TABLE 423-3 CAUSES OF HYPERPHOSPHATEMIA

I. Impaired renal phosphate excretion
  A. Renal insufficiency
  B. Hypoparathyroidism
    1. Developmental
    2. Autoimmune
    3. After neck surgery or radiation
    4. Activating mutations of the calcium-sensing receptor
  C. Parathyroid suppression
    1. Parathyroid-independent hypercalcemia
      a. Vitamin D or vitamin A intoxication
      b. Sarcoidosis, other granulomatous diseases
      c. Immobilization, osteolytic metastases
      d. Milk-alkali syndrome
    2. Severe hypermagnesemia or hypomagnesemia
  D. Pseudohypoparathyroidism
  E. Acromegaly
  F. Tumoral calcinosis
  G. Heparin therapy
II. Massive extracellular fluid phosphate loads
  A. Rapid administration of exogenous phosphate (intravenous, oral, rectal)
  B. Extensive cellular injury or necrosis
    1. Crush injuries
    2. Rhabdomyolysis
    3. Hyperthermia
    4. Fulminant hepatitis
    5. Cytotoxic therapy
    6. Severe hemolytic anemia
  C. Transcellular phosphate shifts
    1. Metabolic acidosis
    2. Respiratory acidosis

suppression, increased intestinal calcium absorption, and focal hyperostosis with large, lobulated periarticular heterotopic ossifications (especially at shoulders or hips) and are accompanied by hyperphosphatemia. In some forms of tumoral calcinosis, serum phosphorus levels are normal.

When large amounts of phosphate are delivered rapidly into the ECF, hyperphosphatemia can occur despite normal renal function. Examples include overzealous IV phosphate therapy, oral or rectal administration of large amounts of phosphate-containing laxatives or enemas (especially in children), extensive soft tissue injury or necrosis (crush injuries, rhabdomyolysis, hyperthermia, fulminant hepatitis, cytotoxic chemotherapy), extensive hemolytic anemia, and transcellular phosphate shifts induced by severe metabolic or respiratory acidosis.

Clinical Findings The clinical consequences of acute, severe hyperphosphatemia are due mainly to the formation of widespread calcium phosphate precipitates and resulting hypocalcemia. Thus, tetany, seizures, accelerated nephrocalcinosis (with renal failure, hyperkalemia, hyperuricemia, and metabolic acidosis), and pulmonary or cardiac calcifications (including development of acute heart block) may occur. The severity of these complications relates to the elevation of serum phosphate levels, which can reach concentrations as high as 7 mmol/L (20 mg/dL) in instances of massive soft tissue injury or tumor lysis syndrome.

TREATMENT HYPERPHOSPHATEMIA

Therapeutic options for management of severe hyperphosphatemia are limited. Volume expansion may enhance renal phosphate clearance. Aluminum hydroxide antacids or sevelamer may be helpful in chelating and limiting absorption of offending phosphate salts present in the intestine. Hemodialysis is the most effective therapeutic strategy and should be considered early in the course of severe hyperphosphatemia, especially in the setting of renal failure and symptomatic hypocalcemia.

MAGNESIUM METABOLISM

Magnesium is the major intracellular divalent cation. Normal concentrations of extracellular magnesium and calcium are crucial for normal neuromuscular activity. Intracellular magnesium forms a key complex with ATP and is an important cofactor for a wide range of enzymes, transporters, and nucleic acids required for normal cellular function, replication, and energy metabolism. The concentration of magnesium in serum is closely regulated within the range of 0.7–1 mmol/L (1.5–2 meq/L; 1.7–2.4 mg/dL), of which 30% is protein-bound and another 15% is loosely complexed to phosphate and other anions. One-half of the 25 g (1000 mmol) of total body magnesium is located in bone, only one-half of which is insoluble in the mineral phase. Almost all extraskeletal magnesium is present within cells, where the total concentration is 5 m*M*, 95% of which is bound to proteins and other macromolecules. Because only 1% of body magnesium resides in the ECF, measurements of serum magnesium levels may not accurately reflect the level of total body magnesium stores.

Dietary magnesium content normally ranges from 6 to 15 mmol/d (140–360 mg/d), of which 30–40% is absorbed, mainly in the jejunum and ileum. Intestinal magnesium absorptive efficiency is stimulated by $1,25(OH)_2D$ and can reach 70% during magnesium deprivation. Urinary magnesium excretion normally matches net intestinal absorption and is ~4 mmol/d (100 mg/d). Regulation of serum magnesium concentrations is achieved mainly by control of renal magnesium reabsorption. Only 20% of filtered magnesium is reabsorbed in the proximal tubule, whereas 60% is reclaimed in the cTAL and another 5–10% in the DCT. Magnesium reabsorption in the cTAL occurs via a paracellular route that requires both a lumen-positive potential, created by NaCl reabsorption, and tight-junction proteins encoded by members of the Claudin gene family. Magnesium reabsorption in the cTAL is increased by PTH but inhibited by hypercalcemia or hypermagnesemia, both of which activate the CaSR in this nephron segment.

HYPOMAGNESEMIA

Causes Hypomagnesemia usually signifies substantial depletion of body magnesium stores (0.5–1 mmol/kg). Hypomagnesemia can result from intestinal malabsorption; protracted vomiting, diarrhea, or intestinal drainage; defective renal tubular magnesium reabsorption; or rapid shifts of magnesium from the ECF into cells, bone, or third spaces (Table 423-4). Dietary magnesium deficiency is unlikely except possibly in the setting of alcoholism. A rare genetic disorder that causes selective intestinal magnesium malabsorption has been described (primary infantile hypomagnesemia). Another rare inherited disorder (hypomagnesemia with secondary hypocalcemia) is caused by mutations in the gene encoding TRPM6, a protein that, along with TRPM7, forms a channel important for both intestinal and distal-tubular renal transcellular magnesium transport. Malabsorptive states, often compounded by vitamin D deficiency, can critically limit magnesium absorption and produce hypomagnesemia despite the compensatory effects of secondary hyperparathyroidism and of hypocalcemia and hypomagnesemia to enhance cTAL magnesium reabsorption. Diarrhea or surgical drainage fluid may contain ≥5 mmol/L of magnesium. Proton pump inhibitors (omeprazole and others) may produce hypomagnesemia by an unknown mechanism that does not involve renal wasting of magnesium.

Several genetic magnesium-wasting syndromes have been described, including inactivating mutations of genes encoding the DCT NaCl co-transporter (Gitelman's syndrome), proteins required for cTAL Na-K-2Cl transport (Bartter's syndrome), claudin 16 or claudin 19 (autosomal recessive renal hypomagnesemia with hypercalciuria), a DCT Na^+,K^+-ATPase γ-subunit (autosomal dominant renal hypomagnesemia with hypocalciuria), DCT K^+ channels (Kv1.1, Kir4.1), and a mitochondrial gene encoding a tRNA. Activating mutations