TREATMENT FLUID, ELECTROLYTE, AND ACID-BASE DISORDERS

Dietary salt restriction and the use of loop diuretics, occasionally in combination with metolazone, may be needed to maintain euvolemia. In contrast, overzealous salt restriction or diuretic use can lead to ECFV depletion and precipitate a further decline in GFR. The rare patient with salt-losing nephropathy may require a sodium-rich diet or salt supplementation. Water restriction is indicated only if there is a problem with hyponatremia. Intractable ECFV expansion, despite dietary salt restriction and diuretic therapy, may be an indication to start renal replacement therapy. Hyperkalemia often responds to dietary restriction of potassium, the use of kaliuretic diuretics, and avoidance of both potassium supplements (including occult sources, such as dietary salt substitutes) and potassium-retaining medications (especially angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]). Kaliuretic diuretics promote urinary potassium excretion, whereas potassium-binding resins, such as calcium resonium or sodium polystyrene, can promote potassium loss through the GI tract and may reduce the incidence of hyperkalemia. Intractable hyperkalemia is an indication (although uncommon) to consider institution of dialysis in a CKD patient. The renal tubular acidosis and subsequent anion-gap metabolic acidosis in progressive CKD will respond to alkali supplementation, typically with sodium bicarbonate. Recent studies suggest that this replacement should be considered when the serum bicarbonate concentration falls below 20–23 mmol/L to avoid the protein catabolic state seen with even mild degrees of metabolic acidosis and to slow the progression of CKD.

DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM

The principal complications of abnormalities of calcium and phosphate metabolism in CKD occur in the skeleton and the vascular bed, with occasional severe involvement of extraosseous soft tissues. It is likely that disorders of bone turnover and disorders of vascular and soft tissue calcification are related to each other (Fig. 335-3).

Bone Manifestations of CKD The major disorders of bone disease can be classified into those associated with high bone turnover with increased PTH levels (including osteitis fibrosa cystica, the classic lesion of secondary hyperparathyroidism) and low bone turnover with low or normal PTH levels (adynamic bone disease and osteomalacia).

The pathophysiology of secondary hyperparathyroidism and the consequent high-turnover bone disease is related to abnormal mineral metabolism through the following events: (1) declining GFR leads to reduced excretion of phosphate and, thus, phosphate retention; (2) the retained phosphate stimulates increased synthesis of both FGF-23 by osteocytes and PTH and stimulates growth of parathyroid gland mass; and (3) decreased levels of ionized calcium, resulting from suppression of calcitriol production by FGF-23 and by the failing kidney, as well as phosphate retention, also stimulate PTH production. Low calcitriol levels contribute to hyperparathyroidism, both by leading to hypocalcemia and also by a direct effect on PTH gene transcription. These changes start to occur when the GFR falls below 60 mL/min.

FGF-23 is part of a family of phosphatonins that promotes renal phosphate excretion. Recent studies have shown that levels of this hormone, secreted by osteocytes, increase early in the course of CKD, even before phosphate retention and hyperphosphatemia. FGF-23 may defend normal serum phosphorus in at least three ways: (1) increased renal phosphate excretion; (2) stimulation of PTH, which also increases renal phosphate excretion; and (3) suppression of the formation of $1,25(OH)_2D_3$, leading to diminished phosphorus absorption from the GI tract. Interestingly, high levels of FGF-23 are also an independent risk factor for left ventricular hypertrophy and mortality in CKD, dialysis, and renal transplant patients. Moreover, elevated levels of FGF-23 may indicate the need for therapeutic intervention (e.g., phosphate restriction), even when serum phosphate levels are within the normal range.

Tumoral Calcinosis in a Dialysis Patient

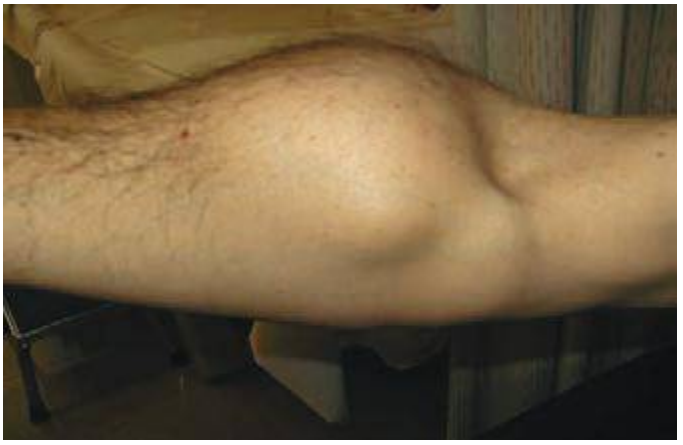

FIGURE 335-4 Tumoral calcinosis. This patient was on hemodialysis for many years and was nonadherent to dietary phosphorus restriction or the use of phosphate binders. He was chronically severely hyperphosphatemic. He developed an enlarging painful mass on his arm that was extensively calcified.

Hyperparathyroidism stimulates bone turnover and leads to *osteitis fibrosa cystica*. Bone histology shows abnormal osteoid, bone and bone marrow fibrosis, and in advanced stages, the formation of bone cysts, sometimes with hemorrhagic elements so that they appear brown in color, hence the term *brown tumor*. Clinical manifestations of severe hyperparathyroidism include bone pain and fragility, brown tumors, compression syndromes, and erythropoietin resistance in part related to the bone marrow fibrosis. Furthermore, PTH itself is considered a uremic toxin, and high levels are associated with muscle weakness, fibrosis of cardiac muscle, and nonspecific constitutional symptoms.

Low-turnover bone disease can be grouped into two categories—adynamic bone disease and osteomalacia. Adynamic bone disease is increasing in prevalence, especially among diabetics and the elderly. It is characterized by reduced bone volume and mineralization and may result from excessive suppression of PTH production, chronic inflammation, or both. Suppression of PTH can result from the use of vitamin D preparations or from excessive calcium exposure in the form of calcium-containing phosphate binders or high-calcium dialysis solutions. Complications of adynamic bone disease include an increased incidence of fracture and bone pain and an association with increased vascular and cardiac calcification. Occasionally the calcium will precipitate in the soft tissues into large concretions termed "tumoral calcinosis" (Fig. 335-4).

Calcium, Phosphorus, and the Cardiovascular System Recent epidemiologic evidence has shown a strong association between hyperphosphatemia and increased cardiovascular mortality rate in patients with stage 5 CKD and even in patients with earlier stages of CKD. Hyperphosphatemia and hypercalcemia are associated with increased vascular calcification, but it is unclear whether the excessive mortality rate is mediated by this mechanism. Studies using computed tomography (CT) and electron-beam CT scanning show that CKD patients have calcification of the media in coronary arteries and even heart valves that appear to be orders of magnitude greater than that in patients without renal disease. The magnitude of the calcification is proportional to age and hyperphosphatemia and is also associated with low PTH levels and low bone turnover. It is possible that in patients with advanced kidney disease, ingested calcium cannot be deposited in bones with low turnover and, therefore, is deposited at extraosseous sites, such as the vascular bed and soft tissues. It is interesting in this regard that there is also an association between osteoporosis and vascular calcification in the general population. Finally, hyperphosphatemia can induce a change in gene expression in vascular cells to an osteoblast-like profile, leading to vascular calcification and even ossification.