action of $1,25(OH)_2D$ is to regulate intestinal calcium absorption. PTH, through $1,25(OH)_2D$, indirectly regulates calcium absorption from the diet by the intestine. The hypocalcemia of hypoparathyroidism is a result, in part, of inadequate intestinal calcium absorption. Conversely, hyperparathyroidism is associated with hypercalciuria and nephrolithiasis, both of which directly result from increases in circulating $1,25(OH)_2D$ levels. Measurement of $1,25(OH)_2D$ can be used as an index of parathyroid function and intestinal calcium absorption.

Calcitonin

Calcitonin is produced by the parafollicular or C cells of the thyroid gland in response to hypercalcemia. It was once viewed as an essential calcium-regulating hormone. Pharmacologic doses of calcitonin may reduce serum calcium levels, but little evidence exists that calcitonin has homeostatic relevance in humans.

Integration of Calcium Homeostasis

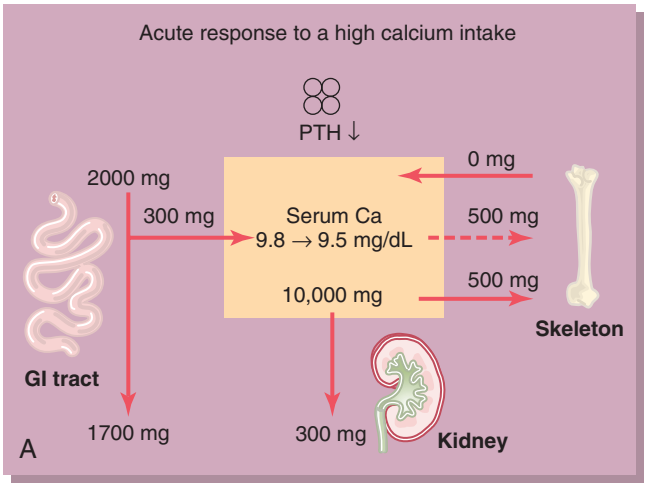
Ingestion of a greater than normal dietary calcium load (Fig. 72-6A) leads to a mild rise in the serum calcium level, followed by immediate suppression of PTH. This action immediately permits marked increases in renal calcium excretion by the distal tubule. It also immediately deceases osteoclastic activity, which prevents continued bone resorption but allows continued calcium entry from the ECF into an unmineralized osteoid sink. These two effects produce a rapid, short-term reduction in serum calcium to normal levels. However, if the high-calcium diet is maintained over the long term, these adaptations are insufficient. Continued renal calcium wasting leads to hypercalciuria (with nephrolithiasis and nephrocalcinosis), and unopposed osteoblastic bone formation leads to excessive skeletal mineralization (i.e., osteopetrosis).

Two additional responses (see Fig. 72-6B) are required to prevent the long-term adverse effects of a high-calcium diet. First, subacute or chronic suppression of PTH reduces circulating $1,25(OH)_2D$. This reduces the efficiency of calcium absorption from the intestine, calcium entry into the ECF, and urinary calcium excretion. Second, a chronic decrement in PTH leads to a chronic decline in osteoblastic activity. No osteoid is formed, and the ability to deposit calcium into the skeletal sink is lost.

Conversely, during brief periods of dietary calcium deficiency (Fig. 72-7A), as occurs between meals, the serum calcium level declines almost imperceptibly and the PTH rises, which immediately prevents renal calcium losses from continuing. At the same time, an acute activation of osteoclasts occurs, delivering calcium into the ECF. The acute response to low calcium intake is the appropriate elimination of renal calcium losses and development of a new source of calcium entry into the ECF.

Over the longer term, the initial response is inadequate and leads to skeletal demineralization. A longer-term solution is required, and the adaptation is twofold (see Fig. 72-7B). First, a chronic low calcium intake, as may occur in a person with lactose intolerance, leads to a chronic elevation in PTH, and over a matter of days to weeks, this leads to an increase in the $1,25(OH)_2D$ level, which increases the efficiency of calcium absorption from the intestine (i.e., increase in the fractional absorption of calcium) to compensate for the reduction in dietary intake. Second, chronically elevated PTH leads to an increase in osteoblast activity and osteoid synthesis, with resultant increases in skeletal calcium deposition. In this steady-state adaptation to a low-calcium diet, PTH levels are elevated, and coupled increases in osteoclastic and osteoblastic activities take place (i.e., increased bone turnover), but net skeletal calcium losses are negligible or normal.

From an evolutionary standpoint, as life moved from a calcium-rich marine environment to a terrestrial setting in which calcium availability was unpredictable, a complex, elegant regulatory mechanism evolved that permitted survival without requiring intentional behavioral adaptations to the vagaries of calcium supply. As discussed in Chapter 73, disorders that cause hypercalcemia or hypocalcemia are always caused by abnormalities at the interfaces of the ECF with the intestine, kidney, and skeleton. The physician need only recall these homeostatic premises to dissect the pathophysiologic process with precision and treat the underlying disorder effectively.



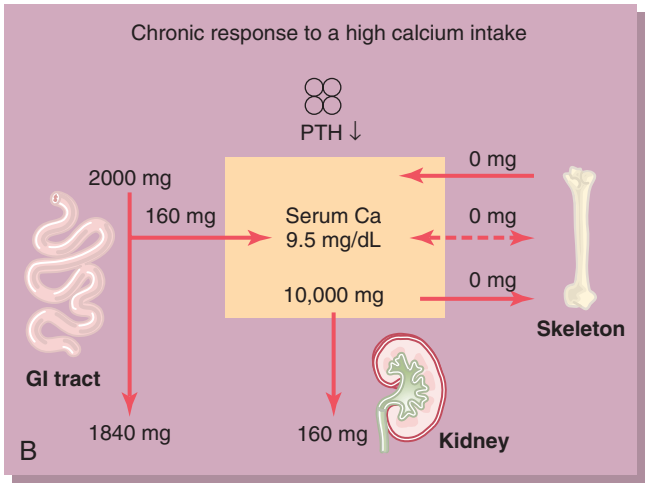


FIGURE 72-6 Responses to increases in calcium intake. **A,** The acute response. **B,** The chronic response. Details are provided in the text. GI, Gastrointestinal.