Chronic Kidney Disease with Mineral Bone Disorder

CKD-MBD

Case Presentation

A 62-year-old woman with chronic kidney disease stage 4 (CKD 4) due to uncontrolled hypertension and diabetes mellitus type 2 is referred for evaluation of elevated parathyroid hormone (PTH). She has had mild diffuse skin itching over the last few months but otherwise feels well without history of bone pain or fractures. On physical exam, she has full range of motion and strength in her joints and extremities. There is no joint inflammation or bony abnormalities. Her skin is well perfused and without rash. Her laboratories are pertinent for serum creatinine 3.2 mg/dL, estimated glomerular filtration rate (eGFR) 20 mL/min, bicarbonate $(HCO_3)^-$ 19 mmol/L (22–31 mmol/L), phosphate 6.2 mg/dL (2.5–4.5 mg/dL), 25-hydroxyvitamin D 18 ng/mL (30–80 ng/mL), 1,25-dihydroxyvitamin D (calcitriol or [1,25-$(OH)_2$-D]) 20 pg/mL (19.9–79.3 pg/mL), calcium (Ca^{2+}) 8.2 mg/dL (8.4–10.5 mg/

dL), albumin 4.0 g/dL, intact PTH 375 pg/mL (15–65 pg/mL), and bone-specific alkaline phosphatase (BALP) 75 μg/L (4–36 μg/L). A CT scan performed 2 months previously showed coronary artery calcifications.

[redacted] A 64-year-old man with end-stage kidney disease due to hypertension has been receiving hemodialysis for 10 years. He is referred for evaluation because of multiple vertebral fractures and a femoral neck T-score of –3.8 on DXA. Long-term medications include calcitriol, 0.5 mcg twice daily, and cinacalcet, 90 mg twice daily.

Laboratory test results:

Serum calcium = 8.1 mg/dL (8.2-10.2 mg/dL) (SI: 2.0 mmol/L [2.1-2.6 mmol/L])

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Total alkaline phosphatase = 48 U/L (50-120 U/L) (SI: 0.80 μkat/L [0.84-2.00 μkat/L])

An iliac crest biopsy is done after double-tetracycline labeling.

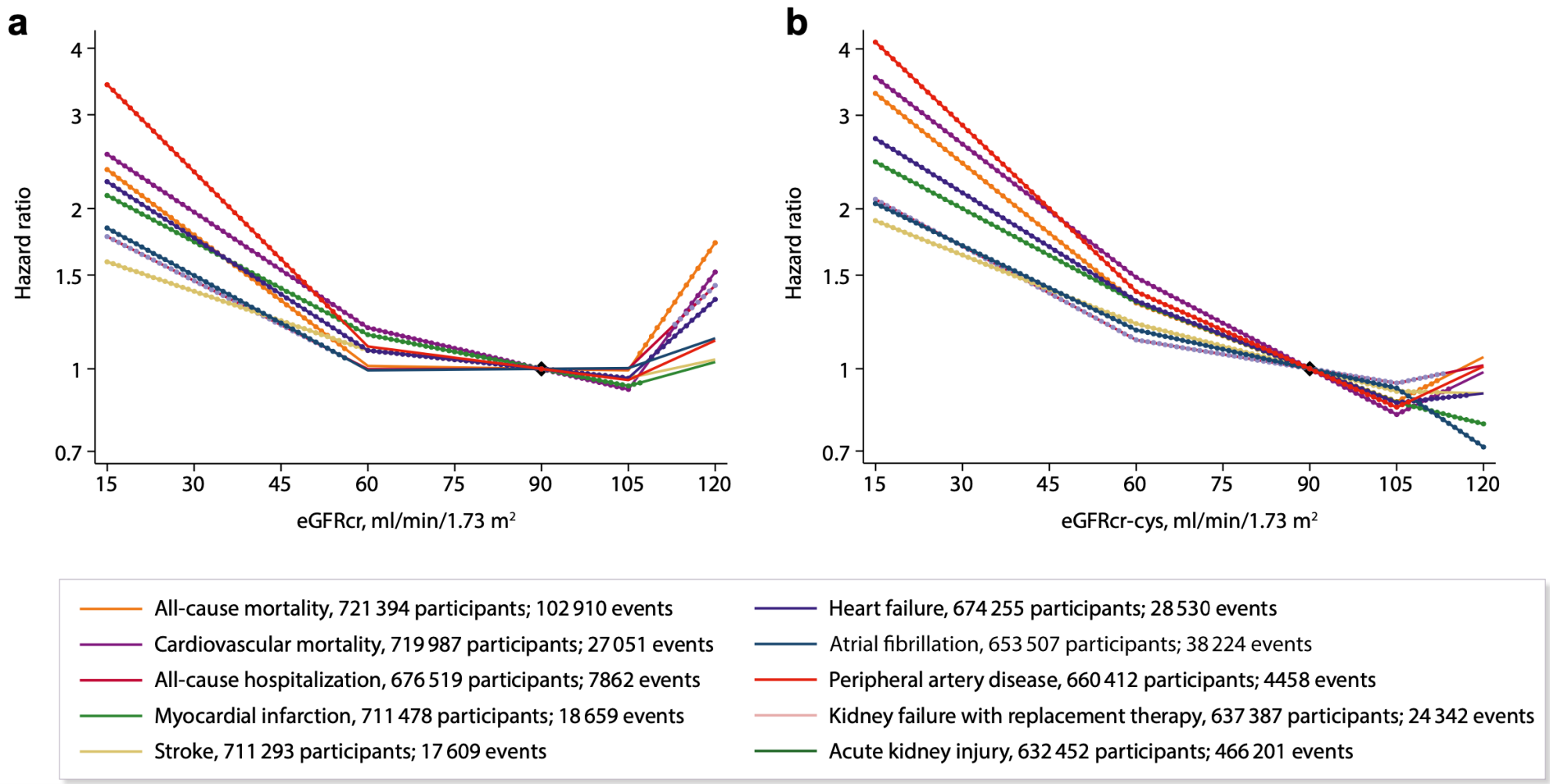
While awaiting bone biopsy results, which of the following changes in management should be made immediately?

A. Begin denosumab
B. Begin teriparatide
C. Decrease the calcitriol dosage
D. Decrease the cinacalcet dosage
E. Increase the calcitriol dosage

Assessment and Diagnosis

Chronic kidney disease with mineral and bone disorder (CKD-MBD) describes the systemic alterations in mineral, metabolic, hormonal, and bone homeostasis that can increase the risk of fractures, vascular calcification, cardiovascular morbidity, and mortality in patients with eGFR <60 mL/min. Patients with CKD are 2–17 times more likely to experience bone fracture than the general population. This risk increases proportionately as kidney function declines, with most CKD patients stages three to five showing signs of high bone turnover and increased PTH [1, 2]. Rates of hip fracture in end-stage kidney disease (ESKD) have increased over the last 30 years. CKD patients with bone fractures have decreased quality of life, longer hospitalizations, incur higher healthcare costs, and experience a 16–60% increase in morbidity and mortality compared to patients who fracture with normal kidney function [3].

KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease


a
b
Hazard ratio
4
3
2
1.5
1
0.7
15
30
45
60
75
90
105
120
eGFRcr, ml/min/1.73 m²
eGFRcr-cys, ml/min/1.73 m²
All-cause mortality, 721 394 participants; 102 910 events
Cardiovascular mortality, 719 987 participants; 27 051 events
All-cause hospitalization, 676 519 participants; 7862 events
Myocardial infarction, 711 478 participants; 18 659 events
Stroke, 711 293 participants; 17 609 events
Heart failure, 674 255 participants; 28 530 events
Atrial fibrillation, 653 507 participants; 38 224 events
Peripheral artery disease, 660 412 participants; 4458 events
Kidney failure with replacement therapy, 637 387 participants; 24 342 events
Acute kidney injury, 632 452 participants; 466 201 events

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	**G1**	Normal or high	≥90	Screen 1	Treat 1	Treat 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Treat 3
	G4	Severely decreased	15–29	Treat* 3	Treat* 3	Treat 4+
	G5	Kidney failure	<15	Treat 4+	Treat 4+	Treat 4+

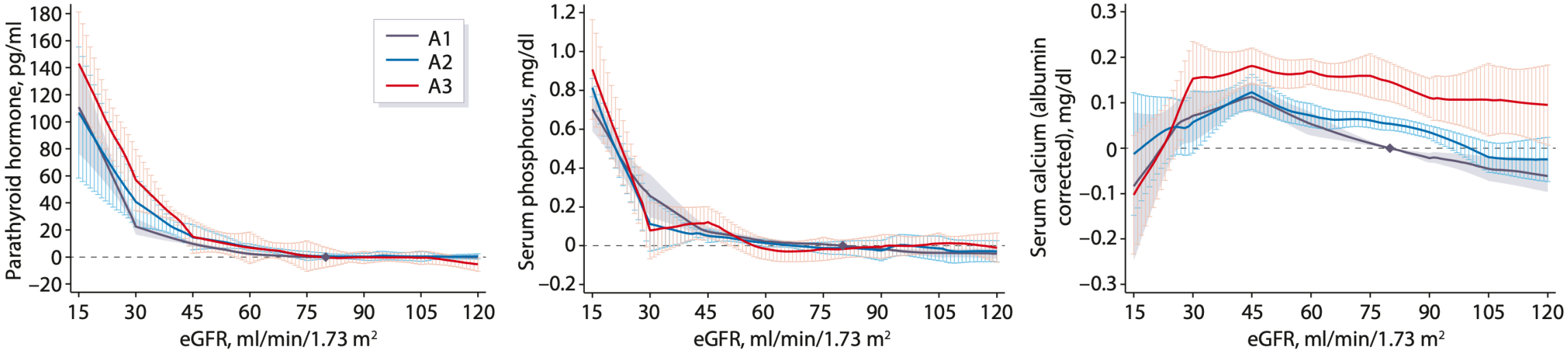


Figure 35 | Association between estimated glomerular filtration rate (eGFR) with serum concentrations of parathyroid hormone, phosphate, and serum calcium in general population and high-risk cohorts from the Chronic Kidney Disease Prognosis Consortium, by level of albuminuria (A1–A3). The *y* axis represents the meta-analyzed absolute difference from the mean adjusted value at an eGFR of 80 ml/min per 1.73 m^2 and albumin excretion <30 mg/g (<3 mg/mmol). A1, albuminuria <30 mg/g (<3 mg/mmol); A2, albuminuria 30–300 mg/g (3–30 mg/mmol); A3, >300 mg/g (>30 mg/mmol). Reproduced from *American Journal of Kidney Diseases*, volume 73, issue 2, Inker LA, Grams ME, Levey AS, et al. Relationship of estimated GFR and albuminuria to concurrent laboratory abnormalities: an individual participant data meta-analysis in a Global Consortium, pages 206–217, Copyright © 2018, with permission from the National Kidney Foundation, Inc.[541]

CKD-MBD affects bone and mineral metabolism in three main areas: serum mineral and hormone imbalance, decreased bone quality and strength, and increased extraskeletal calcifications.

Serum biomarkers used to assess CKD-MBD include phosphate, 1,25-dihydroxyvitamin D, calcium, bicarbonate, PTH, and fibroblast growth factor-23 (FGF-23) (Table 10.1). As eGFR declines, phosphate clearance is reduced, triggering the rise in phosphaturic hormones PTH and FGF-23 in a feedback loop to increase kidney excretion of phosphate. Hyperphosphatemia and elevated FGF-23 along with reduced kidney function result in low 1,25-dihydroxyvitamin D which causes hypocalcemia, yet another trigger for PTH release. Chronic overproduction of parathyroid hormone results in the typical high turnover bone disease seen in these patients (Fig. 10.1). Additionally, metabolic acidosis is frequent in CKD and directly causes bone loss, impaired bone mineralization, and increased FGF-23 (Table 10.1) [4].

Table 10.1 Serum biomarkers of CKD-MBD

	↑ [Phosphate]	↓ [1,25-$(OH)_2$-D]	↓ [Calcium]	↑ [FGF-23]	↑ [PTH]	↓ [HCO3-]
Driven by	CKD (reduced ability of the kidney to excrete Phosphate)	↑ FGF-23 ↑ Phosphate ↓ Calcidiol conversion to calcitriol due to CKD and FGF-23 (via ↓ renal tubular 1α hydroxylase)	↓ 1,25-$(OH)_2$D	↑ Phosphate ↑ PTH Metabolic acidosis	↑ Phosphate ↓ 1,25-$(OH)_2$D ↓ Ca^{2+}	CKD (reduced ability of the kidney to generate ammonia and excrete H+)
Results in	↑ PTH ↑ FGF23 ↓ 1,25-$(OH)_2$-D ↑ CVD + mortality	↓ Ca^{2+} ↑ PTH	↑ PTH	↑ Kidney phosphate excretion ↓ Renal tubular 1α hydroxylase Parathyroid hyperplasia ↓ Bone formation and mineralization ↓ BALP ↑ CVD + mortality	↑ Kidney phosphate excretion ↑ FGF-23 Parathyroid hyperplasia ↑ Bone resorption ↑ Bone formation ↑ CVD + mortality	↑ FGF23 ↓ Bone formation ↑ Bone resorption

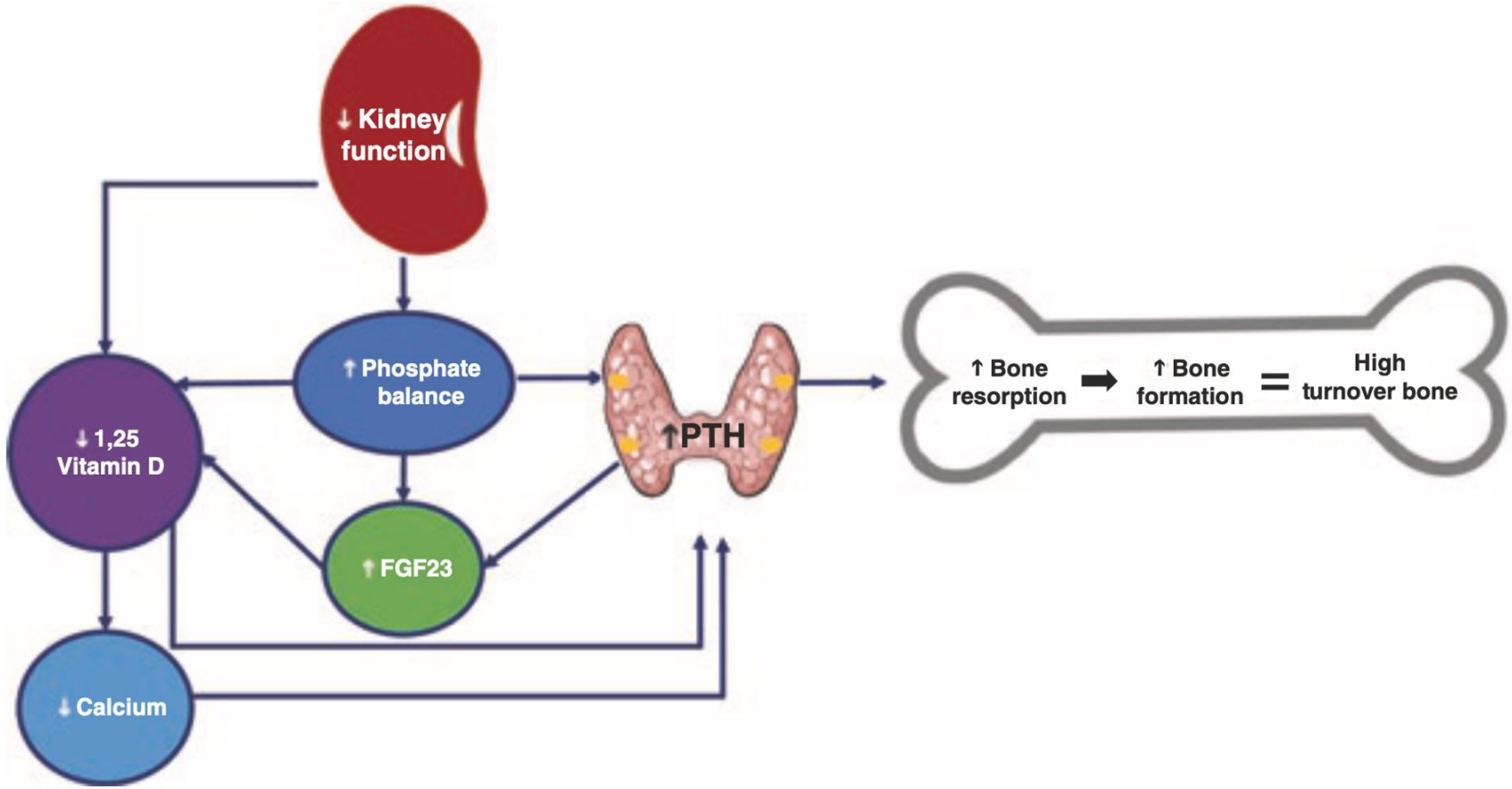


Fig. 10.1 Drivers of secondary hyperparathyroidism in CKD-MBD

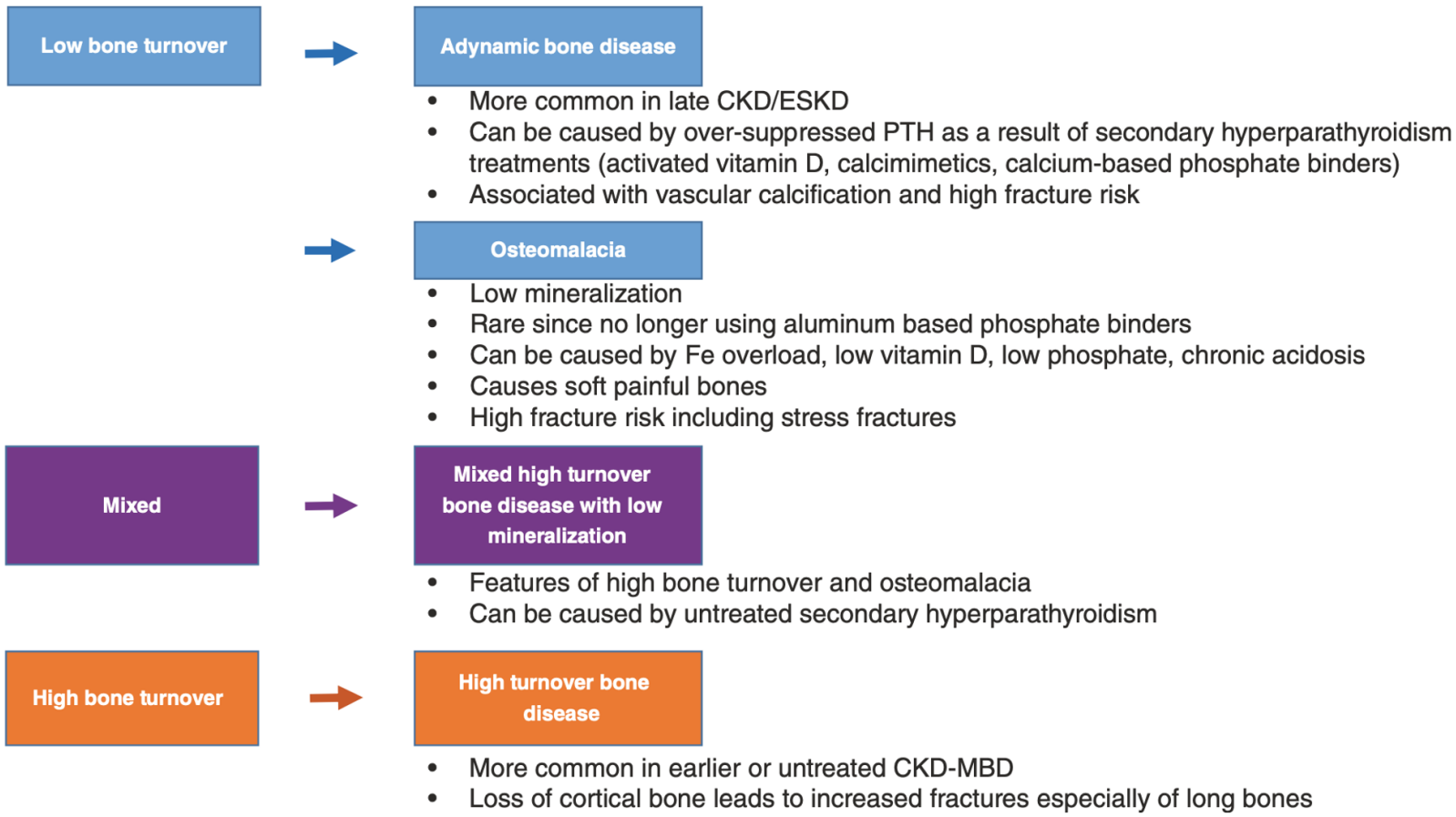


Fig. 10.2 Four types of renal osteodystrophy

The third component of CKD-MBD is extraskeletal calcification. Accelerated vascular calcification is one of the strongest predictors of cardiovascular events and mortality in CKD [5]. Hyperphosphatemia has been consistently shown to increase mortality, likely due to its direct calcifying effect on coronary vessels and valves [6]. Many other mineral and hormonal altera-

tions in CKD-MBD and their treatments have been associated with increased vascular calcification, cardiovascular events, and mortality, including hypercalcemia, the use of calcium-based phosphate binders, high FGF-23, and both high and low PTH [7–9]. Calcimimetics such as cinacalcet that reduce PTH and calcium levels may possibly reduce vascular calcification risk in ESKD [10]. Calciphylaxis is a rare but often deadly condition associated with CKD-MBD seen almost exclusively in advanced CKD/ESKD. It is thought to be caused by hydroxyapatite deposition within vessel layers and surrounding subcutaneous adipose tissue resulting in painful skin ulcerations that turn necrotic and are easily infected. These patients need immediate referral to a multidisciplinary care team including a nephrologist, vascular surgeon, and dermatologist, as the 1-year mortality rate is greater than 50% [11].

Management

The management of CKD-MBD is centered on preventing the adverse consequences associated with secondary hyperparathyroidism.

Hyperphosphatemia

- Low phosphate diet
- Phosphate binders

Hyperphosphatemia drives secondary hyperparathyroidism, increased serum FGF-23, and inhibits vitamin D activation in CKD. As such, an important early intervention in CKD-MBD is counseling the patient on dietary phosphate restriction, less than 800–1000 mg/day, to keep phosphate "toward normal range" [12]. Controlling phosphate intake can be challenging for patients. The typical American diet includes highly processed foods with large amounts of inorganic phosphate additives. These foods contain nearly 60% more phosphate than similar organic sources without additives, and inorganic phosphate is 100% bioavailable [13]. Two recent trials have shown that dietary guidance on

removing foods containing phosphate additives in ESKD patients led to significantly lower serum phosphate levels [14, 15]. Plant-based sources of dietary phosphate, such as grains and legumes, are less bioavailable than natural animal-based sources like dairy, and both of these natural phosphate sources are less bioavailable than foods with inorganic phosphate additives [16, 17].

While dietary control is imperative in hyperphosphatemia, inorganic phosphate additives are ubiquitous and difficult to avoid. Patients will often need medication to help reduce their serum phosphate. Calcium-containing phosphate binders (calcium carbonate and calcium acetate) are the most frequently used worldwide as they are readily available and affordable. However, guidelines now suggest "restricting the dose" of calcium-based binders due to their association with adynamic bone disease, vascular calcification, and mortality, likely attributable to the calcium component [12, 16]. Non-calcium-based binders (sevelamer carbonate and sevelamer hydrochloride) are the most common alternatives; however, like calcium-based binders, their use is limited by pill burden, compliance, and gastrointestinal side effects. Newer phosphate binders contain iron (sucroferric oxyhydroxide and ferric citrate) which have the additional benefit of improving

anemia which is common in CKD patients. A recent trial showed that sucroferric oxyhydroxide slowed vascular calcification in dialysis patients [18]. Intestinal phosphate transport inhibitors, tenapanor and nicotinamide, are currently in preclinical testing. Rather than binding gut phosphorous each meal, these agents block paracellular transport of phosphate, reducing intestinal absorption [17]. How these agents will compare to phosphate binders in terms of efficacy, gastrointestinal side effects, and decreased pill burden remains to be determined.

Secondary Hyperparathyroidism

- Decrease serum phosphate
- Increase 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D
- Decrease PTH with activated vitamin D and/or calcimimetics

The optimal PTH level in CKD is not known. KDIGO suggests reducing "progressively rising or persistently elevated" PTH [12]. Lowering PTH in secondary hyperparathyroidism involves normalizing serum phosphate and repleting both nutritional 25-hydroxyvitamin D deficiency and acquired 1,25-dihydroxyvitamin D deficiency. Activated vitamin D (calcitriol or its analogs doxercalciferol, paricalcitol, and alfacalcidol) is frequently used to effectively lower PTH. These medications can result in hypercalcemia, increased intestinal phosphate absorption, and over-suppression of PTH, so careful attention to

dosing and monitoring of serum calcium, phosphate, and PTH levels is prudent [19, 20]. Current guidelines suggest using activated vitamin D only in patients with CKD 4, 5, and ESKD who have "severe and progressive hyperparathyroidism" [12].

Calcimimetics such as cinacalcet or etelcalcetide can be used as an alternative to or in conjunction with activated vitamin D to treat secondary hyperparathyroidism, but they are currently only approved for use in ESKD. Calcimimetics suppress PTH secretion by binding the calcium-sensing receptor on the parathyroid gland. They effectively control PTH in dialysis patients and are especially useful in patients who have hypercalcemia and hyper-

phosphatemia which limit the use of activated vitamin D. However, despite cinacalcet effectively lowering PTH in a large trial of dialysis patients with severe hyperparathyroidism, there was no reduction in fracture risk or cardiovascular events [21]. Multiple gland parathyroidectomy is ultimately recommended for those with severe hyperparathyroidism who do not respond to or who develop contraindications to medical therapy [12].

Chronic Metabolic Acidosis

Metabolic acidosis is extremely common among CKD patients and can directly contribute to bone loss. Acutely, the bone buffers acid, releasing calcium. Chronic metabolic acidosis tilts the bone turnover scale toward increased resorption and decreased bone formation. It also increases osteoblast production of FGF-23 which further decreases bone formation as well as mineralization [4]. There have been accumulating data that treating metabolic acidosis may slow the progression of kidney disease [22], so CKD guidelines recommend administering base when the serum bicarbonate is less than 22 meq/L. [23] Whether treating metabolic acidosis in CKD improves bone disease has not yet been specifically studied. We treat metabolic acidosis in CKD with a reduced acid diet (lower animal protein) and oral sodium bicarbonate. A new agent, veverimer, that acts as a hydrogen and chloride binder in the gastrointestinal tract, is under investigation for treating metabolic acidosis in CKD and has shown efficacy in early studies [24], although bone effects have not been evaluated.

Osteoporosis

- Assess bone mineral density in CKD 3–5 and ESRD with DXA
- Assess bone turnover, using PTH and bone-specific alkaline phosphatase

It is suggested that any CKD patient with evidence of renal osteodystrophy and fracture should be considered as having osteoporosis, as their bone quality and strength are similarly impaired [1]. New to KDIGO guidelines in 2017, the use of DXA to determine BMD is now recommended in patients with CKD 3 and up, who have "evidence of CKD-MBD or risk factors for osteoporosis" [12]. Treating low BMD in CKD first involves assessing the degree of bone turnover. While a bone biopsy is the gold standard in assessing bone turnover and quality, it is an invasive and lengthy process that is rarely performed clinically [25, 26]. Measuring bone turnover markers such as PTH and BALP is a more practical way to assess bone turnover rates, though these have limitations [1, 27, 28]. Significantly high PTH and BALP levels in CKD patients correlate with high bone turnover, and significantly low levels correlate to low bone turnover states. Unfortunately, intermediate levels are difficult to interpret, and a bone biopsy would be ideal in such patients [1].

- If high bone turnover, consider these agents:
  - Bisphosphonates (dose caution, nephrotoxicity of intravenous forms)
  - Denosumab (monitoring for hypocalcemia)
- If low bone turnover, consider osteoanabolic agents

Treatment of osteoporosis in CKD can be challenging. Bisphosphonates are cleared by the kidney resulting in a prolonged blood half-life, although this is dwarfed by the bone half-life so the clinical implications are unclear [29]. Nephrotoxicity has been reported, particularly with intravenous agents. Pamidronate is associated with focal glomerular sclerosis (especially with multiple high doses), and zoledronic acid has been reported to cause acute tubular injury even at the 4 mg dose [29, 30]. However, recent data suggest that with careful attention to dosing, infusion rates, and treatment frequency in CKD, nephrotoxicity is rare [1]. Denosumab is not cleared by the kidney; however, serum calcium needs to be monitored frequently posttreatment as it can cause severe hypocalcemia in CKD [31]. While bisphosphonates should be avoided in low bone turnover disease, osteoanabolic agents are likely useful in this setting [1]. Teriparatide has been studied in small numbers of patients with

ESKD and low bone turnover [32, 33]. Abaloparatide may have an advantage over teriparatide in that it is less likely to cause hypercalcemia, but this has not been tested in CKD [34].

KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

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

4.2.1: In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we 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 with CKD G3a–G5 not on dialysis, we suggest that 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 children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range (*Not Graded*).

4.2.3: In patients with CKD G5D, we suggest maintaining iPTH levels in the range of approximately 2 to 9 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 G5D requiring PTH-lowering therapy, we 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 (HPT) who fail to respond to medical or pharmacological therapy, we suggest parathyroidectomy (*2B*).

Case Presentation

A 62-year-old woman with chronic kidney disease stage 4 (CKD 4) due to uncontrolled hypertension and diabetes mellitus type 2 is referred for evaluation of elevated parathyroid hormone (PTH). She has had mild diffuse skin itching over the last few months but otherwise feels well without history of bone pain or fractures. On physical exam, she has full range of motion and strength in her joints and extremities. There is no joint inflammation or bony abnormalities. Her skin is well perfused and without rash. Her laboratories are pertinent for serum creatinine 3.2 mg/dL, estimated glomerular filtration rate (eGFR) 20 mL/min, bicarbonate $(HCO_3)^-$ 19 mmol/L (22–31 mmol/L), phosphate 6.2 mg/dL (2.5–4.5 mg/dL), 25-hydroxyvitamin D 18 ng/mL (30–80 ng/mL), 1,25-dihydroxyvitamin D (calcitriol or [1,25-$(OH)_2$-D]) 20 pg/mL (19.9–79.3 pg/mL), calcium (Ca^{2+}) 8.2 mg/dL (8.4–10.5 mg/

dL), albumin 4.0 g/dL, intact PTH 375 pg/mL (15–65 pg/mL), and bone-specific alkaline phosphatase (BALP) 75 μg/L (4–36 μg/L). A CT scan performed 2 months previously showed coronary artery calcifications.

Outcome

We educated our patient to avoid highly bioavailable dietary phosphate loads, such as processed foods with inorganic phosphate additives (e.g., canned food, dark sodas/colas, deli meat), as well as animal-derived phosphate sources including dairy. At her follow-up visit, her serum phosphate remained above normal, and she admitted to struggling with limiting her milk consumption. Sevelamer carbonate was initiated at 800 mg three times daily with meals to bind dietary phosphate in the gut and limit its absorption, with the goal of returning serum phosphate toward normal levels.

We started cholecalciferol 5000 IU daily, achieving a 25-hydroxyvitamin D level of 40 ng/mL. On follow-up, her 1,25-dihydroxyvitamin D and calcium levels remained in the low normal range; however, her PTH was still quite elevated at 288 pg/mL. Calcitriol 0.25 μg 3× weekly was started, which increased her 1,25-dihydroxyvitamin D and calcium levels to the mid-normal range, and reduced PTH to 109 pg/mL.

We added sodium bicarbonate tablets of 650 mg three times daily to our patient's regimen, with improvement in serum HCO_3- level to 23 mEq/L.

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D. Decrease the cinacalcet dosage
E. Increase the calcitriol dosage

ANSWER: D) Decrease the cinacalcet dosage

Thank You