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In Practice

Long-term Management of CKD–Mineral and Bone Disorder

Kevin J. Martin, MB, BCh, and Esther A. González, MD

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is the term used to describe the abnormalities of bone and mineral metabolism that occur in the setting of kidney disease. The spectrum of these abnormalities is wide, ranging from severe high-turnover bone disease on one end to marked low bone turnover bone disease on the other. Similarly, some patients have severe vascular calcifications while others do not, and the values for biochemistry determinations, including calcium, phosphorus, and parathyroid hormone, also may vary widely among patients. This variability may be influenced by such things as the chronicity of the particular kidney disease, effects of therapies such as corticosteroids on modifying the course of kidney disease, and comorbid conditions, such as diabetes, heart disease, age, and osteoporosis. The heterogeneity of CKD-MBD makes strict protocol-driven therapeutic approaches difficult; accordingly, considerable individualized therapy is required. Using a case history, we explore several of the variables and difficulties involved in patient management.
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INDEX WORDS: Chronic kidney disease–mineral and bone disorder (CKD-MBD); hyperparathyroidism; renal osteodystrophy.

CASE PRESENTATION

A 56-year-old white woman with a history of lupus nephritis class 4, which had been treated with prednisone and intravenous cyclophosphamide with an apparent good response, returned to the nephrology clinic after a 6-year absence. During that time, she had remained asymptomatic, discontinued all medications, and did not seek medical care. Evaluation showed the following values: serum creatinine, 4.1 mg/dL (362.44 μmol/L; estimated glomerular filtration rate [eGFR], 12 mL/min/1.73 m^2 [0.20 mL/s/1.73 m^2]), which previously was 1.2 mg/dL (106.1 μmol/L); calcium, 8.9 mg/dL (2.22 mmol/L); phosphorus, 4.8 mg/dL (1.55 mmol/L); 25-hydroxyvitamin D, 14 ng/mL (34.94 nmol/L); intact parathyroid hormone (iPTH), 432 pg/mL (432 ng/L); and hemoglobin, 9.4 g/dL (94 g/L). Ultrasound showed kidney size to be 9.1 and 8.7 cm. Urinary protein-creatinine ratio was 2.4 g/g. Urine sediment was unremarkable. Anti–double-stranded DNA was negative and C3 and C4 levels were normal. Blood pressure was 152/82 mm Hg, and there was mild peripheral edema. Therapy was initiated with furosemide; lisinopril; ergocalciferol, 50,000 units every 2 weeks; darbepoetin; and calcium carbonate, 500 mg, with meals. After 3 months of treatment, 25-hydroxyvitamin D level increased to 26 ng/mL (64.90 nmol/L), and iPTH level decreased to 296 pg/mL (296 ng/L). During the next 6 months, serum creatinine level slowly increased, and hemodialysis therapy was initiated when serum creatinine level reached 8.7 mg/dL (769.1 μmol/L; eGFR, 5 mL/min/1.73 m^2 [0.08 mL/s/1.73 m^2]) through an arteriovenous fistula. While receiving hemodialysis, the patient remained clinically well during the next 2 years and was placed on the transplant list. Cardiac stress echocardiography was negative for ischemia, but left ventricular hypertrophy and modest calcification of the mitral valve were noted. Calcium carbonate therapy was stopped and sevelamer was begun as a phosphate binder to treat phosphorus values ranging from 5.4-6.2 mg/mL (1.74-2.0 mmol/L). iPTH levels progressively increased, peaking at 562 pg/mL (562 ng/L); treatment with paricalcitol, 2 μg per dialysis treatment, was begun. PTH level remained at 364-486 pg/mL (364-486 ng/L) for the next year. After approximately 3 years on dialysis therapy, the patient began to notice vague pains in her hip and knee joints and legs and back. Pain was aggravated by exercise, and overall, she felt that her health was declining. These symptoms gradually became worse during the ensuing months. Review of laboratory values for the past year showed calcium values in the low-normal range, phosphorus values of 5.1-6.2 mg/dL (1.6-2.0 mmol/L), and iPTH values of 372-463 pg/mL (372-463 ng/L). Alkaline phosphatase level was 192 U/L, having increased from 139 U/L 1 year earlier. Dual-energy x-ray absorptiometry showed a T score of −2.3 at the hip. Bone biopsy showed severe osteitis fibrosa. Paricalcitol therapy was intensified, and iPTH values stabilized near 200 pg/mL (200 ng/L) during the next 6 months, with a marked decrease in skeletal symptoms occurring after 3 months of intensified paricalcitol therapy.

INTRODUCTION

Our view of the consequences of abnormal bone and mineral metabolism in the setting of chronic kidney disease (CKD) has evolved from focusing entirely on the skeleton to a broader perspective in which not only are bone abnormalities observed and require therapy, but these abnormalities also seem to be related to cardiovascular disease (specifically vascular calcification) and are implicated in increased mortality risk. Accordingly, the term renal osteodystrophy can be considered to represent the skeletal abnormalities, whereas the broader term CKD–mineral and bone disorder (CKD-MBD) spans the full spectrum of the consequences of abnormal bone and mineral metabolism in people with CKD.[1] Secondary hyperpara-

From the Division of Nephrology, Saint Louis University, St Louis, MO.

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Address correspondence to Kevin J. Martin, MB, BCh, Division of Nephrology, Saint Louis University Medical Center, Division of Nephrology (9-FDT), 3635 Vista Ave, St Louis, MO 63110. E-mail: martinkj@slu.edu

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thyroidism is a major part of the MBD spectrum and has been one focus of research to understand the factors that generate and maintain hyperparathyroidism.[2]

To date, it is well established that phosphate retention and abnormalities in vitamin D metabolism result from CKD and, either directly or by inducing changes in serum calcium levels, stimulate the growth and activity of the parathyroid glands. The resultant high levels of PTH in blood can affect the bone, causing osteitis fibrosa (high-turnover bone disease), manifest with demineralization of bone, predisposition to fractures, and not infrequently, bone pain. In addition, the consequences of high PTH levels may extend to nonskeletal tissue, contributing to abnormalities in multiple systems throughout the body, most notably cardiovascular disease, with manifestations including left ventricular hypertrophy, vascular calcification, and hypertension.

Abnormalities in vitamin D metabolism occur early in the course of CKD, with 1,25-dihydroxyvitamin D levels having been shown to decrease progressively, thereby promoting increases in PTH levels. One reason for the decrease in 1,25-dihydroxyvitamin D levels is phosphate retention, which may directly suppress the activity of 1-hydroxylase or may act indirectly by increasing levels of fibroblast growth factor 23 (FGF-23), which in turn will decrease 1α-hydroxylase activity and increase 24-hydroxylase activity.[3,4] Compensatory efforts to maintain the concentration of 1,25-dihydroxyvitamin D are compromised because 25-hydroxyvitamin D levels have been shown to be reduced in many people with CKD, possibly contributing to the inability of the damaged kidney to augment 1,25-dihydroxyvitamin D production when needed, even in the presence of hyperparathyroidism.[5] The accumulation of N-terminally truncated PTH fragments also may decrease 1α-hydroxylase activity.[6] Ultimately, when kidney disease is advanced, 1,25-dihydroxyvitamin D production may be limited most by the marked decrease in renal parenchymal mass.

PRINCIPLES OF THERAPY

As the pathophysiology of secondary hyperparathyroidism has been elucidated over the past, our understanding of this pathophysiology has provided a rational framework for therapy in which the abnormalities noted to contribute to hyperparathyroidism are directly targeted with therapeutic efforts. As listed in Box 1, the principles of therapy for hyperparathyroidism are to control phosphorus levels and prevent phosphate retention, correct hypocalcemia if it is present because this is the major driver of PTH secretion, supply vitamin D sterols to counteract the abnormalities in vitamin D metabolism, and, finally, consider the use of a calcimimetic agent or parathyroidectomy to directly control PTH secretion at the level of the parathyroid gland. These measures are undertaken in the context of minimizing the calcium burden to the patient to prevent excessive calcium loading, which may aggravate the progression of vascular calcification.

Box 1. Principles of Therapy of Hyperparathyroidism in ESRD

Consider calcium balance

- Control hyperphosphatemia/phosphate retention
- Correct hypocalcemia (if present)
- Consider vitamin D sterols

Consider use of calcimimetic therapy or parathyroidectomy in select patients

Abbreviation: ESRD, end-stage renal disease.

Just as there is a wide spectrum of clinical and biochemical abnormalities in patients with CKD, there is also a wide spectrum of therapeutic approaches to the patient with CDK-MBD, as illustrated in Fig 1. Thus, some clinicians favor a vitamin D–based approach with calcimimetic as add-on therapy, whereas others favor the use of a low-dose vitamin D sterol as background for calcimimetic-based therapy. The details of individual patients likely determine the appropriate approach, as well as issues of treatment adherence, cost, and comorbid conditions. There presently are no definitive long-term data to compare these approaches. These principles have been derived mostly from observations in patients with end-stage renal disease (ESRD), but to some degree may be applied to the earlier stages of CKD when the abnormalities in bone and mineral homeostasis begin. Calcimimetic therapy is not approved for use in patients with CKD not on dialysis therapy and therefore is not recommended for such patients at this time.

In the patient under discussion, the opportunity to begin therapy early in the course of CKD was not possible because of loss of follow-up. However, in general, therapy should be undertaken at this time if possible. Because clinically measurable hyperphosphatemia does not occur until GFR is $<$20 mL/min/1.73 m^2 ($<$0.33 mL/s/1.73 m^2), the use of phosphate binders is not part of routine clinical practice. However, phosphate binders perhaps should be considered in light of extensive experimental observations in animals, in which dietary phosphorus restriction in proportion to the decrease in GFR was shown to be effective in preventing the development of secondary hyperparathyroidism.[7,8] It is possible that in the future, measurements of FGF-23 might be useful in early CKD because these values may increase even before elevations in PTH levels are seen.[9] However, current practice guidelines