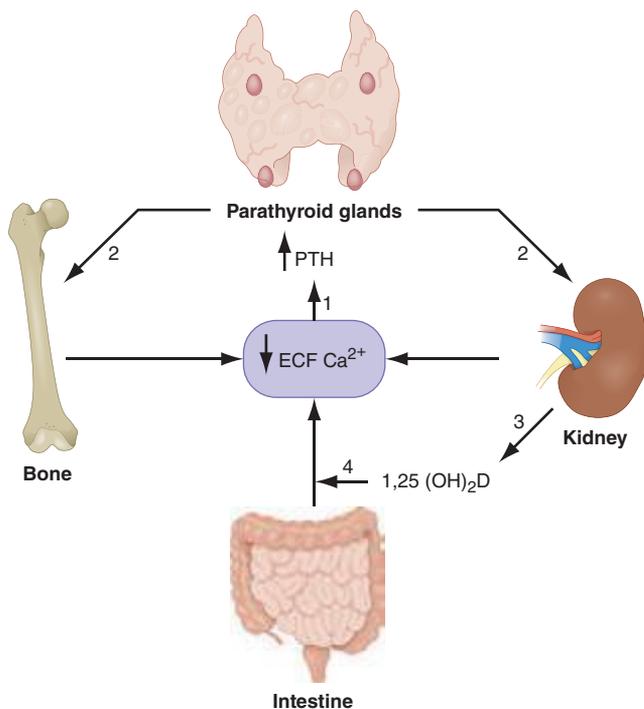


The calcium ion plays a critical role in normal cellular function and signaling, regulating diverse physiologic processes such as neuromuscular signaling, cardiac contractility, hormone secretion, and blood coagulation. Thus, extracellular calcium concentrations are maintained within an exquisitely narrow range through a series of feedback mechanisms that involve parathyroid hormone (PTH) and the active vitamin D metabolite 1,25-dihydroxyvitamin D [ $1,25(\text{OH})_2\text{D}$ ]. These feedback mechanisms are orchestrated by integrating signals between the parathyroid glands, kidney, intestine, and bone (Fig. 65-1; Chap. 423). Disorders of serum calcium concentration are relatively common and often serve as a harbinger of underlying disease. This chapter provides a brief summary of the approach to patients with altered serum calcium levels. See Chap. 424 for a detailed discussion of this topic.

## HYPERCALCEMIA

### ETIOLOGY

The causes of hypercalcemia can be understood and classified based on derangements in the normal feedback mechanisms that regulate serum calcium (Table 65-1). Excess PTH production, which is not appropriately suppressed by increased serum calcium concentrations, occurs in primary neoplastic disorders of the parathyroid glands (parathyroid adenomas; hyperplasia; or, rarely, carcinoma) that are associated with



**FIGURE 65-1** Feedback mechanisms maintaining extracellular calcium concentrations within a narrow, physiologic range (8.9–10.1 mg/dL [2.2–2.5 mM]). A decrease in extracellular (ECF) calcium ( $\text{Ca}^{2+}$ ) triggers an increase in parathyroid hormone (PTH) secretion (1) via the calcium sensor receptor on parathyroid cells. PTH, in turn, results in increased tubular reabsorption of calcium by the kidney (2) and resorption of calcium from bone (2) and also stimulates renal  $1,25(\text{OH})_2\text{D}$  production (3).  $1,25(\text{OH})_2\text{D}$ , in turn, acts principally on the intestine to increase calcium absorption (4). Collectively, these homeostatic mechanisms serve to restore serum calcium levels to normal.

**TABLE 65-1** CAUSES OF HYPERCALCEMIA

Excessive PTH production
Primary hyperparathyroidism (adenoma, hyperplasia, rarely carcinoma)
Tertiary hyperparathyroidism (long-term stimulation of PTH secretion in renal insufficiency)
Ectopic PTH secretion (very rare)
Inactivating mutations in the CaSR or in G proteins (FHH)
Alterations in CaSR function (lithium therapy)
Hypercalcemia of malignancy
Overproduction of PTHrP (many solid tumors)
Lytic skeletal metastases (breast, myeloma)
Excessive $1,25(\text{OH})_2\text{D}$ production
Granulomatous diseases (sarcoidosis, tuberculosis, silicosis)
Lymphomas
Vitamin D intoxication
Primary increase in bone resorption
Hyperthyroidism
Immobilization
Excessive calcium intake
Milk-alkali syndrome
Total parenteral nutrition
Other causes
Endocrine disorders (adrenal insufficiency, pheochromocytoma, VIPoma)
Medications (thiazides, vitamin A, antiestrogens)

**Abbreviations:** CaSR, calcium sensor receptor; FHH, familial hypocalciuric hypercalcemia; PTH, parathyroid hormone; PTHrP, PTH-related peptide.

increased parathyroid cell mass and impaired feedback inhibition by calcium. Inappropriate PTH secretion for the ambient level of serum calcium also occurs with heterozygous inactivating calcium sensor receptor (CaSR) or G protein mutations, which impair extracellular calcium sensing by the parathyroid glands and the kidneys, resulting in familial hypocalciuric hypercalcemia (FHH). Although PTH secretion by tumors is extremely rare, many solid tumors produce PTH-related peptide (PTHrP), which shares homology with PTH in the first 13 amino acids and binds the PTH receptor, thus mimicking effects of PTH on bone and the kidney. In PTHrP-mediated hypercalcemia of malignancy, PTH levels are suppressed by the high serum calcium levels. Hypercalcemia associated with granulomatous disease (e.g., sarcoidosis) or lymphomas is caused by enhanced conversion of  $25(\text{OH})\text{D}$  to the potent  $1,25(\text{OH})_2\text{D}$ . In these disorders,  $1,25(\text{OH})_2\text{D}$  enhances intestinal calcium absorption, resulting in hypercalcemia and suppressed PTH. Disorders that directly increase calcium mobilization from bone, such as hyperthyroidism or osteolytic metastases, also lead to hypercalcemia with suppressed PTH secretion as does exogenous calcium overload, as in milk-alkali syndrome, or total parenteral nutrition with excessive calcium supplementation.

### CLINICAL MANIFESTATIONS

Mild hypercalcemia (up to 11–11.5 mg/dL) is usually asymptomatic and recognized only on routine calcium measurements. Some patients may complain of vague neuropsychiatric symptoms, including trouble concentrating, personality changes, or depression. Other presenting symptoms may include peptic ulcer disease or nephrolithiasis, and fracture risk may be increased. More severe hypercalcemia (>12–13 mg/dL), particularly if it develops acutely, may result in lethargy, stupor, or coma, as well as gastrointestinal symptoms (nausea, anorexia, constipation, or pancreatitis). Hypercalcemia decreases renal concentrating ability, which may cause polyuria and polydipsia. With longstanding hyperparathyroidism, patients may present with bone pain or pathologic fractures. Finally, hypercalcemia can result in significant electrocardiographic changes, including bradycardia, AV block, and short QT interval; changes in serum calcium can be monitored by following the QT interval.