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# Normal Physiology of Bone and Mineral Homeostasis

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## CALCIUM HOMEOSTASIS

The maintenance of normal calcium homeostasis is critical to survival for at least three reasons. First, the serum calcium concentration regulates the degree of membrane excitability in muscle and nervous tissue. Increases in serum calcium levels produce refractoriness to stimulation of neurons and muscle cells, which translates clinically into coma and muscular weakness. Conversely, reductions in serum calcium levels lead to increases in neuromuscular excitability that translate clinically into convulsions and spontaneous muscle cramps and contractions referred to as *carpopedal spasm* or *tetany*. Second, terrestrial life requires the existence of a skeleton, and calcium is the major structural cation in the skeleton. The mineral phase of the skeleton is composed of a calcium salt called *hydroxyapatite*, and reductions in bone mineral content lead to spontaneous fractures. Third, intracellular calcium has a major intracellular signaling role, and control of intracellular calcium is essential to the survival of all cells. This mechanism is used to advantage pharmacologically through the widespread clinical use of drugs that regulate intracellular calcium concentrations and calcium-channel activity for the treatment of a wide variety of human diseases. Physicians, regardless of their specialty, encounter disorders of calcium homeostasis on a regular basis.

The serum total calcium concentration is normally maintained at about 9.5 mg/dL. Of this total amount, about 4.5 mg/dL is bound to serum proteins, principally albumin, and about 0.5 mg/dL circulates as insoluble complexes such as calcium sulfate, phosphate, and citrate. The remaining 4.5 mg/dL circulates as free or unbound or ionized calcium. This free, ionized serum calcium is important clinically and physiologically. This calcium is available to be filtered at the glomerulus, to interact with cell membranes to regulate their electrical potential or excitability, and to enter and exit the skeletal hydroxyapatite crystal lattice.

It is important to maintain normal levels of ionized serum calcium, although total serum calcium is customarily measured in most clinical laboratories. In some instances, total serum calcium can change without a change in the ionized calcium level. For example, if the serum albumin level declines as a result of hepatic cirrhosis or the nephrotic syndrome, the total serum calcium also declines, but the ionized serum calcium concentration remains normal. Measuring the ionized serum calcium level directly is sometimes important.

A complex group of regulatory processes have evolved to protect the integrity of this system. When a physician encounters patients in whom hypercalcemia, hypocalcemia, or disorders of skeletal mineralization have occurred, multiple safety control points have been breached (discussed later).

To maintain homeostatic control, the calcium ion interfaces with three important compartments, as shown in the calcium physiologic black box in Figure 72-1. Although intracellular calcium is important in intracellular signaling, it is quantitatively unimportant in overall systemic calcium homeostasis. The three critical regulatory fluxes that maintain normal serum calcium concentration are those of the intestine, kidney, and skeleton.

### Calcium Fluxes into and out of Extracellular Fluid

#### Intestinal Calcium Absorption

The normal dietary calcium intake for an adult is about 1000 mg per day. About 300 mg of the total is absorbed (i.e., unidirectional absorption is about 30%), and this absorption occurs in the duodenum and proximal jejunum. About 150 mg of calcium per day is secreted by the liver (in bile), the pancreas (in pancreatic secretions), and the intestinal glands such that net absorption (called *fractional absorption*) of calcium is about 15% of intake.

The efficiency of calcium absorption is regulated at the level of the small intestinal epithelial cell, the enterocyte, by the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D),

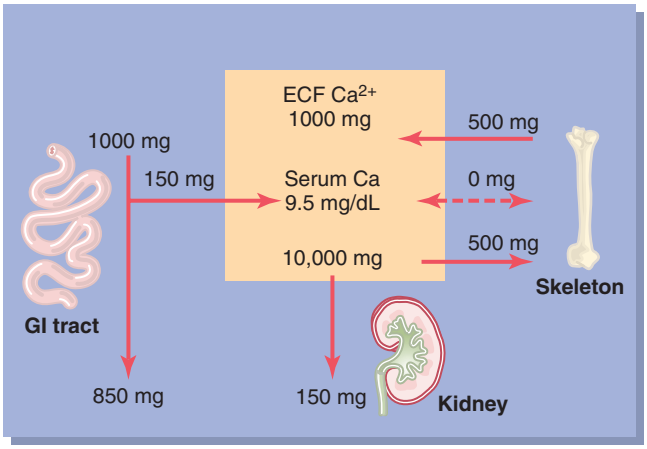


**FIGURE 72-1** The calcium physiologic black box. The central box represents extracellular fluid (ECF), which contains a total of about 1000 mg of calcium. It has three regulatory interfaces with the gastrointestinal (GI) tract, skeleton, and kidney. The fluxes into and out of the ECF are measured in milligrams per day.