are related to clinical outcomes, including relative risk of mortality. They also correlate with some of the histomorphometric measurements.
- Collagen-based markers of bone turnover, measured in the serum, show correlations with findings on bone biopsies but their diagnostic utility is limited.
- Collagen-based markers of bone turnover have not been extensively evaluated in patients with CKD G4-G5. The available studies show that these markers do not predict clinical outcomes or bone histology any better than do circulating PTH or b-ALP; therefore, they are not recommended for diagnostic purposes in patients with later-stage CKD-MBD.

What the Guideline Statements Say

In patients with CKD G3a-G5D:

- ★ **(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)**
- ★ **(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)

CHAPTER 3.3

DIAGNOSIS OF CKD-MBD: Vascular Calcification

KEY CONCEPTS

- 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.

What the Guideline Statements Say

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)

CHAPTER
4.1

TREATMENT OF CKD-MBD: Serum Phosphate and Calcium

KEY CONCEPTS

- Serum calcium, phosphate, and PTH are interdependent factors and the prognostic implications of these individual factors have been demonstrated to largely depend on their context with regard to the full array of CKD-MBD biomarkers.
- Clinical decisions should not be based on a single result, but on the trends of serial results, because these tests are influenced by a variety of factors. They may also have significant diurnal changes even in patients with CKD.
- Treatment should be aimed at overt hyperphosphatemia rather than prevention of hyperphosphatemia because:
  - The majority of studies found phosphate to be consistently associated with excess mortality at levels above and below the limits of normal but not in the normal range.
  - There is an absence of data supporting that efforts to maintain serum phosphate in the normal range are of benefit and there may be some safety concerns in patients with CKD G3a-G4.
- Phosphate-lowering treatment decisions should be based on progressively or persistently elevated serum phosphate.
- Avoid hypercalcemia and limit the use of calcium-containing phosphate binders in adults.
- Treatment of hypocalcemia should be individualized. Mild and asymptomatic hypocalcemia, especially in the context of calcimimetics treatment, may be tolerated in order to avoid a positive calcium balance.
- It is reasonable to consider phosphate source in making dietary recommendations.

What the Guideline Statements Say

In patients with CKD G3a-G5D:

- **(4.1.1) Treatments of CKD-MBD should be based on serial assessments of phosphate, calcium and PTH levels, considered together. (Not Graded)**
- **(4.1.2) Suggest lowering elevated serum phosphate levels towards the normal range. (2C)**
- **(4.1.3) Suggest avoiding hypercalcemia in adult patients. (2C)**
- **(4.1.5) Decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. (Not Graded)**
- **(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)
- **(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)

CHAPTER
4.2 TREATMENT OF ABNORMAL PTH LEVELS IN CKD-MBD

KEY CONCEPTS

- The optimal PTH level is not known in patients with CKD G3a-G5 not on dialysis.
- There is still an absence of randomized controlled trials (RCTs) that define an optimal PTH level for patients with CKD G3a-G5, or clinical endpoints of hospitalization, fracture, or mortality.
- Modest increases in PTH may represent an appropriate adaptive response to declining kidney function.
- Treatment should not be based on a single elevated PTH value but on progressively rising levels or levels persistently above the upper normal limit.
- Two recent RCTs of vitamin D analogs (PRIMO and OPERA) failed to demonstrate an improvement in surrogate cardiac endpoints but reported an increased risk of hypercalcemia.
- These results, combined with the opinion that moderate PTH elevations may represent an appropriate adaptive response, led to the conclusion that the risk-benefit ratio of treating moderate PTH elevations was no longer favorable.
- An alternative to calcitriol and its analogs is "nutritional" vitamin D supplementation (cholecalciferol and ergocalciferol) which can also suppress PTH (especially in CKD G3a-G3b) and decrease hypercalcemia; however, no studies of sufficient duration were identified in this evidence review, and thus this therapy remains unproven.
- The use of extended-release calcifediol, a novel vitamin D prohormone, to correct low serum 25(OH) vitamin D levels and lower PTH has also been recently studied.

What the Guideline Statements Say

In patients with CKD G3a-G5 not on dialysis:

★ **(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)**

★ **(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)

★ **(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)

CHAPTER 4.3

Treatment of Bone with Biphosphonates, Other Osteoporosis Medications, and Growth Hormone

KEY CONCEPTS

- When treatment choices are considered, their specific side effects must also be taken into account (e.g., antiresorptives will exacerbate low bone turnover, denosumab may induce significant hypocalcemia).
- Risk of treatment administration must be weighed against the accuracy of the diagnosis of the underlying bone phenotype.

What the Guideline Statements Say

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:

★ **(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)**

CHAPTER 5

KIDNEY TRANSPLANT BONE DISEASE

KEY CONCEPTS

- Fracture risk is four-fold higher in patients with end-stage kidney disease as compared to the general population and further increases in the early post-transplant period.
- Monitor and evaluate serum calcium, phosphate, and PTH following kidney transplant; base the frequency on the rate of progression of CKD.

What the Guideline Statements Say 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)

★ **(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)**

Frequency of Monitoring

Frequency of monitoring: CKD G1T-G5T

	Frequency of Monitoring	CKD G1T-G3T	CKD G4T	CKD G5T
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		✔	
	Once; subsequent intervals based on CKD progression	✔		
Alkaline Phosphatases	Every 12 Months or more frequently in presence of ↑PTH		✔ (CKD G3T-G5T)	

What the Guideline Statements Say 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)

★ **(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 m^2 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

What the Guideline Statements Say

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

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

★ **(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

★ **(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.**

This Guide was developed through the support of OPKO Health Renal Division. KDIGO is solely responsible for the content of this Guide.

OPKO HEALTH Renal Division