Guidelines

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Executive Summary: Clinical Practice Guideline of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD) in China

Zhi-Hong Liu[a] Guisen Li[b] Ling Zhang[c] Jianghua Chen[d] Xiaonong Chen[e] Jinghong Zhao[f] Xinling Liang[g] CKD-MBD Guideline Working Group and National Clinical Research Center for Kidney Disease

[a]Department of Nephrology, Nanjing General Hospital, National Clinical Research Center of Kidney Diseases, Nanjing, China; [b]Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science, Chengdu, China; [c]Department of Nephrology, Sino-Japanese Friendship Hospital, Beijing, China; [d]Department of Nephrology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [e]Department of Nephrology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [f]Department of Nephrology, Third Military Medical University, Chongqing, China; [g]Department of Nephrology, Guangdong General Hospital, Guangzhou, China

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Abstract
Chronic kidney disease (CKD) is a global health concern. The prevalence of CKD in Chinese adults is over 10%. Chronic kidney disease-mineral and bone disorder (CKD-MBD) is one of the complications of CKD, which may cause many serious adverse outcomes such as disability and death in CKD patients. In recent years, a series of guidelines for the diagnosis and treatment of CKD-MBD have been developed by several international organizations for kidney disease. In 2013, the working group developed the *Guidance for Diagnosis and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder*, which greatly promoted clinical management and researches of CKD-MBD in China. In the past five years, Chinese clinicians have been deepening their understanding and standardized management of CKD-MBD and implemented a large number of clinical and basic researches on CKD-MBD. In combination with international research results, the working group updated the guidelines. This guideline includes five chapters: introduction and definition of CKD-MBD; diagnosis of CKD-MBD; prevention and treatment of CKD-MBD; prevention and treatment of osteoporosis in patients with CKD; and evaluation and treatment of CKD-MBD in kidney transplant recipients; and five appendixes. In this summary, we highlight the main recommendations and suggestions of the guideline.

Chapter 1: Introduction and Definition of Chronic Kidney Disease–Mineral and Bone Disorder

The diagnosis and categories of chronic kidney disease (CKD) follow the concepts of Kidney Disease: Improving Global Outcomes (KDIGO). The definition of chronic kidney disease-mineral and bone disorder (CKD-MBD)

E-Mail karger@karger.com
www.karger.com/kdd

Prof. Zhihong Liu
Department of Nephrology, Nanjing General Hospital
National Clinical Research Center of Kidney Diseases
Nanjing 210002 (China)
E-Mail zhihong_liu@hotmail.com

Table 1. Monitoring frequency for MBD-related biochemical indicators at various stages of CKD

CKD stage	Serum phosphorus	Serum calcium	ALP	iPTH	25(OH)D
G1–G2	6–12 months	6–12 months	6–12 months	Determine based on the baseline level and CKD progression	
G3a/G3b	6–12 months	6–12 months	6–12 months	Determine based on the baseline level and CKD progression	Determine based on the baseline level and treatment interventions
G4	3–6 months	3–6 months	6–12 months, which can be shortened if iPTH is elevated	6–12 months	Determine based on the baseline level and treatment interventions
G5	1–3 months	1–3 months	6–12 months, which can be shortened if iPTH is elevated	3–6 months	Determine based on the baseline level and treatment interventions

MBD, mineral and bone disorder; CKD, chronic kidney disease; ALP, alkaline phosphatase; iPTH, intact parathyroid hormone. CKD G5 includes CKD G5D; CKD G1–G5T refers to CKD G1–G5.

was developed from the guideline of KDIGO: a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following: (1) abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; (2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; (3) vascular or other soft-tissue calcification.

Chapter 2: Diagnosis of CKD-MBD

2.1 Detection and Monitoring of Biochemical Abnormalities

2.1.1 For adult CKD patients, we suggest monitoring serum levels of calcium, phosphorus, iPTH, and alkaline phosphatase (ALP) activity, beginning in CKD G3a. We also suggest to detect serum level of 25(OH)D. (*Not Graded*)

2.1.2 For patients with CKD G3–G5D, the monitoring frequency can be determined according to the presence and magnitude of abnormalities in serum calcium, phosphorus, ALP, iPTH, and 25(OH)D levels, as well as the progression rate of CKD. Reasonable monitoring intervals are as follows (Table 1). (*Not Graded*)

1 Patients with CKD G3a–G3b: we suggest monitoring serum calcium, phosphorus, and ALP levels every 6–12 months; the interval of iPTH examinations can be determined by the baseline level of iPTH and the progression of CKD.
2 Patients with CKD G4: we suggest detecting serum calcium, phosphorus, and ALP levels every 3–6 months and detecting iPTH levels every 6–12 months.
3 Patients with CKD G5 and G5D: we suggest detecting serum calcium, phosphorus, and ALP levels every 1–3 months and detecting iPTH levels every 3–6 months.
4 Patients with CKD G4–G5D: we suggest detecting ALP levels every 6–12 months; if iPTH levels are elevated, the frequency of detection should be increased.
5 Patients with CKD G3a–G5D: we suggest detecting 25(OH)D levels and determining the frequency of repeated examination based on the baseline level and treatment interventions.

For CKD patients who have received treatment for serum biochemical abnormalities of CKD-MBD, it is reasonable to increase the frequency of measurements to monitor for trends, treatment efficacy and side effects.

2.1.3 For patients with CKD G3a–G5D, we recommend that therapeutic decisions should be based on trends rather than on a single laboratory value, taking into account all available assessments for CKD-MBD. (*1C*)

2.1.4 For patients with CKD G3a–G5D, we suggest that individual values of serum calcium and phosphorus, evaluated together, be used to guide clinical practice rather than the results of calcium-phosphorus product. (*2D*)

2.1.5 In the laboratory reports for patients with CKD stages G3a–G5D, we recommend that clinical laboratories should provide clinicians with information on the actually used assay method and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data. (*1B*)

2.2 Assessment of Bone Diseases

2.2.1 For patients with CKD G3a–G5 and CKD-MBD evidence, bone mineral density (BMD) cannot be used to predict the type of renal osteodystrophy. The predictive value of the risk of fracture in patients with CKD stages G3a–G5 still needs further evaluation. It is reasonable to perform BMD detection if knowledge of the type of renal osteodystrophy will impact treatment decisions. (*2B*)

2.2.2 Bone biopsy is the gold standard for the diagnosis of CKD-MBD. However, due to difficulties in clinical implementation and lack of data, bone biopsy is not recommended as a routine examination item for patients with CKD G3a–G5 and CKD-MBD evidence. (*Not Graded*)

For patients with the following indications, where conditions permit, bone biopsy is recommended to confirm the diagnosis: unexplained fracture, persistent bone pain, unexplained hypercalcemia, unexplained hypophosphatemia, possible aluminum toxicity, and prior to the use of bisphosphonate for the treatment of CKD-MBD. (*Not Graded*)

2.2.3 For patients with CKD G3a–G5, we recommend that measurements of serum iPTH and ALP or bone-specific ALP can be used to evaluate bone disease because markedly high or low values predict underlying bone turnover. (*2B*)

2.2.4 For patients with CKD G3a–G5, where conditions permit, bone-derived collagen metabolism markers can be detected to assess the severity of bone disease. (*2C*)

2.3 Detection and Evaluation of Vascular Calcification

2.3.1 Cardiovascular calcification assessment is recommended for patients with significant hyperphosphatemia requiring individualized high-dose phosphorus-binding agents for treatment, patients awaiting renal transplantation, patients with CKD G5D, and patients who are considered to be in need of examination after physician evaluation. (*Not Graded*)

2.3.2 For patients with CKD G3–G5D, lateral abdominal radiography can be used to detect vascular calcification, and echocardiography can be used to detect valvular calcification. Where conditions permit, electron beam tomography and multi-slice computed tomography can be used to assess cardiovascular calcification. (*2C*)

2.3.3 We suggest performing a cardiovascular calcification assessment every 6–12 months. (*Not Graded*)

2.3.4 We suggest that patients with CKD G3–G5D with known vascular/valvular calcification should be considered at the highest cardiovascular risk. (*2A*) It is reasonable to use this information to guide the management of CKD-MBD. (*Not Graded*)

Chapter 3: Prevention and Treatment of CKD-MBD

3.1 Lowering High Serum Phosphorus and Maintaining Serum Calcium

3.1.1 For patients with CKD G3a–G5D, treatment of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together. (*Not Graded*)

3.1.2 For patients with CKD G3a–G5D, we suggest lowering elevated phosphate levels toward the normal range. (*2C*)

3.1.3 For adult patients with CKD G3a–G5D, we suggest avoiding hypercalcemia. (*2C*)

3.1.4 For patients with CKD G3a–G5D whose serum phosphorus exceeds the target value, we suggest reducing dietary phosphorus intake (800–1,000 mg/day) alone or in combination with other phosphorus reduction treatment. (*2D*)

We suggest restricting the total amount of protein intake, choosing foods with low phosphorus/protein ratio and low phosphorus absorption rate, and avoiding the intake of foods containing large amounts of phosphate additives. (*Not Graded*)

3.1.5 For patients with CKD G5D, we recommend professional intensive education to improve serum phosphorus management. (*2B*)

3.1.6 For patients with CKD G5D, we suggest using a dialysate calcium concentration between 1.25 and 1.50 mmol/L (hemodialysis) or 1.25 mmol/L (peritoneal dialysis). (*2C*)

3.1.7 We suggest that patients with CKD G5D on hemodialysis should receive adequate dialysis, and increased time or frequency of dialysis would be more effectively removing serum phosphorus. (*2C*)

3.1.8 For patients with CKD G3a–G5D, we suggest starting phosphate-lowering treatment, while serum

phosphorus is progressively and persistently elevated. (*Not Graded*)

3.1.9 For patients with CKD G3a–G5D receiving phosphate-lowering treatment, we suggest restricting the dose of calcium-based phosphate binders. (*2B*)

3.1.10 For patients with CKD G3a–G5D, individualization of the use of phosphorus-binding agents should be emphasized. (*Not Graded*)

3.1.11 For patients with CKD G3a–G5D, the importance of secondary hyperthyroidism (SHPT) management should be taken into account during the management of abnormalities of serum calcium and phosphorus. (*Not Graded*)

3.2 Treatment of SHPT

3.2.1 The target iPTH for non-dialysis patients with CKD G3a–G5: the optimal PTH level for non-dialysis patients with CKD G3a–G5 is currently not known. We suggest that patients with progressively elevated iPTH levels or iPTH persistently above the upper normal limit for the assay be evaluated for modifiable factors: hyperphosphatemia, hypocalcemia, high phosphorus intake, and vitamin D deficiency. (*2C*)

3.2.2 For patients with CKD G5D, we suggest maintaining iPTH levels in the range of approximately 2–9 times the upper normal limit for the assay. (*2C*)

3.2.3 For adult patients with CKD G3a–G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used. (*2C*) Patients with CKD G4–G5 with severe and progressive hyperparathyroidism could use calcitriol and vitamin D analogs. (*Not Graded*)

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

3.2.4 For patients with CKD G5D requiring PTH-lowering therapy, we recommend calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs. (*2B*)

3.2.5 Indication for parathyroidectomy: patients with CKD G3a–G5D complicated with severe SHPT for which medical therapy has proven ineffective are recommended to receive parathyroidectomy. (*2B*)

3.2.6 Parathyroidectomy is recommended under the following conditions: (*Not Graded*)

1 iPTH is persistently more than 800 pg/mL;
2 Persistent hypercalcemia and/or hyperphosphatemia for which medical therapy has proven ineffective;
3 There is imaging evidence of at least one enlargement of the parathyroid glands. For example, high-frequency color ultrasound shows enlarged parathyroid glands, >1 cm in diameter with abundant blood flow;
4 There is previous resistance to active vitamin D and its analogues.

Severe SHPT is defined as serum iPTH persistently >800 pg/mL.

3.2.7 There are three main types of parathyroidectomy: total parathyroidectomy + autologous transplantation, subtotal parathyroidectomy, and total parathyroidectomy. (*Not Graded*)

3.3 Prevention and Management of Vascular Calcification

3.3.1 We suggest treating hyperphosphatemia in patients with CKD to reduce the risk of vascular calcification. The prevention and treatment methods include restricting dietary phosphorus intake, selecting an appropriate phosphorus binder, receiving adequate dialysis, or increasing the removal of phosphorus by dialysis, as well as effectively controlling SHPT. (*Not Graded*)

3.3.2 For patients with CKD G3a–G5D requiring phosphorus binder therapy, we suggest restricting the dose of calcium-containing phosphate binders. (*2B*)

3.3.3 We suggest avoiding hypercalcemia in patients with CKD to reduce the risk of vascular calcification. We suggest using a dialysate with a calcium concentration between 1.25 and 1.5 mmol/L. (*2C*) We suggest to accurately grasp the indications of calcium-containing drugs and active vitamin D and its analogues. (*Not Graded*)

3.3.4 We suggest managing SHPT by appropriately using active vitamin D and its analogues and calcimimetics or parathyroidectomy. Serum calcium and phosphorus levels should be monitored during treatment to avoid hypercalcemia and hyperphosphatemia. (*Not Graded*)

Chapter 4: Prevention and Treatment of Osteoporosis in Patients with CKD

4.1 Diagnosis and Evaluation of Osteoporosis

4.1.1 We suggest the monitoring frequency of biochemical parameters in osteoporotic CKD patients not on dialysis should refer to the CKD G3 regimen: (*Not Graded*)

1 Monitor serum calcium, phosphorus, and ALP levels every 6–to 12 months;

2 Determine the interval between iPTH tests according to the baseline level of iPTH and the progression of CKD;
3 We suggest detecting 25(OH)D levels and determining the frequency of repeated examination based on the baseline level and treatment interventions.

4.1.2 We suggest measuring the BMD of the lumbar spine and hip in patients with CKD G1–G2 regularly to evaluate patients with osteoporosis. (*Not Graded*)

4.1.3 We recommend measuring the BMD in CKD G3a–G5D patients with CKD-MBD and/or risk of osteoporosis to evaluate the risk of fracture. (*2B*)

4.1.4 We recommend predicting the risk of osteoporotic fracture in patients with CKD. The more widely used prediction methods are the Asian Osteoporosis Self-screening Tool (OSTA) and the WHO fracture risk assessment tool (FRAX). (*Not Graded*)

4.2 Basic Therapy of Osteoporosis

Lifestyle change is important for the prevention and treatment of osteoporosis. The main measures include: keep a balanced diet, take appropriate exercise, avoid smoking and drinking alcohol, be careful as drugs may interfere with bone metabolism, try to prevent falls, as well as strengthen oneself and environmental protection measures.

4.3 Timing of Treatment for Osteoporosis

4.3.1 Drug treatment should be considered if one of the following conditions is met: (*Not Graded*)

1 Patients diagnosed with osteoporosis (BMD: t value ≤ -2.5) with or without fractures;
2 Patients with low bone mass (BMD: $-2.5 < t$ value ≤ -1.0) and more than one risk factor for osteoporosis with or without fractures;
3 When there is no condition for BMD measurement, drug treatment should also be considered if one of the following conditions is met: (1) the patient has experienced a fragile fracture; (2) OSTA screening shows that the subject is at high risk; (3) the hip fracture probability calculated with the FRAX tool is ≥3%, or the probability of occurrence of osteoporotic fractures in any important part is ≥20%.

4.4 Medications for Osteoporosis

4.4.1 Indications for the use of bisphosphonates in patients with CKD:

1 In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, we recommend using bisphosphonates as for the general population; (*2B*)
2 In patients with CKD G3–G4 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; (*Not Graded*)
3 In patients with CKD G5, we suggest to exclude adynamic bone disease based on biochemical abnormalities or bone biopsy when using bisphosphonate. (*2B*)

4.4.2 In CKD patients with osteoporosis and/or high risk of fracture, the use of bisphosphonates should be based on the characteristics of each drug. (*Not Graded*)

4.4.3 In CKD patients with osteoporosis and/or high risk of fracture, we suggest that patients with bisphosphonate should be considered for their type of bone turnover, renal function, and bisphosphonate characteristics, as well as adverse drug reactions. (*Not Graded*)

4.4.4 In CKD patients with osteoporosis and/or high risk of fracture, we recommend treating with active vitamin D and analogues and calcium:

1 In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, we recommend the same treatment regimen as for the general population. (*2B*)
2 In patients with CKD G3a–G3b who have a PTH level within the normal range, osteoporosis, and/or high risk of fracture, we recommend the same treatment regimen as for the general population. (*2B*)
3 In patients with CKD G3a–G5D with biochemical abnormalities of CKD-MBD, and/or 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*)

4.4.5 Indications for calcitonin therapy in patients with CKD include:

1 In patients with osteoporosis for whom other drug treatments have proven ineffective, such as high turnover osteoporosis, senile osteoporosis, and glucocorticoid-induced osteoporosis, we recommend supplementing calcium and vitamin D according to individual needs to prevent progressive loss of bone mass; (*2B*)
2 Bone pain due to osteolysis or osteopenia; (*Not Graded*)
3 CKD patients with severe hypercalcemia. (*2B*)

4.4.6 In patients with female postmenopausal osteoporosis and male primary or sexually impaired osteoporosis and glucocorticoid-induced osteoporosis with high risk

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of fracture, especially those for whom antiresorptive agents have proven ineffective, recombinant PTH can increase bone density and improve bone remodeling. We recommend recombinant PTH for treatment. (*2C*)

4.4.7 In patients with CKD G1–G2 with estrogen deficiency-induced osteoporosis, such as menopausal women under the age of 60 or postmenopausal women, especially with menopausal symptoms and genitourinary atrophy, estrogen agents could be used for the treatment of osteoporosis. (*2B*)

4.4.8 In patients with CKD G1–G2 with severe osteoporosis or fractures, women who are definitely diagnosed with postmenopausal osteoporosis can be treated with estrogen receptor modulators (2B); postmenopausal women with CKD G3–G5D can consider using estrogen receptor modulators when PTH is well controlled. (*Not Graded*)

Chapter 5: Evaluation and Treatment of CKD-MBD in Kidney Transplant Recipients

5.1 Diagnosis of Bone Diseases in Kidney Transplant Recipients

5.1.1 At the early stage of renal transplantation, we recommend measuring serum levels of calcium and phosphorus at least weekly until they are stable. (*1B*)

5.1.2 After the early stage of renal transplantation, the monitoring frequency of serum calcium, phosphorus, and iPTH levels depends on the magnitude of the biochemical abnormalities and the progression rate of CKD. (*Not Graded*)

The recommended interval is:

1 In patients with CKD G1T–G3T: serum calcium and phosphorus levels should be detected every 6–12 months; after the first detection of iPTH, the frequency of iPTH testing should be determined based on the baseline level and progression rate of CKD;
2 In patients with CKD G4T: serum calcium and phosphorus levels should be detected every 3–6 months, and iPTH levels every 6–12 months;
3 In patients with CKD G5T: serum calcium and phosphorus levels should be detected every 1–3 months, and iPTH levels every 3–6 months;
4 In patients with CKD G3T–G5T, ALP activity should be detected every 6–12 months; if there is a trend for increasing iPTH level, the frequency of detection could be increased.

For kidney transplant recipients receiving CKD-MBD treatment or those who have biochemical abnormalities, the detection frequency could be reasonably increased to monitor for trends, treatment efficacy, and adverse drug reaction. (*Not Graded*)

5.1.3 For patients with CKD G1T–G5T, we recommend investigating serum level of 25(OH)D and determining the frequency of repeated detection based on baseline values and treatment intervention. (*2C*)

5.1.4 For patients with CKD G1T–G5T with risk for osteoporosis, while the values of BMD could change the treatment strategy, it is recommended to detect BMD to assess the risk of fracture. (*2C*)

5.2 Management of Biochemical Abnormalities

5.2.1 In patients with biochemical abnormalities, including abnormal calcium, phosphorus, iPTH, and other abnormalities, for the recommend treatment regimen refer to that of patients with CKD G3–G5. (*Not Graded*)

5.3 Management of Vitamin D Deficiency and Insufficiency

5.3.1 In kidney transplant recipients with vitamin D deficiency and insufficiency, we recommend the same correcting regimen as for the population at the corresponding stage of CKD. (*2C*)

5.4 Treatment of Low BMD

5.4.1 For patients with eGFR >30 mL/(min × 1.73 m^2) and low BMD within 12 months after renal transplantation, we recommend treatment with vitamin D, active vitamin D and its analogues, or bisphosphonates. (*2D*)

1 The presence or absence of CKD-MBD should be considered during the selection of a therapeutic agent; it should be based on assessments of calcium, phosphorus, PTH, ALP, and 25(OH)D. (*2C*)
2 A bone biopsy can be considered to guide treatment. (*Not Graded*)
3 There is currently not enough data to guide the treatment of patients beyond 12 months after renal transplantation.

5.4.2 For patients with CKD G4T–G5T and reduced BMD, the recommended treatment regimen is similar to that for patients with CKD G4–G5 not on dialysis. (*2C*)

5.5 Medications of Low BMD

5.5.1 In renal transplantation recipients, vitamin D and active vitamin D might be beneficial in preventing BMD reduction. (*Not Graded*)

5.5.2 In kidney transplant recipients, the effect of bisphosphonates in the prevention and treatment of osteoporosis is still unclear.

5.6 Parathyroidectomy in Renal Transplant Recipients

5.6.1 We recommend that parathyroidectomy would be performed when persistent hypercalcemia occurs after renal transplantation. (*2D*)

5.6.2 In recipients with stable renal function and not on dialysis, parathyroidectomy or autologous transplantation is not recommended. Instead, it is recommended to remove only the parathyroid adenoma or adenoma-like tissue or to perform subtotal parathyroidectomy. (*Not Graded*)

Disclosure Statement

The authors have no conflicts of interest to disclose.

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