increase in serum phosphate as a result of diminished glomerular filtration. However, hypercalcemia may occur in patients with chronic renal failure as a result of calcium antacid use or as a result of $1,25(OH)_2D$ or paracalcitol treatment to prevent renal osteodystrophy.

Parenteral Nutrition

Enteric and parenteral forms of nutrition have been associated with hypercalcemia. Large doses of oral calcium provided in hypercaloric enteric feeding regimens, particularly in the setting of reduced renal function, may lead to a form of the milk-alkali syndrome. More mysterious is the well-described hypercalcemic syndrome occurring in patients treated with total parenteral nutrition (TPN). These patients typically have short-bowel syndrome and are on long-term TPN. In some patients, the hypercalcemia can be traced to large amounts of calcium, vitamin D, or aluminum in the TPN solution.

Hyperproteinemia

About 50% of circulating calcium is bound to serum albumin and other proteins. Increases in serum proteins naturally lead to an artifactual increase in total, but not ionized, serum calcium concentrations. This increase is commonly observed in settings of volume depletion and dehydration. Patients with this syndrome do not display features typical of authentic hypercalcemia: reduced mental status, prolonged QTc interval on the electrocardiogram, and hypercalciuria. Treatment of the "hypercalcemia" should be avoided, because it may lead to hypocalcemic symptoms and signs such as paresthesia, tetany, and seizures.

Treatment of Hypercalcemia

A point worth emphasizing is that not everyone requires treatment for hypercalcemia. Patients with mild HPT with borderline serum calcium values and without other complications may be observed. Patients with end-stage refractory cancer with severe hypercalcemia arguably may be best served by withholding therapy. Familial hypocalciuric hypercalcemia is best left untreated.

Therapy for hypercalcemia is optimally directed at reversing the underlying pathophysiologic abnormality. Disorders associated with increased intestinal calcium absorption (e.g., sarcoid, milk-alkali syndrome, $1,25[OH]_2D_3$-secreting lymphomas) are best treated by consuming a low-calcium diet and avoiding vitamin D. Hypercalcemia in the setting of volume depletion and diminished renal function is managed by expanding the ECF volume and GFR with saline and encouraging diuresis with loop diuretics.

Medications that induce hypercalcemia should be discontinued. Disorders associated with increased osteoclastic bone resorption, such as MAHC and immobilization hypercalcemia, are best treated using inhibitors of bone resorption such as the bisphosphonates pamidronate or zoledronate. Disorders with multiple abnormalities require combinations of these measures. Resection of parathyroid tissue in patients with parathyroid disease is effective, and cinacalcet or bisphosphonates may be used if parathyroid surgery cannot be performed.

HYPOCALCEMIA

Symptoms and Signs

Hypocalcemia leads to a reduction in the potential difference across cell membranes, producing hyperexcitability, particularly of cells of the neuromuscular class (see Chapter 72). Neuromuscular cells spontaneously fire and produce spontaneous seizures, paresthesias, and skeletal muscle contractions (i.e., carpal spasm, pedal spasm, or tetany).

Two physical signs are observed on examination: Trousseau sign, which is spontaneous contraction of the forearm muscles in response to application of a blood pressure cuff around the upper arm and inflation to above systolic pressure, and Chvostek sign, which is twitching of the facial muscles with gentle tapping of the facial nerve as it exits the parotid gland. An electrocardiographic sign is a prolonged QTc interval. Prolonged hypoparathyroidism may be associated with basal ganglia calcification, which is asymptomatic but impressive on computed tomography scans and plain x-ray films of the skull.

Pathophysiology

Hypocalcemia may result from five mechanisms: a reduction in serum binding proteins (e.g., albumin), an increase in serum phosphate with a resultant increase in the calcium-phosphate solubility product, an increase in renal calcium excretion, a reduction in intestinal calcium absorption, or a loss of calcium from the ECF into the skeleton. In practice, several of these factors are operative in several disorders. For example, in hypoparathyroidism, a reduction in intestinal calcium absorption combines with an inability to reabsorb calcium from the distal tubule to cause hypocalcemia, or in breast cancer with extensive osteoblastic metastases, increases in osteoblast activity remove calcium from the ECF, and anorexia leads to a reduction in intestinal calcium intake. This knowledge is important because effective therapy requires the underlying disorder to be appropriately managed. Giving oral vitamin D supplements to a patient with sprue may not be effective unless the underlying malabsorption is treated; parenteral vitamin D may be more effective.

Differential Diagnosis

Disorders that may lead to hypocalcemia are summarized in the following sections and Table 73-2.

Hypoparathyroidism

Hypoparathyroidism causes hypocalcemia as a result of a decrease in intestinal calcium absorption combined with reduced renal calcium reabsorption in the distal tubule. Hypoparathyroidism may be idiopathic or autoimmune, occurring in isolation or as part of the polyglandular failure syndrome in association with Graves' hyperthyroidism, Hashimoto's thyroiditis, Addison's disease, type 1 diabetes, vitiligo, mucocutaneous candidiasis, and other autoimmune disorders. Hypoparathyroidism may commonly be encountered as surgical hypoparathyroidism in patients who have undergone thyroid, parathyroid, or laryngeal surgery. Surgical and autoimmune hypoparathyroidism together account for most patients with hypoparathyroidism. Less common causes include congenital hypoparathyroidism caused by DiGeorge syndrome, isolated parathyroid failure, or genetic mutations. Rarely,