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APPENDICES

APPENDIX A

K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease 2003 (Statement)

GUIDELINE 1. EVALUATION OF CALCIUM AND PHOSPHORUS METABOLISM (p S52)

1.1 Serum levels of calcium, phosphorus, and intact plasma parathyroid hormone (PTH) should be measured in all patients with CKD and GFR <60 mL/min/1.73 m^2. (EVIDENCE) The frequency of these measurements should be based on the stage of chronic kidney disease (Table 17). (OPINION)

Table 17 Frequency of Measurement of PTH and Calcium/Phosphorus by Stage of CKD.

CKD Stage	GFR Range (mL/min/1.7 m^2)	Measurement of PTH	of Measurement of Calcium/Phosphorus
3	30-59	Every 12 months	Every 12 months
4	15-29	Every 3 months	Every 3 months
5	<15 or dialysis	Every 3 months	Every months

1.2 These measurements should be made more frequently if the patient is receiving concomitant therapy for the abnormalities in the serum levels of calcium, phosphorus, or PTH, as detailed in Guidelines 4, 5, 7, and 8, and in transplant recipient, Guideline 16.

1.3 Measurement of plasma PTH levels may be done less frequently for those with levels within the low end of the target levels (Table 15). (OPINION)

1.4 The target range of plasma levels of intact PTH in the various stages of CKD are denoted in Table 18.

Table 18 Target Range of Intact Plasma PTH by Stage of CKD.

CKD Stage	GFR Range (mL/min/1.7 m^2)	Target "intact" PTH (pg/mL[pmol/L])
3	30-59	35-70[3.85-7.7 pmol/l] (OPINION)
4	15-29	70-110[7.7-12.1] pmol/L
5	<15 or dialysis	

GUIDELINE 2. ASSESSMENT OF BONE DISEASE ASSOCIATED WITH CKD (p S57)

2.1 The most accurate diagnostic test for determining the type of bone disease associated with CKD is iliac crest bone biopsy with double tetracycline labeling and bone histomorphometric analysis. (EVIDENCE)

2.2 It is not necessary to perform bone biopsy for most situations in clinical practice. However, a bone biopsy should be considered in patients with kidney failure (Stage 5) who have:

2.2a Fractures with minimal or no trauma (pathological fractures); (OPINION)

2.2b Intact plasma PTH levels between 100 and 500 pg/mL (11.0 to 55.0 pmol/L) (in CKD Stage 5) with coexisting conditions such as unexplained hypercalcemia, severe bone pain, or unexplained increases in bone alkaline phosphatase activity; (OPINION) 2.2c Suspected aluminum bone disease, based upon clinical symptoms or history of aluminum exposure. (OPINION) (See Guideline 11)

2.3 Bone radiographs are not indicated for the assessment of bone disease of CKD, (EVIDENCE) but they are useful in detecting severe peripheral vascular calcification (OPINION) and bone disease due to β2 microglobulin amyloidosis. (See Guideline 10) (EVIDENCE)

2.4 Bone mineral density (BMD) should be measured by dual energy X-ray absorptiometry (DEXA) in patients with fractures and in those with known risk factors for osteoporosis. (OPINION)

GUIDELINE 3. EVALUATION OF SERUM PHOSPHORUS LEVELS (p S62)

3.1 In CKD patients (Stages 3 and 4), the serum level of phosphorus should be maintained at or above 2.7 mg/dL (0.87 mmol/L) (EVIDENCE) and no higher than 4.6 mg/dL (1.49 mmol/L). (OPINION)

3.2 In CKD patients with kidney failure (Stage 5) and those treated with hemodialysis or peritoneal dialysis, the serum levels of phosphorus should be maintained between 3.5 to 5.5 mg/dL (1.13 to 1.78 mmol/L). (EVIDENCE)

GUIDELINE 4. RESTRICTION OF DIETARY PHOSPHORUS IN PATIENTS WITH CKD (p S63)

4.1 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted for dietary protein needs) when the serum phosphorus levels are elevated >4.6 mg/dL (1.49 mmol/L) at Stages 3 and 4 of CKD, (OPINION) and >5.5 mg/dL (1.78 mmol/L) in those with kidney failure (Stage 5). (EVIDENCE)

4.2 Dietary phosphorus should be restricted to 800 to 1,000 mg/day (adjusted to dietary protein needs) when the plasma levels of intact PTH are elevated above target range of the CKD Stage (see Table 15 in Guideline 1). (EVIDENCE)

4.3 The serum phosphorus levels should be monitored every month following the initiation of dietary phosphorus restriction. (OPINION)

GUIDELINE 5. USE OF PHOSPHATE BINDERS IN CKD (p S70)

In CKD Patients (Stages 3 and 4):

5.1 If phosphorus or intact PTH levels cannot be controlled within the target range (see Guidelines 1, 3), despite dietary phosphorus restriction (see Guideline 4), phosphate binders should be prescribed. (OPINION)

5.2 Calcium-based phosphate binders are effective in lowering serum phosphorus levels (EVIDENCE) and may be used as the initial binder therapy. (OPINION)

In CKD Patients with Kidney Failure (Stage 5):

5.3 Both calcium-based phosphate binders and other noncalcium-, nonaluminum-, and nonmagnesium-containing phosphate-binding agents (such as sevelamer HCl) are effective in lowering serum phosphorus levels (EVIDENCE) and either may be used as the primary therapy. (OPINION)

5.4 In dialysis patients who remain hyperphosphatemic (serum phosphorus >5.5 mg/dL [1.78 mmol/L]) despite the use of either of calcium-based phosphate binders or other noncalcium-, nonaluminum-, nonmagnesium-containing phosphate-binding agents, a combination of both should be used. (OPINION)

5.5 The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg/day (OPINION), and the total

intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day. (OPINION)

5.6 Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcemic (corrected serum calcium of >10.2 mg/dL [2.54 mmol/L]), or whose plasma PTH levels are <150 pg/mL (16.5 pmol/L) on 2 consecutive measurements. (EVIDENCE)

5.7 Noncalcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft-tissue calcifications. (OPINION)

5.8 In patients with serum phosphorus levels >7.0 mg/dL (2.26 mmol/L), aluminum-based phosphate binders may be used as a short-term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate binders. (OPINION) In such patients, more frequent dialysis should also be considered. (EVIDENCE)

GUIDELINE 6. SERUM CALCIUM AND CALCIUM-PHOSPHORUS PRODUCT (p S77)

In CKD Patients (Stages 3 and 4):

6.1 The serum levels of corrected total calcium should be maintained within the "normal" range for the laboratory used. (EVIDENCE)

In CKD Patients With Kidney Failure (Stage 5):

6.2 Serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION)

6.3 In the event corrected total serum calcium level exceeds 10.2 mg/dL (2.54 mmol/L), therapies that cause serum calcium to rise should be adjusted as follows:

6.3a In patients taking calcium-based phosphate binders, the dose should be reduced or therapy switched to a noncalcium-, nonaluminum-, nonmagnesium-containing phosphate binder. (OPINION) See Guideline 5.

6.3b In patients taking active vitamin D sterols, the dose should be reduced or therapy discontinued until the serum levels of corrected total

calcium return to the target range (8.4 to 9.5 mg/dL [2.10 to 2.37 mmol/L]). (OPINION) See Guideline 8B.

6.3c If hypercalcemia (serum levels of corrected total calcium >10.2 mg/dL [2.54 mmol/L]) persists despite modification of therapy with vitamin D and/or discontinuation of calcium-based phosphate binders, dialysis using low dialysate calcium (1.5 to 2.0 mEq/L) may be used for 3 to 4 weeks. (OPINION) See Guideline 9.

In CKD Patients (Stages 3 to 5):

6.4 Total elemental calcium intake (including both dietary calcium intake and calcium-based phosphate binders) should not exceed 2,000 mg/day. (OPINION) See Guideline 5.

6.5 The serum calcium-phosphorus product should be maintained at <55 mg2/dL2. (EVIDENCE) This is best achieved by controlling serum levels of phosphorus within the target range. (OPINION) See Guidelines 3, 4, and 5.

6.6 Patients whose serum levels of corrected total calcium are below the lower limit for the laboratory used (<8.4 mg/dL [2.10 mmol/L]) should receive therapy to increase serum calcium levels if:

6.6a There are clinical symptoms of hypocalcemia such as paresthesia, Chvostek's and Trousseau's signs, bronchospasm, laryngospasm, tetany, and/or seizures (OPINION); or

6.6b The plasma intact PTH level is above the target range for the CKD Stage. (See Table 15 in Guideline 1.) (OPINION)

6.7 Therapy for hypocalcemia should include calcium salts such as calcium carbonate (EVIDENCE) and/or oral vitamin D sterols. (EVIDENCE) See Guideline 8B.

GUIDELINE 7. PREVENTION AND TREATMENT OF VITAMIN D INSUFFICIENCY AND VITAMIN D DEFICIENCY IN CKD PATIENTS (Algorithm 1) (p S84)

In CKD Patients (Stages 3 and 4):

7.1 If plasma intact PTH is above the target range for the stage of CKD (Table 15, Guideline 1) serum 25-hydroxyvitamin D should be measured at first encounter. If it is normal, repeat annually. (EVIDENCE)

7.2 If the serum level of 25-hydroxyvitamin D is <30 ng/mL, supplementation with vitamin D2 (ergocalciferol) should be initiated (Table 26). (OPINION)

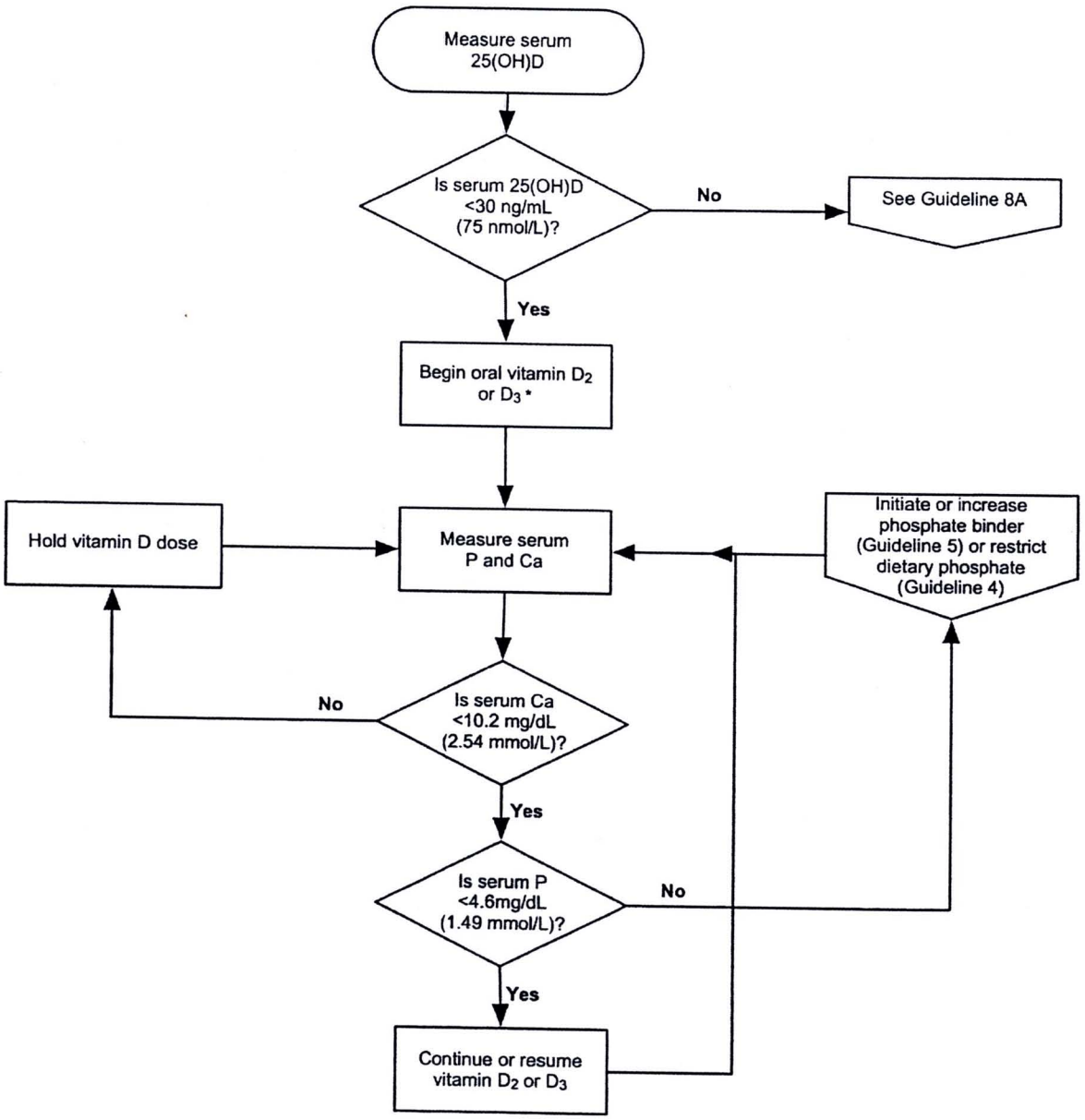
7.3 Following initiation of vitamin D therapy:

7.3a The use of ergocalciferol therapy should be integrated with the serum calcium and phosphorus (Algorithm 1).

7.3b The serum levels of corrected total calcium and phosphorus should be measured at least every 3 months. (OPINION)

7.3c If the serum levels of corrected total calcium exceeds 10.2 mg/dL (2.54 mmol/L), discontinue ergocalciferol therapy and all forms of vitamin D therapy. (OPINION)

In CKD patients with serum P <4.6 mg/dL (1.99 mmol/L), serum Ca <9.5 mg/dL (2.37 mmol/L), and serum PTH in the higher level of the target range for CKD stage (Stage 3: 35-70 pg/mL [3.85-7.7 pmol/L]; Stage 4: 70-110 pg/mL [7.7-12.1 pmol/L])



* Vitamin D_2 (ergocalciferol) may be safer than D_3 (cholecalciferol). When the 25(OH)D level is <15 ng/ml (37 nmol/L), 50,000 IU weekly for 4 doses followed by monthly for 4 doses is effective. With 25(OH)D levels of 20-30 ng/mL (50-75 nmol/L), 50,000 IU monthly for 6 months is recommended

Algorithm 1. Vitamin D supplementation in CKD (Stages 3 and 4).

Table 19 Recommended Supplementation for vitamin D Deficiency/Insufficiency in Patients with CKD Stages 3 and 4.

Serum 25 (OH)D (ng/mL) [nmol/L]	Definition	Ergocalciferol Dose (Vitamin D_2)	Duration (monthe)	Comment
<5 [12]	Severe vitamin D deficiency	50,000 IU/wk orally x 12 Wks; then monthly	6 months	Measure 25 (OH) D levels after 6 months
5-15 [12-37]	Mild Vitamin D Deficiency	500,000 IU/wk x 4 weeke, Then 50,000 IU/month Orally	6 months	Assure patient adherence; Measure 25 (OH)D at 6 months
16-30 [40-75]	Vitamin D Insufficiency	50,000 IU/month orally	6 months	Measure 25 (OH)D levels after 6 months

7.3d If the serum phosphorus exceeds 4.6 mg/dL, add or increase the dose of phosphate binder. (See Guidelines 4 and 5.) If hyperphosphatemia persists, discontinue vitamin D therapy. (OPINION)

7.3e Once patients are replete with vitamin D, continued supplementation with a vitamin-D–containing multi-vitamin preparation should be used with annual reassessment of serum levels of 25-hydroxyvitamin D, and the continued assessment of corrected total calcium and phosphorus every 3 months. (OPINION)

In CKD Patients With Kidney Failure (Stage 5):

7.4 Therapy with an active vitamin D sterol (calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) should be provided if the plasma levels of intact PTH are >300 pg/mL. (OPINION) See Guideline 8B.

GUIDELINE 8. VITAMIN D THERAPY IN CKD PATIENTS (p S89)

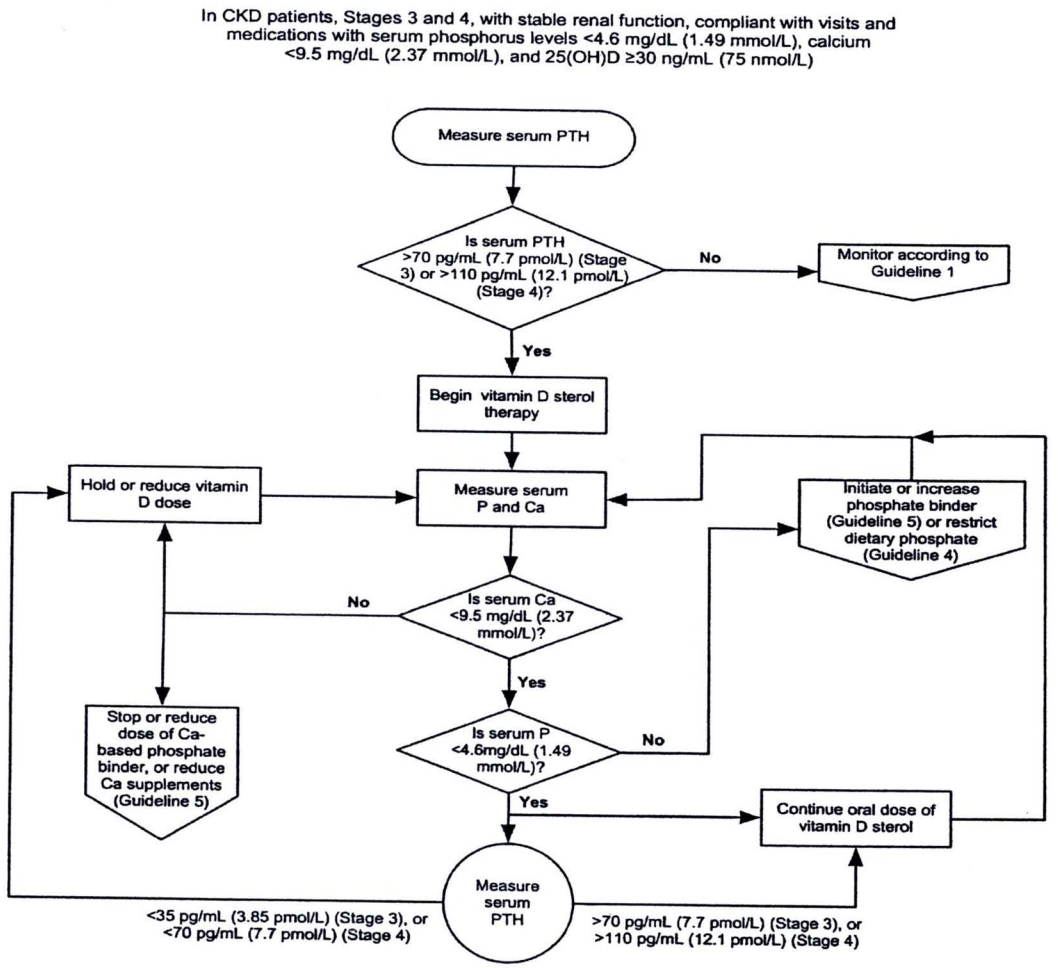
This Guideline encompasses 2 parts: Guideline 8A, which deals with active vitamin D sterol therapy in CKD Stages 3 and 4, and Guideline 8B, which deals with CKD Stage 5.

GUIDELINE 8A. ACTIVE VITAMIN D THERAPY IN PATIENTS WITH STAGES 3 AND 4 CKD (Algorithm 2) (p S89)

8A.1 In patients with CKD Stages 3 and 4, therapy with an active oral vitamin D sterol (calcitriol, alfacalcidol, or doxercalciferol) is indicated when serum levels of 25(OH)vitamin D are >30 ng/mL (75 nmol/L) and plasma levels of intact PTH are above the target range for the CKD stage (see Table 15, Guideline 1). (EVIDENCE) The initial doses are provided in Table 20.

Table 20 Serum Levels of PTH Calcium and Phosphate for Initiation of Oral Vitamin D Sterol Therapy, and Recommended Initial Doses in Patients with stages 3 and 4

Plasma PTH pg/mL or [pmol/L]	Serum Ca mg/dL [mmol/L]	Serum P mg/dL [mmol/l]	Dose Oral Calcitriol	Dose Oraql Alfacalcidol	Dose Oral Doxercalciferol
>70 [7.7] (CKD Stage 3) or >110 [12.1] (CKD Stage 4)	<95 [2.37]	<4.6 [1.49]	0.25µ g/day	0.25µ g/day	0.25µ g 3x/week



Oral active vitamin D sterols available include calcitriol, alfacalcidol, and doxercalciferol; calcitriol (USA, Canada) and alfacalcidol (Canada and Europe) are approved for use in CKD, Stages 3 and 4. Initial doses should be low (calcitriol 0.25 µg/day or alfacalcidol, 0.25 µg/day). The dose of calcitriol should rarely exceed 0.5 µg/day and then only if the corrected levels of calcium increase by less than 0.2-0.3 mg/dL.

Algorithm 2. Management of CKD patients (Stages 3 and 4) with active Vitamin D sterols.

8A.1 a Treatment with an active vitamin D sterol should be undertaken only in patients with serum levels of corrected total calcium <9.5 mg/dL (2.37 mmol/L) and serum phosphorus <4.6 mg/dL (1.49 mmol/L). (OPINION)

8A.1 b Vitamin D sterols should not be prescribed for patients with rapidly worsening kidney function or those who are noncompliant with medications or follow-up. (OPINION)

Table 21 Recommended Initial Dosing for Vitamin D Sterols by Serum Levels of Intact PHT, Calcium, Phosphorus, and Ca-P Product.

Plasma PTH pg/mL or [pmol/L]	Serum Ca Mg/dL [mmol/L]	Serum P Mg/dL [mmol/L]	Ca-P product	Dose per HD Calcitriolt*	Dose per HD Paricalcitol*	Dose per HD Doxercalciferolt*
300-600 [33-36]	<9.5[2.37]	<5.5 [1.78]	<55	IV: 0.5-1.5 μ g Oral: 0.5-1.5 μ g	2.5-5.0 μ g	Oral: 5 μ g IV: 2 μ G
600-1000 [66-110]	<9.5[2.37]	<5.5 [1.78]	<55	IV: 1.0-3.0 μ g Oral: 1-4 μ g	6.0-10 μ g	Oral: 5-10 μ g IV: 2-4 μ G
>1000 [110]	<10.0 [2.50]	<5.5 [1.78]	<55	IV: 3.0-5.0 μ g Oral: 3.7 μ g	10-15 μ g	Oral: 10-20 μ g IV: 4-8 μ G

*Intravenous, [t] Oral

8A.2 During therapy with vitamin D sterols, serum levels of calcium and phosphorus should be monitored at least every month after initiation of therapy for the first 3 months, then every 3 months thereafter. Plasma PTH levels should be measured at least every 3 months for 6 months, and every 3 months thereafter. (OPINION)

8A.3 Dosage adjustments for patients receiving active vitamin D sterol therapy should be made as follows:

8A.3a If plasma levels of intact PTH fall below the target range for the CKD stage (Table 15, Guideline 1), hold active vitamin D sterol therapy until plasma levels of intact PTH rise to above the target range, then resume treatment with the dose of active vitamin D sterol reduced by half. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)

8A.3b If serum levels of corrected total calcium exceed 9.5 mg/dL (2.37 mmol/L), hold active vitamin D sterol therapy until serum calcium returns to <9.5 mg/dL (2.37 mmol/L), then resume treatment at half the previous dose. If the lowest daily dose of the active vitamin D sterol is being used, reduce to alternate-day dosing. (OPINION)

8A.3c If serum levels of phosphorus rise to >4.6 mg/dL (1.49 mmol/L), hold active vitamin D therapy, initiate or increase dose of phosphate binder until the levels of serum phosphorus fall to <4.6 mg/dL (1.49 mmol/L); then resume the prior dose of active vitamin D sterol. (OPINION)

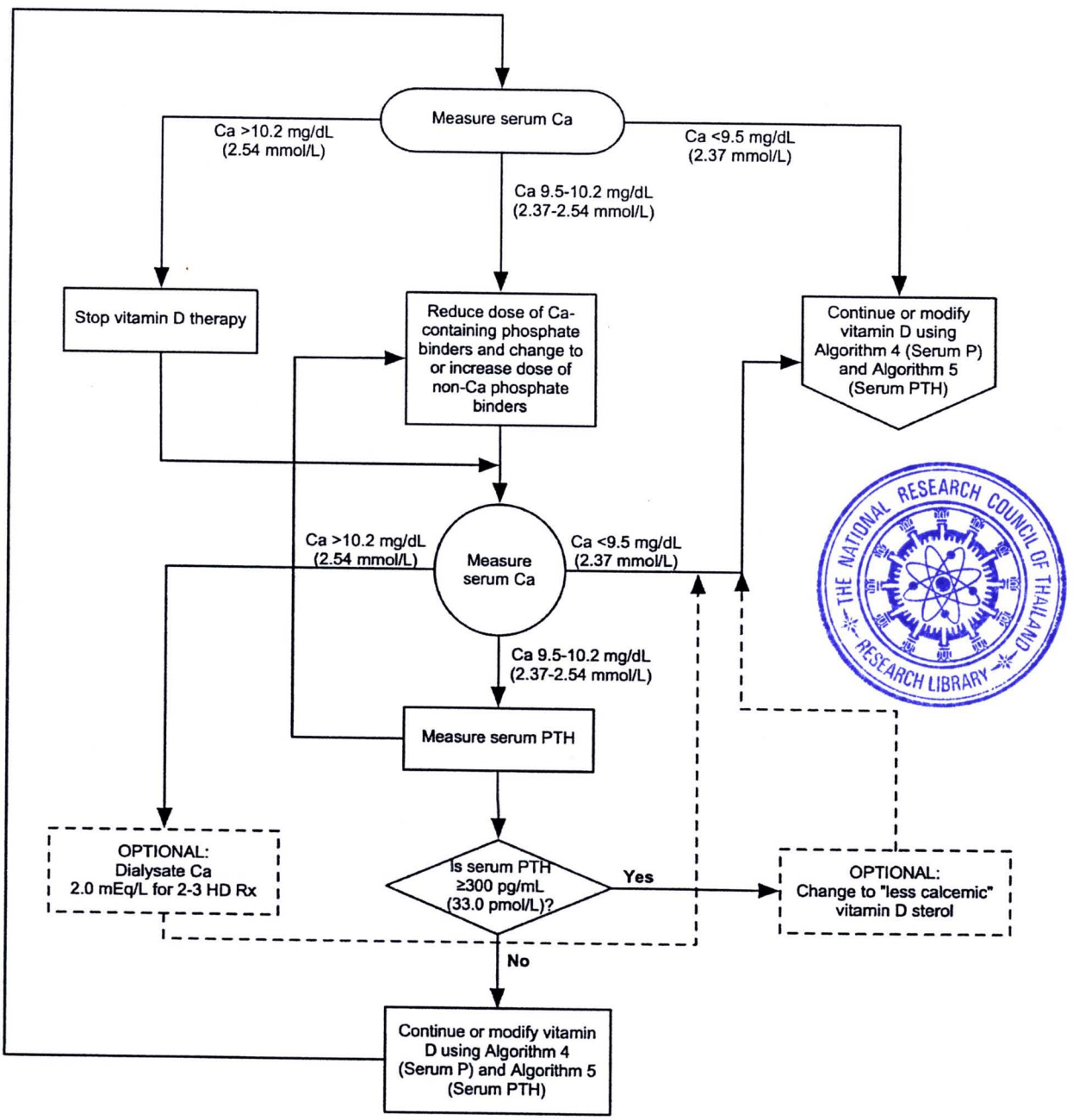
GUIDELINE 8B. VITAMIN D THERAPY IN PATIENTS ON DIALYSIS (CKD STAGE 5) (p S92)

8B.1 Patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol; see Table 28) to reduce the serum levels of PTH to a target range of 150 to 300 pg/mL. (EVIDENCE) 8B.1a The intermittent, intravenous administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels. (EVIDENCE) 8B.1b In patients with corrected serum calcium and/or phosphorus levels above the target range (see Guidelines 3 and 6, respectively), a trial of alternative vitamin D analogs, such as paricalcitol or doxercalciferol may be warranted. (OPINION)

8B.2 When therapy with vitamin D sterols is initiated or the dose is increased, serum levels of calcium and phosphorus should be monitored at least every 2 weeks for 1 month and then monthly thereafter. The plasma PTH should be measured monthly for at least 3 months and then every 3 months once target levels of PTH are achieved. (OPINION) 8B.3 For patients treated with peritoneal dialysis, oral doses of calcitriol (0.5 to 1.0 μg) or doxercalciferol (2.5 to 5.0 μg) can be given 2 or 3 times weekly. Alternatively, a lower dose of calcitriol (0.25 μg) can be administered daily. (OPINION)

8B.4 When either hemodialysis or peritoneal dialysis patients are treated with active vitamin D sterols, management should integrate the changes in serum calcium, serum phosphorus, and plasma PTH. Each of these 3 variables is

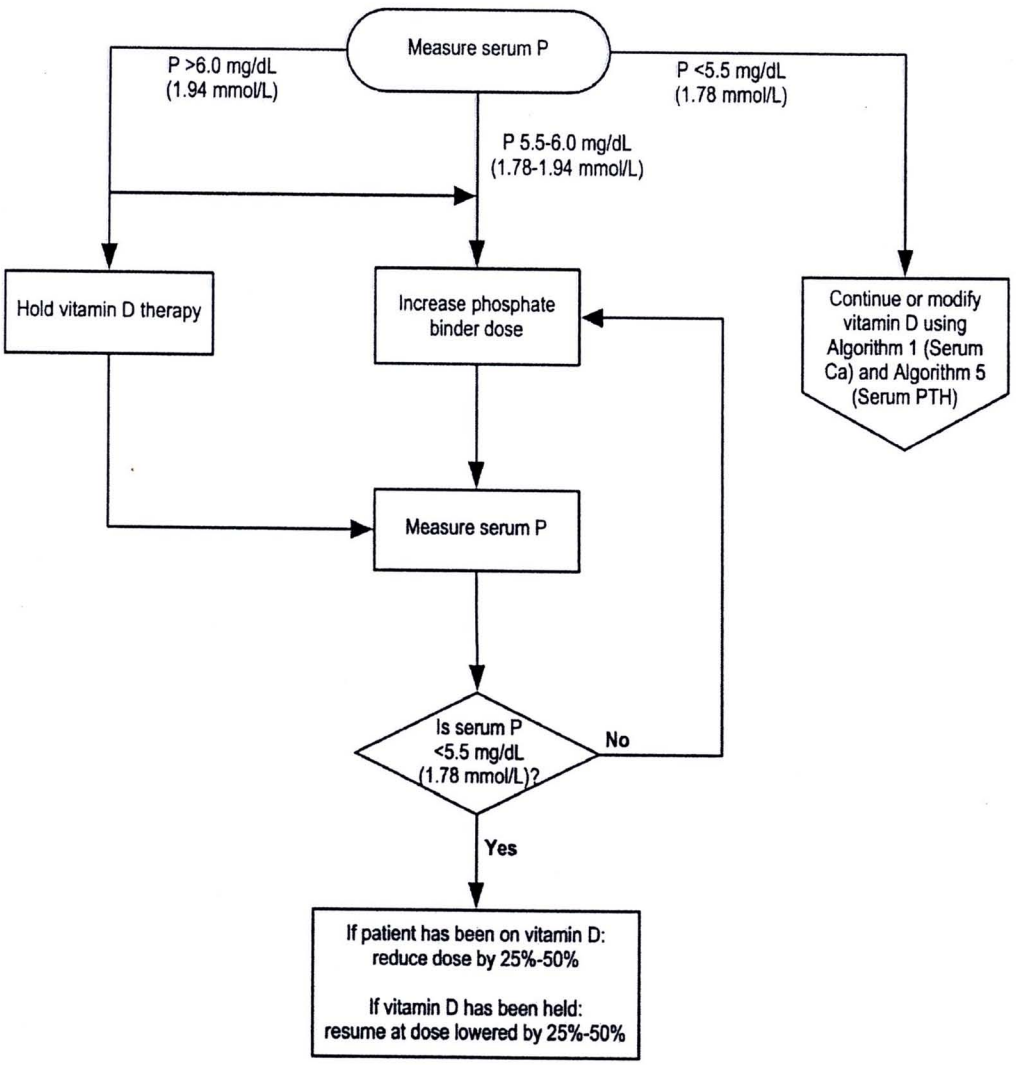
considered separately with suggested interventions based on the various values obtained in Algorithm 3, Algorithm 4, and Algorithm 5. (OPINION)



Algorithm 3. Managing Vitamin D sterols based on serum calcium levels.

GUIDELINE 9. DIALYSATE CALCIUM CONCENTRATIONS (p S99)

9.1 The dialysate calcium concentration in hemodialysis or peritoneal dialysis should be 2.5 mEq/L (1.25 mmol/L). (OPINION)



Algorithm 4. Managing Vitamin D sterols based on serum phosphorus levels.

9.2 Higher or lower dialysate calcium levels are indicated in selected patients. (See Clinical Applications.) (OPINION)

GUIDELINE 10. β2-MICROGLOBULIN AMYLOIDOSIS (p S102)

10.1 Screening for β2-microglobulin amyloidosis, including measurement of serum levels of β2-microglobulin, is not recommended. (OPINION)

10.1a No currently available therapy (except kidney transplantation) can stop disease progression of β2-microglobulin amyloidosis or provide symptomatic relief. (EVIDENCE)

10.1b Kidney transplant should be considered to stop disease progression or provide symptomatic relief in patients with β2-microglobulin amyloidosis. (EVIDENCE)

10.1c In patients with evidence of, or at risk for, β2-microglobulin amyloidosis noncuprophane (EVIDENCE), high-flux dialyzers (OPINION) should be used.

GUIDELINE 11. ALUMINUM OVERLOAD AND TOXICITY IN CKD (p S108)

11.1 To prevent aluminum toxicity, the regular administration of aluminum should be avoided and the dialysate concentration of aluminum should be maintained at <10 μg/L. (EVIDENCE)

11.1a CKD patients ingesting aluminum should not receive citrate salts simultaneously. (EVIDENCE)

11.2 To assess aluminum exposure and the risk of aluminum toxicity, serum aluminum levels should be measured at least yearly and every 3 months in those receiving aluminum-containing medications. (OPINION) 11.2a Baseline levels of serum aluminum should be <20 μg/L. (OPINION)

11.3 A deferoxamine (DFO) test should be performed if there are elevated serum aluminum levels (60 to 200 μg/L); clinical signs and symptoms of aluminum toxicity (Table 31, p S109), or prior to parathyroid surgery if the patient has had aluminum exposure. (EVIDENCE) (Algorithms 6 and 7)

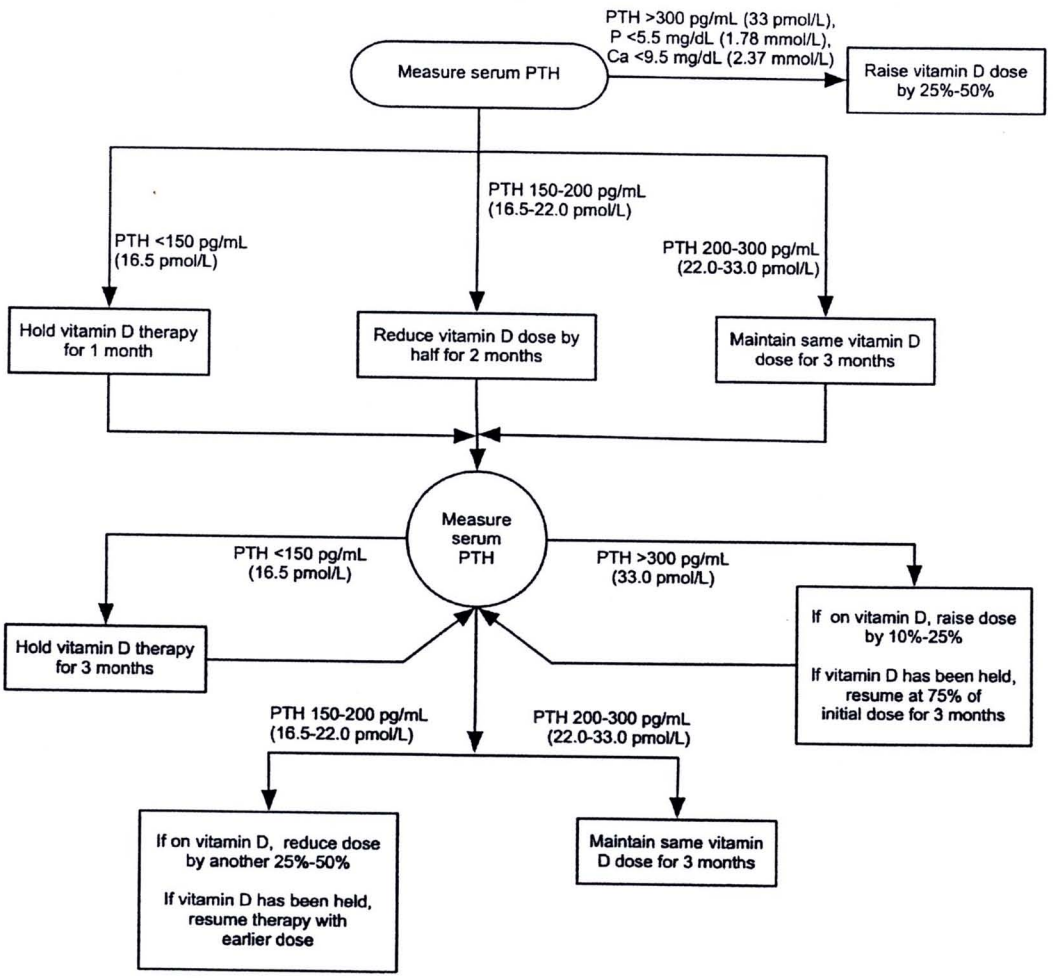
11.3a The test is done by infusing 5 mg/kg of DFO during the last hour of the dialysis session with a serum aluminum measured before DFO infusion and 2 days later, before the next dialysis session. (OPINION)

11.3b The test is considered positive if the increment of serum aluminum is >50 μg/L. (OPINION)

11.3c A DFO test should not be performed if the serum levels of aluminum are >200 μg/L to avoid DFO-induced neurotoxicity. (OPINION)

11.4 The presence of aluminum bone disease can be predicted by a rise in serum aluminum of >50 μg/L following DFO challenge combined with plasma

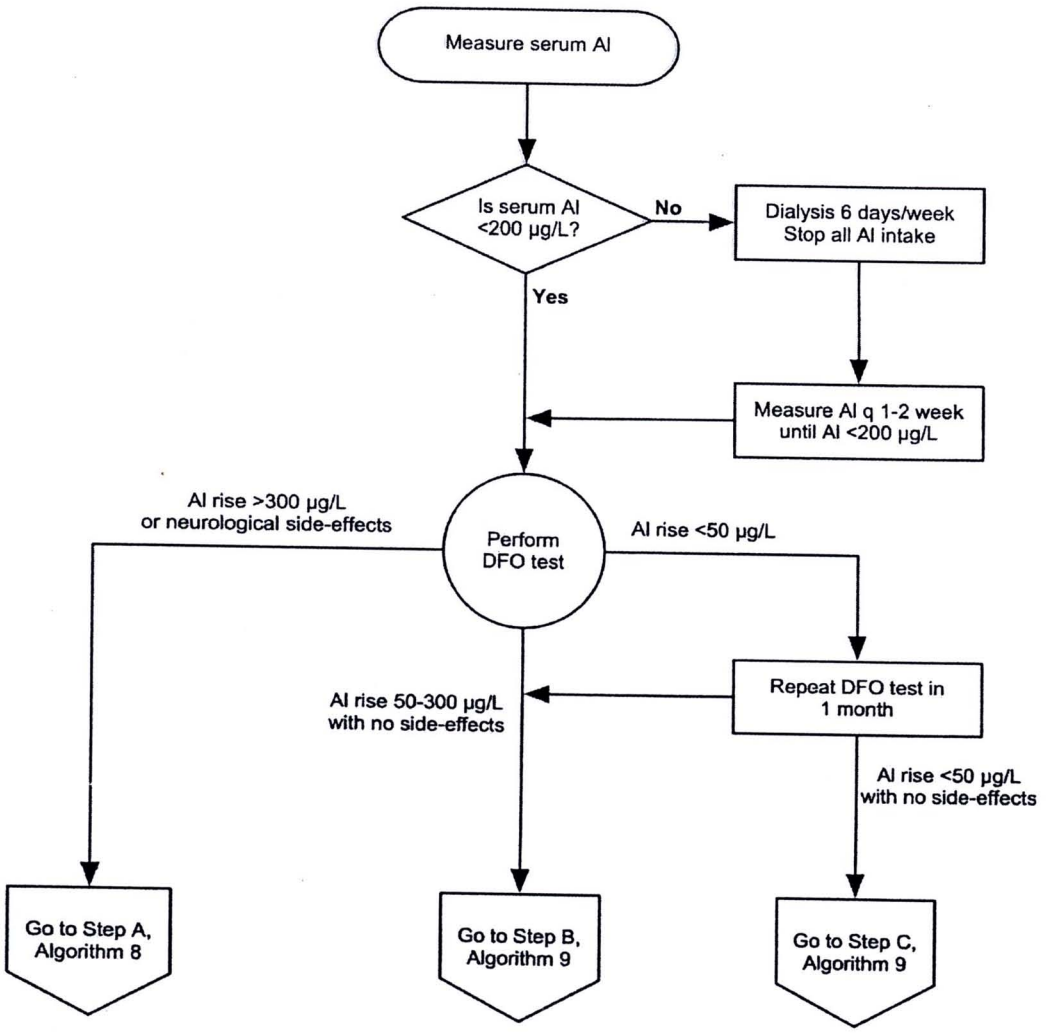
levels of intact PTH of <150 pg/mL (16.5 pmol/L). (OPINION) However, the gold standard for the diagnosis of aluminum bone disease is a bone biopsy showing increased aluminum staining of the bone surface (>15% to 25%) using aluminum stain and often adynamic bone or osteomalacia. (EVIDENCE)



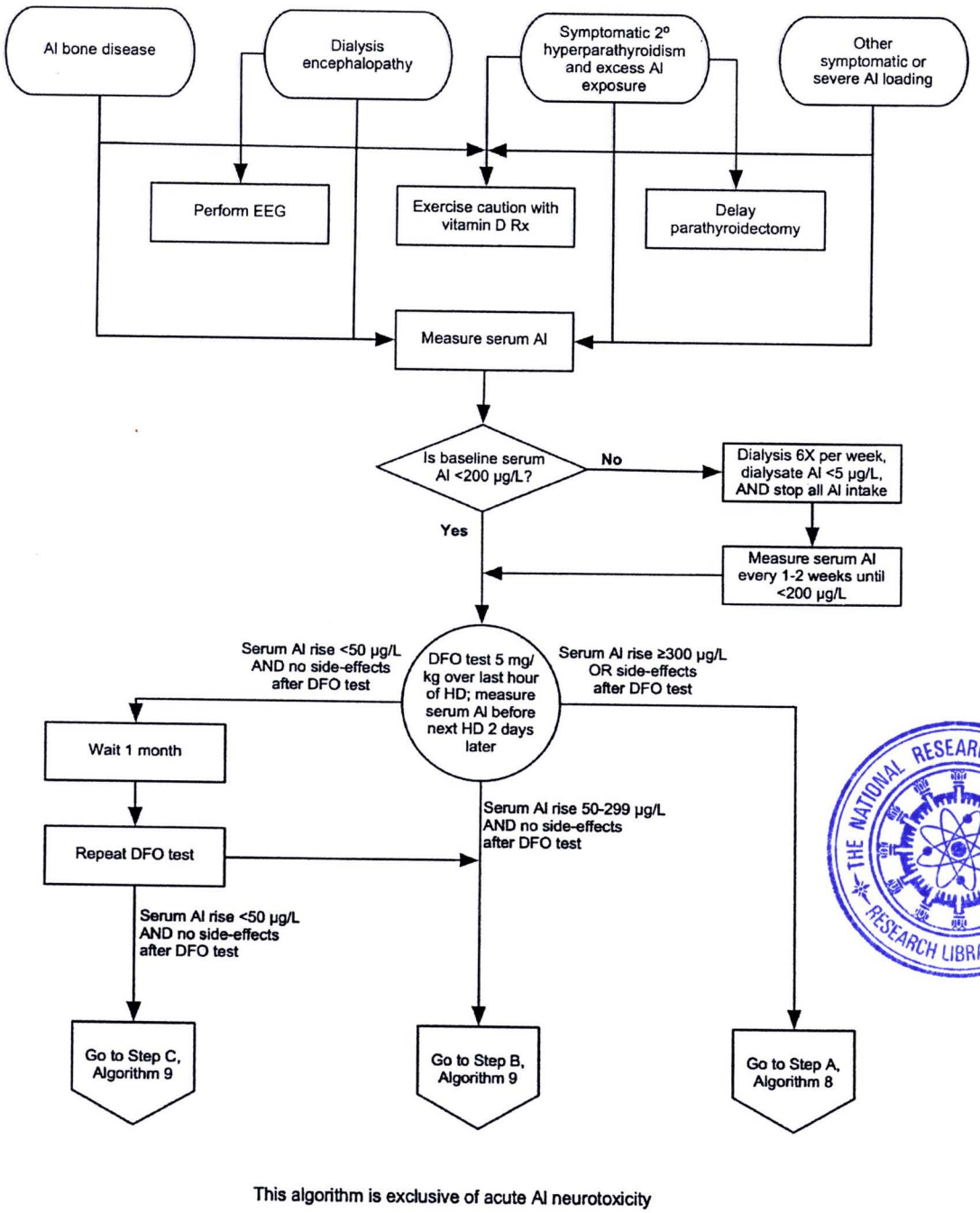
When intact serum PTH is between 300-500 pg/mL (33.0-55.0 pmol/L) and changes on two successive determinations are small (<25%), there is no need to modify vitamin D dose as long as P and Ca are within the desired limits (see Algorithms 3 and 4).

When intact PTH is persistently >500-800 pg/mL (55.0-88.0 pmol ng/L) and P is 5.5-6.5 mg/dL (1.78-1.94 mmol/L) and/or Ca is 10.2-10.5 mg/dL (2.54-2.62 mmol/L), a trial with a "less calcemic" analog may be warranted for 3-5 months; if such a patient fails to respond, parathyroidectomy may be required.

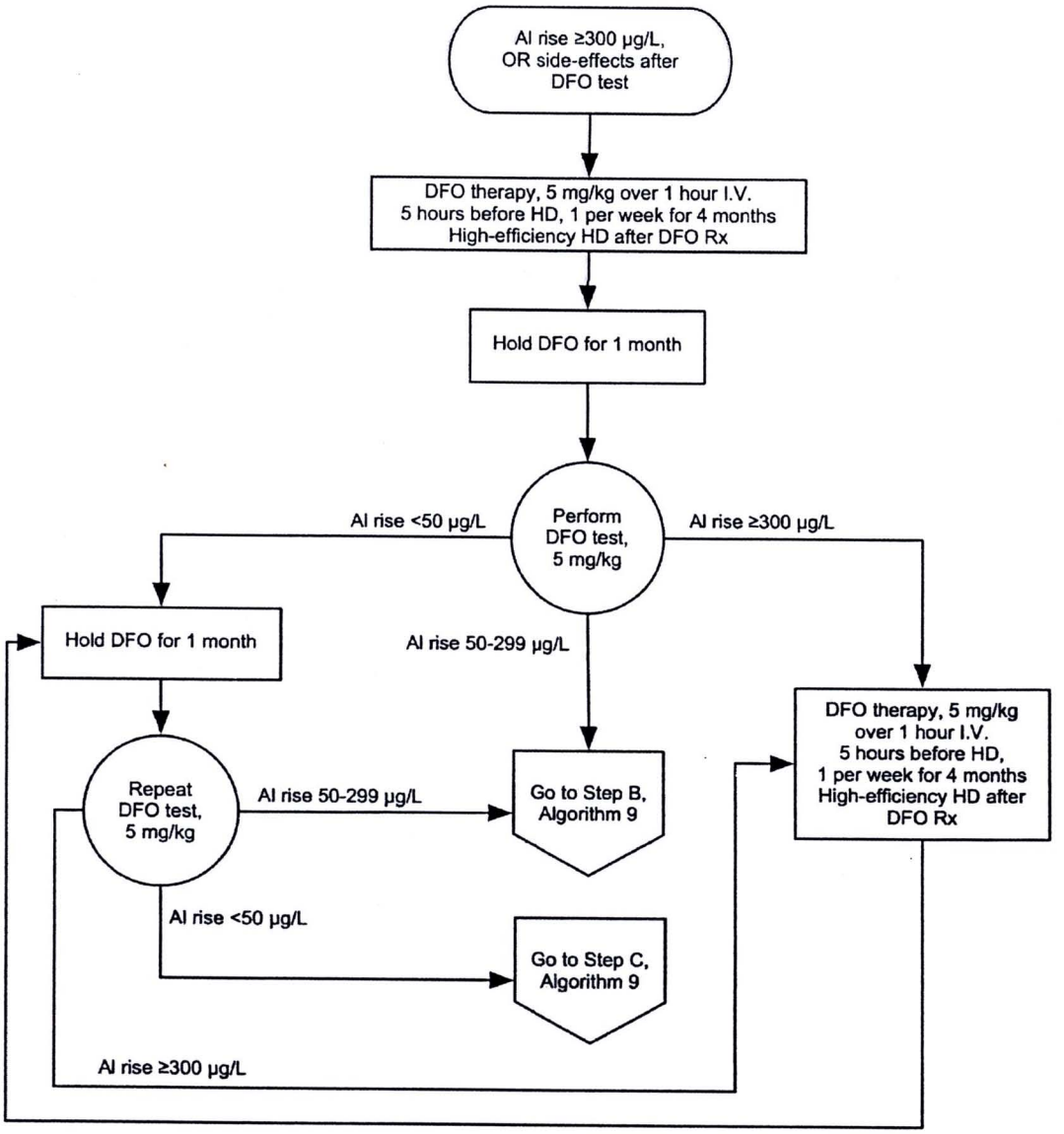
Algorithm 5. Managing Vitamin D sterols based on intact PTH levels.



Algorithm 6 Evaluation of aluminum neurotoxicity.



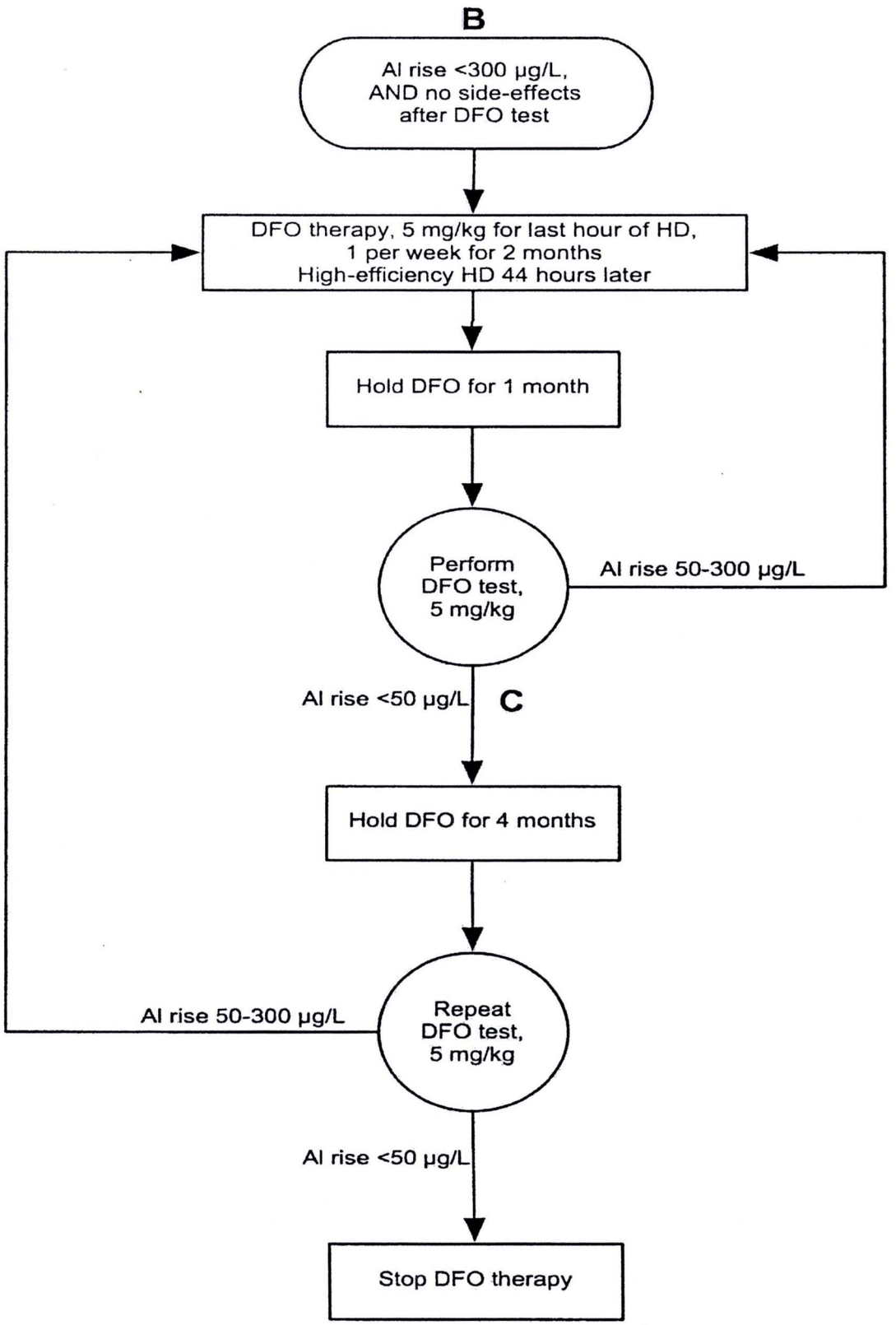
Algorithm 7. Evaluation of aluminum-related disorders: considerations for DFO test and subsequent DFO treatment.



Algorithm 8. DFO treatment after PAl rise >300 µg/L.

GUIDELINE 12. TREATMENT OFALUMINUMTOXICITY (Algorithm 8 and Algorithm 9) (p S116)

12.1 In all patients with baseline serum aluminum levels >60 µg/L, a positive DFO test, or clinical symptoms consistent with aluminum toxicity (Guideline 11, Table 31) the source of aluminum should be identified and eliminated. (OPINION)



Algorithm 9. DFO treatment after PAl rise between 50 and 300 µg/L.

12.2 In symptomatic patients with serum aluminum levels >60 μg/L but <200 μg/L or a rise in aluminum after DFO >50 μg/L, DFO should be given to treat the aluminum overload. (See Algorithm 8 and Algorithm 9). (OPINION)

12.3 To avoid DFO-induced neurotoxicity in patients with serum aluminum >200 μg/L, DFO should not be given until intensive dialysis (6 days per week) with high-flux dialysis membrane and a dialysate aluminum level of <5 μg/L and until the pre-dialysis serum aluminum level has been reduced to <200 μg/L. (OPINION)

GUIDELINE 13. TREATMENT OF BONE DISEASE IN CKD (p S122)

The therapeutic approach to bone disease in CKD is based on its specific type. As such, this Guideline encompasses 3 parts: Guideline 13A deals with high-turnover and mixed bone disease, Guideline 13B with osteomalacia, and Guideline 13C with adynamic bone disease.

GUIDELINE 13A. HYPERPARATHYROID (HIGH-TURNOVER) AND MIXED (HIGH-TURNOVER WITH MINERALIZATION DEFECT) BONE DISEASE (p S123)

13A.1 In CKD patients (Stages 3 and 4) who have plasma levels of intact PTH >70 pg/mL (7.7 pmol/L) (Stage 3) or >110 pg/mL (12.1 pmol/L) (Stage 4) on more than 2 consecutive measurements, dietary phosphate intake should be restricted. If this is ineffective in lowering plasma PTH levels, calcitriol (EVIDENCE) or one of its analogs [alfacalcidol (EVIDENCE) or doxercalciferol (OPINION)] should be given to prevent or ameliorate bone disease. (See Guideline 8A.)

13A.2 In CKD patients (Stage 5) who have elevated plasma levels of intact PTH (>300 pg/mL [33.0 pmol/L]), calcitriol (EVIDENCE) or one of its analogs (doxercalciferol, alfacalcidol, or paricalcitol) (OPINION) should be used to reverse the bone features of PTH overactivity (ie, high-turnover bone disease) and to treat defective mineralization. (See Guideline 8B.)

GUIDELINE 13B. OSTEOMALACIA (p S124)

13B.1 Osteomalacia due to aluminum toxicity should be prevented in dialysis patients by maintaining aluminum concentration in dialysate fluid at <10 μg/L and avoiding the use of aluminum-containing compounds (including sucralfate). (OPINION)

13B.2 Aluminum overload leading to aluminum bone disease should be treated with deferoxamine (DFO). (See Guidelines 11 and 12.) (OPINION)

13B.3 Osteomalacia due to vitamin D2 or D3 deficiency or phosphate depletion, though uncommon, should be treated with vitamin D2 or D3 supplementation (see Guideline 7) and/or phosphate administration, respectively. (OPINION)

13B.3a If osteomalacia due to vitamin D deficiency fails to respond to ergocalciferol or cholecalciferol, particularly in patients with kidney failure (Stage 5), treatment with an active vitamin D sterol may be given. (OPINION) (See Guideline 8B.)

13B.3b Doses of phosphate supplementation should be adjusted upwards until normal serum levels of phosphorus are achieved. (OPINION)

GUIDELINE 13C. ADYNAMIC BONE DISEASE (p S125)

13C.1 Adynamic bone disease in Stage 5 CKD (as determined either by bone biopsy or intact PTH <100 pg/mL [11.0 pmol/L]) should be treated by allowing plasma levels of intact PTH to rise in order to increase bone turnover. (OPINION)

13C.1a This can be accomplished by decreasing doses of calcium-based phosphate binders and vitamin D or eliminating such therapy. (OPINION)

GUIDELINE 14. PARATHYROIDECTOMY IN PATIENTS WITH CKD (p S127)

14.1 Parathyroidectomy should be recommended in patients with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL [88.0 pmol/L]), associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy. (OPINION)

14.2 Effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy or total parathyroidectomy with parathyroid tissue autotransplantation. (EVIDENCE)

14.3 In patients who undergo parathyroidectomy the following should be done:

14.3a The blood level of ionized calcium should be measured every 4 to 6 hours for the first 48 top 72 hours after surgery, and then twice daily until stable. (OPINION)

14.3b If the blood levels of ionized or corrected total calcium fall below normal (<0.9 mmol/L or <3.6 mg/dL corresponding to corrected total calcium of 7.2 mg/dL [1.80 mmol/L]), a calcium gluconate infusion should be initiated at a rate of 1 to 2 mg elemental calcium per kilogram body weight per hour and adjusted to maintain an ionized calcium in the normal range (1.15 to 1.36 mmol/L or 4.6 to 5.4 mg/dL). (OPINION) A 10-mL ampule of 10% calcium gluconate contains 90 mg of elemental calcium.

Table 22. Frequency for Measurement of Serum Levels of Total CO_2.

CKD Stage	GFR Range (mL/min/1.73 m^2)	Frequency Of Measurement
3	30-59	At least every 12 months
4	15-29	At least every 3 months
5	<15	At least every 3 months
	Dialysis	At least every months

14.3c The calcium infusion should be gradually reduced when the level of ionized calcium attains the normal range and remains stable. (OPINION)

14.3d When oral intake is possible, the patient should receive calcium carbonate 1 to2g3 times a day, as well as calcitriol of up to 2 μg/day, and these therapies should be adjusted as necessary to maintain the level of ionized calcium in the normal range. (OPINION)

14.3e If the patient was receiving phosphate binders prior to surgery, this therapy may need to be discontinued or reduced as dictated by the levels of serum phosphorus. (OPINION)

14.4 Imaging of parathyroid glands with 99Tc-Sestamibi scan, ultrasound, CT scan, or MRI should be done prior to re-exploration parathyroid surgery. (OPINION)

GUIDELINE 15. METABOLIC ACIDOSIS (p S129)

15.1 In CKD Stages 3, 4, and 5, the serum level of total CO2 should be measured.

15.1a The frequency of these measurements should be based on the stage of CKD as shown in Table 32. (OPINION)

15.2 In these patients, serum levels of total CO2 should be maintained at >22 mEq/L (22 mmol/L). (EVIDENCE) If necessary, supplemental alkali salts should be given to achieve this goal. (OPINION)

GUIDELINE 16. BONE DISEASE IN THE KIDNEY TRANSPLANT RECIPIENT (p S130)

16.1 Serum levels of calcium, phosphorus, total CO2 and plasma intact PTH should be monitored following kidney transplantation. (OPINION)

16.1a The frequency of these measurements should be based on the time following transplantation, as shown in Table 33. (OPINION)

16.2 During the first week after kidney transplantation, serum levels of phosphorus should be measured daily. Kidney transplant recipients who develop persistently low levels of serum phosphate (<2.5 mg/dL [0.81 mmol/L]) should be treated with phosphate supplementation. (OPINION)

16.3 To minimize bone mass loss and osteonecrosis, the immunosuppressive regimen should be adjusted to the lowest effective dose of glucocorticoids. (EVIDENCE)

Table 23 Frequency of Measurement of Calcium, Phosphorus, PTH and total CO_2 after Kidney Transplantation.

Parameter	First 3 Months	3 Months to year
Calcium	Every 2 Weeks	Monthly
Phosphorus	Every 2 Weeks	Monthly
PTH	Monthly	Every 2 Weeks
Total CO2	Every 2 Weeks	Monthly

16.4 Kidney transplant recipients should have bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) to assess the presence or development of osteoporosis. (OPINION)

16.4a DEXA scans should be obtained at time of transplant and 1 year and 2 yearspost-transplant. (OPINION)

16.4b If BMD t-score is equal to or less than -2 at the time of the transplant, or at subsequent evaluations, therapy with parenteral amino-bisphosphonates should be considered. (OPINION)

16.5 Treatment of disturbances in bone and mineral metabolism is determined by the level of kidney function in the transplant recipient as provided in Guidelines 1 through 15 for CKD patients. (OPINION)

APPENDIX B

KDIGO clinical practice guideline for the diagnosis, evaluation, prevention and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD) 2009 (Chapter 1)

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

kidney INTERNATIONAL

KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES

KDIGO®

KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)

VOLUME 76 | SUPPLEMENT 113 | AUGUST 2009

Supplement to Kidney International

http://www.kidney-international.org

Chapter 1: Introduction and definition of CKD–MBD and the development of the guideline statements

Kidney International (2009) 76 (Suppl 113), S3–S8; doi:10.1038/ki.2009.189

INTRODUCTION AND DEFINITION OF CKD–MBD

Chronic kidney disease (CKD) is an international public health problem affecting 5–10% of the world population. As kidney function declines, there is a progressive deterioration in mineral homeostasis, with a disruption of normal serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones. These include parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D), and other vitamin D metabolites, fibroblast growth factor-23 (FGF-23), and growth hormone. Beginning in CKD stage 3, the ability of the kidneys to appropriately excrete a phosphate load is diminished, leading to hyperphosphatemia, elevated PTH, and decreased 1,25(OH)2D with associated elevations in the levels of FGF-23. The conversion of 25(OH)D to 1,25(OH)2D is impaired, reducing intestinal calcium absorption and increasing PTH. The kidney fails to respond adequately to PTH, which normally promotes phosphaturia and calcium reabsorption, or to FGF-23, which also enhances phosphate excretion. In addition, there is evidence at the tissue level of a downregulation of vitamin D receptor and of resistance to the actions of PTH. Therapy is generally focused on correcting biochemical and hormonal abnormalities in an effort to limit their consequences.

The mineral and endocrine functions disrupted in CKD are critically important in the regulation of both initial bone formation during growth (bone modeling) and bone structure and function during adulthood (bone remodeling). As a result, bone abnormalities are found almost universally in patients with CKD requiring dialysis (stage 5D), and in the majority of patients with CKD stages 3–5. More recently, there has been an increasing concern of extraskeletal calcification that may result from the deranged mineral and bone metabolism of CKD and from the therapies used to correct these abnormalities.

Numerous cohort studies have shown associations between disorders of mineral metabolism and fractures, cardiovascular disease, and mortality (see Chapter

3). These observational studies have broadened the focus of CKD-related mineral and bone disorders (MBDs) to include cardiovascular disease (which is the leading cause of death in patients at all stages of CKD). All three of these processes (abnormal mineral metabolism, abnormal bone, and extraskeletal calcification) are closely interrelated and together make a major contribution to the morbidity and mortality of patients with CKD.

The traditional definition of renal osteodystrophy did not accurately encompass this more diverse clinical spectrum, based on serum biomarkers, noninvasive imaging, and bone abnormalities. The absence of a generally accepted definition and diagnosis of renal osteodystrophy prompted Kidney Disease: Improving Global Outcomes (KDIGO) to sponsor a controversies conference, entitled 'Definition, Evaluation, and Classification of Renal Osteodystrophy,' held on 15–17 September 2005 in Madrid, Spain. The principal conclusion was that the term 'CKD–Mineral and Bone Disorder (CKD–MBD)' should be used to describe the broader clinical syndrome encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD (Table 1). It was also recommended that the term 'renal osteodystrophy' be restricted to describing the bone pathology associated with CKD. The evaluation and definitive diagnosis of renal osteodystrophy require a bone biopsy, using an expanded classification system that was developed at the consensus conference based on parameters of bone turnover, mineralization, and volume (TMV).

The KDIGO CKD–MBD Clinical Practice Guideline Document

KDIGO was established in 2003 as an independently incorporated nonprofit foundation governed by an international board of directors with the stated mission to 'improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines'. The 2005 consensus conference sponsored by KDIGO was seen as an initial step in raising awareness of the importance of this disorder. The next stage was to develop an international clinical practice guideline that provides guidance on the management of this disorder.

CHALLENGES IN DEVELOPING THIS GUIDELINE

The development of this guideline proved challenging for a number of reasons. First, the definition of CKD–MBD was new and had not been applied to characterize populations in published clinical studies. Thus, each of the three components of CKD–MBD had to be addressed separately. Second, the complexity of the pathogenesis of CKD–MBD make it difficult to completely differentiate a consequence of the disease from a consequence of its treatment. Moreover, different stages of CKD are associated with different features and degrees of severity of CKD–MBD. Third, differences exist throughout the world in nutrient intake, availability of medications, and clinical practice. Fourth, many of the local guidelines that already exist are based largely on expert opinion rather than on strong evidence, whereas KDIGO aims to base its guidelines on an extensive and systematic analysis of the available evidence. Finally, this is a disorder unique to CKD patients, meaning that there are no randomized controlled trials in the non-CKD population that can be generalized to CKD patients, and only a few large studies involving CKD patients.

Table 24 KDIGO classification of CKD–MBD and renal osteodystrophy

Definition of CKD–MBD
A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
• Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
• Abnormalities in bone turnover, mineralization, volume, linear growth, or strength.
• Vascular or other soft-tissue calcification.
Definition of renal osteodystrophy
• Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
• It is one measure of the skeletal component of the systemic disorder of CKD–MBD that is quantifiable by histomorphometry of bone biopsy.

CKD, chronic kidney disease; CKD–MBD, chronic kidney disease–mineral and bone disorder; KDIGO, Kidney Disease: Improving Global Outcomes; PTH, parathyroid hormone.

Adapted with permission from Moe et al

COMPOSITION OF THE WORK GROUP AND PROCESSES

A Work Group of international experts charged with developing the present guideline was chosen by the Work Group Chairs, who in turn were chosen by the KDIGO Executive Committee. The Work Group defined the questions and developed the study inclusion criterion a priori. When it came to evaluating the impact of therapeutic agents, the Work Group agreed a priori to evaluate only randomized controlled trials of a 6-month duration with a sample size of at least 50 patients. An exception was made for studies involving children or using bone biopsy criterion as an end point, in which smaller sample sizes were accepted because of the inherent difficulties in conducting these studies.

Defining end points

End points were categorized into three levels for evaluation: those of direct importance to patients (for example, mortality, cardiovascular disease events, hospitalizations fracture, and quality of life), intermediate end points (for example, vascular calcification, bone mineral density (BMD), and bone biopsy), and biochemical end points (for example, serum calcium, phosphorus, alkaline phosphatases, and PTH). Importantly, the Work Group acknowledged that these intermediate and biochemical end points are not validated surrogate end points for hard clinical events unless such a connection had been made in a prospective treatment trial (Figure 1).

CONTENT OF THE GUIDELINE

The guideline includes detailed evidence-based recommendations for the diagnosis and evaluation of the three components of CKD–MBD—abnormal biochemistries, vascular calcification, and disorders of the bone (Chapter 3)— and recommendations for the treatment of CKD–MBD (Chapter 4). In preparing Chapter 3, studies that assessed the diagnosis, prevalence, natural history, and risk relationships of CKD–MBD were evaluated. Unfortunately, there was frequently no high-quality evidence to support recommendations for specific diagnostic tests, thresholds for defining disease, frequency of testing, or precisely which populations to test. Multiple studies were reviewed that allowed the generation of overview tables listing a

selection of pertinent studies. For the treatment questions, systematic reviews were undertaken of randomized controlled trials and the bodies of evidence were appraised following the Grades of Recommendation Assessment, Development, and Evaluation approach.

Public review version

The initial version of the CKD–MBD guideline was developed by using very rigorous standards for the quality of evidence on which clinical practice recommendations should be based. Thus, the Work Group limited its recommendations to areas that it felt were supported by high-or moderate-quality evidence rather than areas in which the recommendation was based on low-or very-low-quality evidence and predominantly expert judgment. The Work Group was most sensitive to the potential misuse and misapplication of recommendations, especially, as pertains to targets and treatment recommendations. The Work Group believed strongly that patients deserved treatment recommendations based on high-quality evidence and physicians should not be forced to adhere to targets and use treatments without sound evidence showing that benefits outweigh harm. The Work Group recognized that there had already been guidelines developed by different entities throughout the world that did not apply these criteria. In the public review draft, the Work Group provided discussions under 'Frequently Asked Questions' at the end of each chapter to provide practical guidance in areas of indeterminate evidence or to highlight areas of controversy.

The public review overwhelmingly agreed with the guideline recommendations. Interestingly, most reviewers requested more specific guidance for the management of CKD–MBD, even if predominantly based on expert judgment, whereas others found the public review draft to be a refreshingly honest appraisal of our current knowledge base in this field.

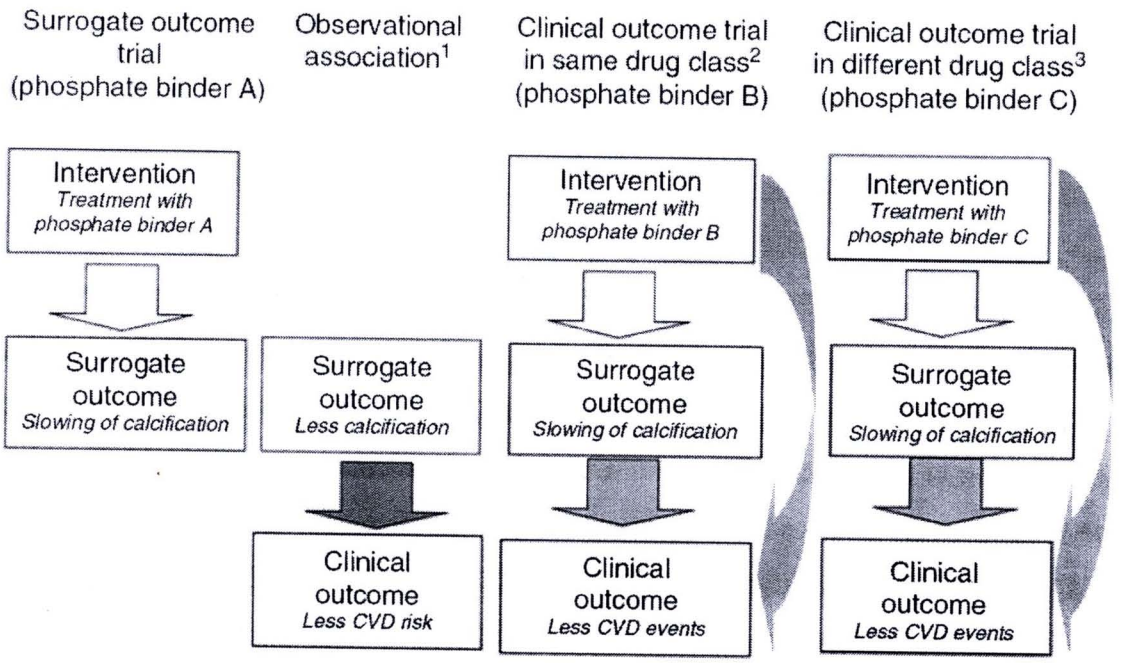


Figure 2 Interpreting a surrogate outcome trial. When interpreting the validity of a surrogate outcome trial, consider the following questions: 1. Is there a strong, independent, consistent association between the surrogate outcome and the clinical outcome? This is a necessary but not, by itself, sufficient prerequisite. 2. Is there evidence from randomized trials in the same drug class that improvements in the surrogate outcome have consistently led to improvements in the clinical outcome? 3. Is there evidence from randomized trials in other drug classes that improvement in the surrogate outcome has consistently led to improvement in the clinical outcome? Both 2 and 3 should apply. This figure illustrates principles outlined in Users' Guide for Surrogate Endpoint Trial and the legend is modified after this reference. Phosphate binders, calcification, and CVD are chosen as an example. CVD, cardiovascular disease.

Responses to review process and modifications

In response to the public review of the CKD–MBD guideline, and in the context of a changing field of guideline development, grading systems, and the need for guidance in complex areas of CKD management, the KDIGO Board in its Vienna session in December 2008 refined its remit to KDIGO Work Groups. It confirmed its

charge to the Work Groups to critically appraise the evidence, but encouraged the Work Groups to issue practical guidance in areas of indeterminate evidence. This practical guidance rests on a combination of the evidentiary base that exists (biological, clinical, and other) and the judgment of the Work Group members, which is directed to ensuring 'best care' in the current state of knowledge for the patients.
In the session of December 2008, the KDIGO Board also revised the grading system for the strength of recommendations to align it more closely with Grades of Recommendation Assessment, Development, and Evaluation (GRADE), an international body committed to the harmonization of guideline grading across different speciality areas. The full description of this grading system is found in Chapter 2, but can be summarized as follows: there are two levels for the strength of recommendation (level 1 or 2) and four levels for the quality of overall evidence supporting each recommendation (grade A, B, C, or D) (see Chapter 2). In addition to graded recommendations, ungraded statements in areas in which guidance was based on common sense and/or the question was not specific enough to undertake a systematic evidence review are also presented. This grading system allows the Work Group to be transparent in its appraisal of the evidence, yet provides practical guidance. The simplicity of the grading system also permits the clinician, patient, and policy maker to understand the statement in the context of the evidentiary base more clearly.

In response to feedback by the KDIGO Board of Directors, the CKD–MBD Work Group reconvened in January 2009, revised some recommendations, and formulated some additional recommendations or ungraded statements, integrating suggestions for patient care previously expressed in the Frequently Asked Questions section. Approval of the final recommendations and rating of their strength and the underlying quality of evidence were established by voting, with two votes taken, one including and one excluding those Work Group members who declared potential conflicts of interest. (Note that the financial relationships of the Work Group participants are listed at the end of this document.) The two votes generally yielded a 490% agreement on all the statements. When an overwhelming agreement could not be reached in support of a recommendation, the issue was instead discussed in the rationale.

Finally, the Work Group made numerous recommendations for further research to improve the quality of evidence for future recommendations in the field of CKD–MBD.

Summary and future directions

The wording has been carefully selected for each statement to ensure clarity and consistency, and to minimize the possibility of misinterpretation. The grading system offers an additional level of transparency regarding the strength of recommendation and quality of evidence at a glance. We strongly encourage the users of the guideline to ensure the integrity of the process by quoting the statements verbatim, and by including the grades assigned after the statement when quoting/reproducing or using the statements, as well as by explaining the meaning of the code that combines an Arabic number (to indicate that the recommendation is 'strong' or 'weak') and an uppercase letter (to indicate that the quality of the evidence is 'high', 'moderate', 'low', or 'very low').

We hope that as a reader and user, you appreciate the rigor of the approach we have taken. More importantly, we strongly urge the nephrology community to take up the challenge of expanding the evidence base in line with our research recommendations. Given the current state of knowledge, clinical equipoise, and the need for accumulating data, we strongly encourage clinicians to enroll patients into ongoing and future studies, to participate in the development of registries locally, nationally, and internationally, and to encourage funding organizations to support these efforts, so that, over time, many of the current uncertainties can be resolved.

SUMMARY OF RECOMMENDATIONS

Chapter 3.1: Diagnosis of CKD–MBD: biochemical abnormalities

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).

3.1.3 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).

3.1.4 In patients with CKD stages 3–5D, we 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 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).

3.1.6 In reports of laboratory tests for patients with CKD stages 3–5D, we recommend that clinical laboratories inform clinicians of the actual assay method in use and report any change in methods, sample source (plasma or serum), and handling specifications to facilitate the appropriate interpretation of biochemistry data (1B).

Chapter 3.2: Diagnosis of CKD–MBD: bone

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).

Chapter 3.3: Diagnosis of CKD–MBD: vascular calcification

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 or 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).

Chapter 4.1: Treatment of CKD–MBD targeted at lowering high serum phosphorus and maintaining serum calcium

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 hyper-phosphatemia 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).

Chapter 4.2: Treatment of abnormal PTH levels in CKD–MBD

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).

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).

Chapter 4.3: Treatment of bone with bisphosphonates, other osteoporosis medications, and growth hormone

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).

Chapter 5: Evaluation and treatment of kidney transplant bone disease

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).

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 efficacy and side-effects (not graded). It is reasonable to manage these abnormalities as for patients with CKD stages 3–5 (not graded) (see Chapters 4.1 and 4.2).

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).

5.5 In patients with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m2,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).

5.6 In patients in the first 12 months after kidney transplant with an estimated glomerular filtration rate greater than approximately 30 ml/min per 1.73 m2 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).

There are insufficient data to guide treatment after the first 12 months.

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)

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