Update on Mineral and Bone Disorders in Chronic Kidney Disease

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KEYWORDS

• Renal secondary hyperparathyroidism • Fibroblast growth factor 23
• Renal osteodystrophy • Hyperphosphatemia

KEY POINTS

- Phosphorus retention occurs early in chronic kidney disease, resulting in elevated serum concentrations of fibroblast growth factor 23 and parathyroid hormone.
- Increased serum concentrations of fibroblast growth factor 23 and parathyroid hormone lead to a constellation of syndromes called bone and mineral disorders in chronic kidney disease and also contribute to progression of kidney disease.
- Minimizing phosphorus retention through dietary therapy and medical intervention can improve these hormone elevations and may prevent or mitigate subsequent consequences.

MINERAL AND BONE DISORDERS IN CHRONIC KIDNEY DISEASE

Disturbances of mineral metabolism, including calcium, phosphorus, and magnesium, are common in patients with chronic kidney disease (CKD). Because of deranged renal handling of these minerals, and particularly phosphorus, aberrations in concentrations of parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), and calcitriol develop. These alterations and the multiple clinical syndromes they lead to are collectively called CKD–mineral and bone disorder (CKD-MBD).[1–4] A summary of known, suspected, and unreported manifestations of CKD-MBD in dogs and cats is listed in **Box 1**.

Renal Secondary Hyperparathyroidism

The central force driving this process is continued intake of phosphorus exceeding the diminished capacity of the kidneys to excrete phosphorus due to reduced glomerular filtration rate (GFR) consequent to CKD.[5] Phosphorus retention initially stimulates FGF-23 production from osteoclasts and then in later stages of CKD phosphorus

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Box 1
Consequences of chronic kidney disease–mineral and bone disorder in dogs and cats

Known to occur
Renal secondary hyperparathyroidism
Accelerated progression of kidney disease
Increased mortality rate
Renal osteodystrophy
Cardiac arrhythmia
Extraskeletal calcification
Hypocalcemia
Hypercalcemia
Hypomagnesemia
Hypermagnesemia
Likely to occur
Decreased bone density
Vessel calcification
Not recognized
Pulmonary hypertension
Atherosclerosis
Valvular calcification
Tertiary hyperparathyroidism
Impaired skeletal response to PTH
Adynamic bone disease

retention, and ultimately hyperphosphatemia, promotes increased synthesis of PTH. FGF-23 needs α-klotho as a coreceptor for most of its actions, although some klotho-independent actions are emerging.[6] α-Klotho is expressed primarily in the kidney and parathyroid glands. FGF-23 binds to the FGF-1 receptor and α-klotho to downregulate the two main sodium-linked phosphate transporters responsible for phosphorus reabsorption in the proximal tubule of the kidney (NPT2a and NPT2c). Reduced reabsorption of phosphorus thereby increases phosphate excretion. FGF-23 also inhibits phosphate absorption from the intestine indirectly by inhibiting the conversion of 25-hydroxycholecalciferol (calcidiol) to 1,25 dihydroxycholecalciferol (calcitriol). In addition, FGF-23 decreases the synthesis of PTH from the parathyroid gland. Similar to FGF-23, PTH also inhibits renal phosphorus reabsorption through downregulation of NPT2a and NPT2c.[7] However, in contrast to the action of FGF-23, PTH increases the synthesis of calcitriol from calcidiol. Calcitriol will result in increased calcium and phosphorus absorption from the gastrointestinal tract (GI) tract. The primary role of PTH is to maintain serum ionized calcium (iCa) concentration; the increased renal excretion of phosphorus is a secondary activity. FGF-23 seems to be mainly involved with serum phosphorus regulation.

Patients with mild reduction in GFR retain sufficient functional nephrons to effectively respond to these increased hormone concentrations. Because FGF-23 and