Disturbances of Serum Calcium

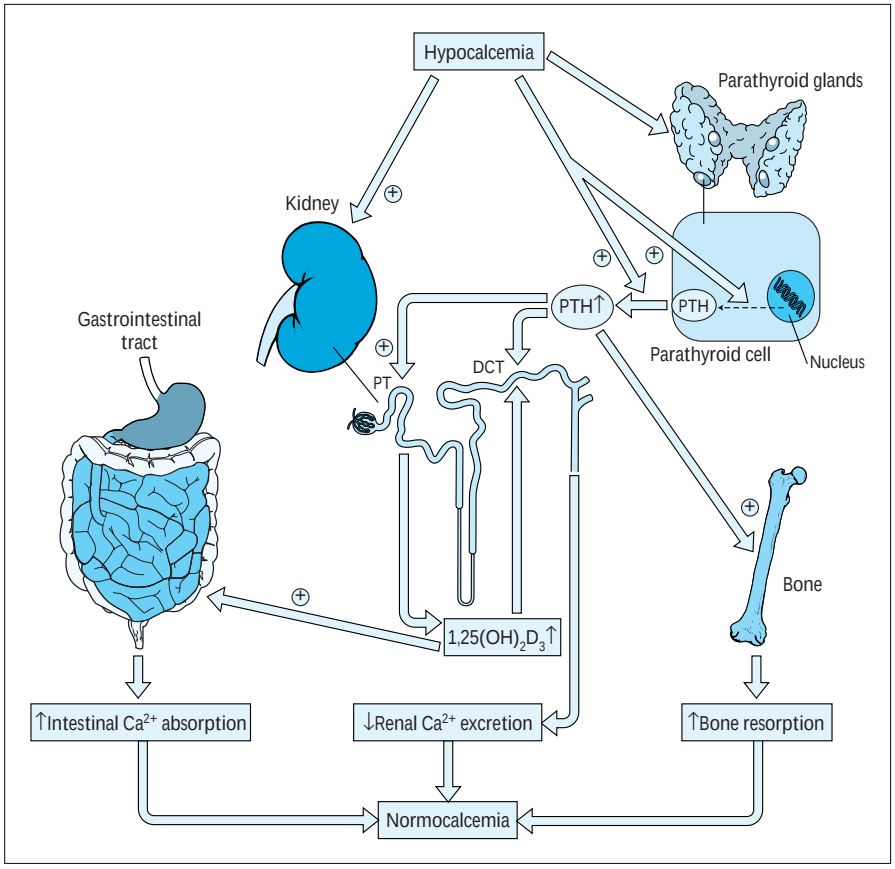

FIGURE 5-17

Physiologic response to hypocalcemia. Hypocalcemia stimulates both parathyroid hormone (PTH) release and PTH synthesis. Both hypocalcemia and PTH increase the activity of the 1-α-hydroxylase enzyme in the proximal tubular (PT) cells of the nephron, which increases the synthesis of 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). PTH increases bone resorption by osteoclasts. PTH and $1,25(OH)_2D_3$ stimulate Ca reabsorption in the distal convoluted tubule (DCT). $1,25(OH)_2D_3$ increases the fractional absorption of dietary Ca by the gastrointestinal (GI) tract. All these mechanisms aid in returning the serum Ca to normal levels [1].

CAUSES OF HYPOCALCEMIA

Lack of parathyroid hormone (PTH)
- After thyroidectomy or parathyroidectomy
- Hereditary (congenital) hypoparathyroidism
- Pseudohypoparathyroidism (lack of effective PTH)
- Hypomagnesemia (blocks PTH secretion)

Lack of Vitamin D
- Dietary deficiency or malabsorption (osteomalacia)
- Inadequate sunlight
- Defective metabolism
  - Anticonvulsant therapy
  - Liver disease
  - Renal disease
  - Vitamin D–resistant rickets

Increased calcium complexation
- "Bone hunger" after parathyroidectomy
- Rhabdomyolysis
- Acute pancreatitis
- Tumor lysis syndrome (hyperphosphatemia)
- Malignancy (increased osteoblastic activity)

FIGURE 5-18

Causes of hypocalcemia (decrease in ionized plasma calcium).

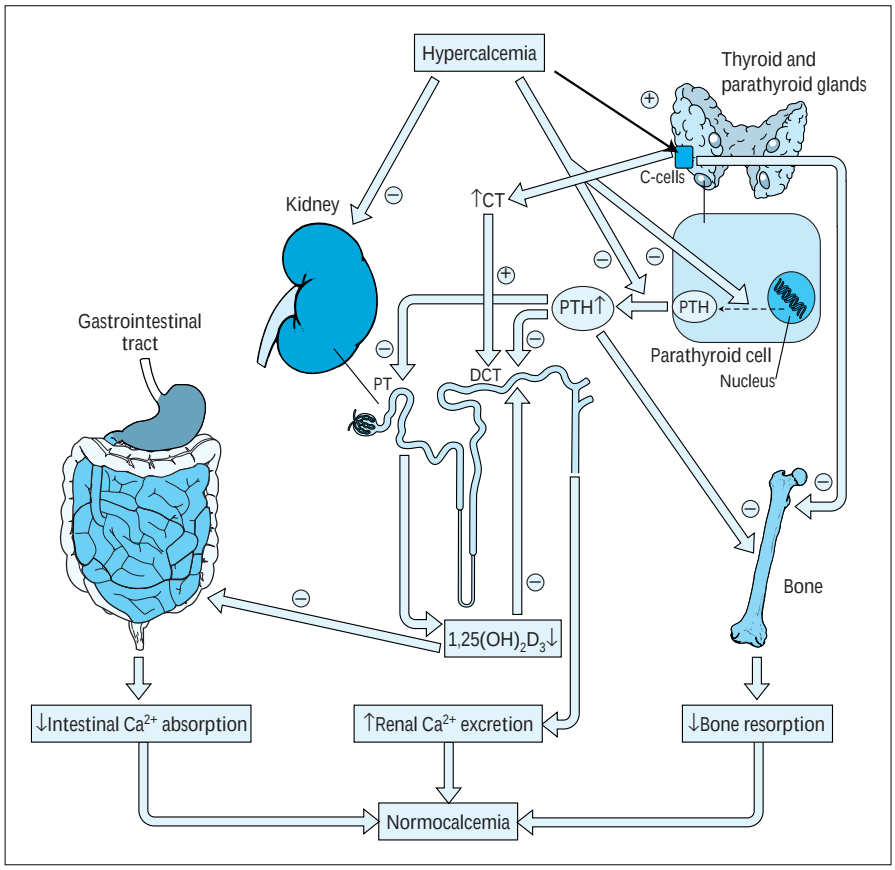

FIGURE 5-19

Physiologic response to hypercalcemia. Hypercalcemia directly inhibits both parathyroid hormone (PTH) release and synthesis. The decrease in PTH and hypercalcemia decrease the activity of the 1-α-hydroxylase enzyme located in the proximal tubular (PT) cells of the nephron, which in turn, decreases the synthesis of 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). Hypercalcemia stimulates the C cells in the thyroid gland to increase synthesis of calcitonin (CT). Bone resorption by osteoclasts is blocked by the increased CT and decreased PTH. Decreased levels of PTH and $1,25(OH)_2D_3$ inhibit Ca reabsorption in the distal convoluted tubules (DCT) of the nephrons and overwhelm the effects of CT, which augment Ca reabsorption in the medullary thick ascending limb leading to an increase in renal Ca excretion. The decrease in $1,25(OH)_2D_3$ decreases gastrointestinal (GI) tract absorption of dietary Ca. All of these effects tend to return serum Ca to normal levels [1].

CAUSES OF HYPERCALCEMIA

Excess parathyroid hormone (PTH) production
- Primary hyperparathyroidism
- "Tertiary" hyperparathyroidism*

Excess 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$)
- Vitamin D intoxication
- Sarcoidosis and granulomatous diseases
- Severe hypophosphatemia
- Neoplastic production of $1,25(OH)_2D_3$ (lymphoma)

Increased bone resorption
- Metastatic (osteolytic) tumors (*eg*, breast, colon, prostate)
- Humoral hypercalcemia
  - PTH-related protein (*eg*, squamous cell lung, renal cell cancer)
  - Osteoclastic activating factor (myeloma)
  - $1,25\ (OH)_2D_3$ (lymphoma)
  - Prostaglandins
- Hyperthyroidism
- Immobilization
- Paget disease
- Vitamin A intoxication

Increased intestinal absorption of calcium
- Vitamin D intoxication
- Milk-alkali syndrome*

Decreased renal excretion of calcium
- Familial hypocalciuric hypercalcemia
- Thiazides

Impaired bone formation and incorporation of calcium
- Aluminum intoxication*
- Adynamic ("low-turnover") bone disease*
- Corticosteroids

*Occurs in renal failure.

FIGURE 5-20

Causes of hypercalcemia (increase in ionized plasma calcium).

AVAILABLE THERAPY FOR HYPERCALCEMIA*

Agent	Mechanism of action
Saline and loop diuretics	Increase renal excretion of calcium
Corticosteroids	Block 1,25-dihydroxy-vitamin D_3 synthesis and bone resorption
Ketoconazole	Blocks P450 system, decreases 1, 25-dihydroxy-vitamin D_3
Oral or intravenous phosphate	Complexes calcium
Calcitonin	Inhibits bone resorption
Mithramycin	Inhibits bone resorption
Bisphosphonates	Inhibit bone resorption

*Always identify and treat the primary cause of hypercalcemia.

FIGURE 5-21
Therapy available for the treatment of hypercalcemia.

Secondary Hyperparathyroidism

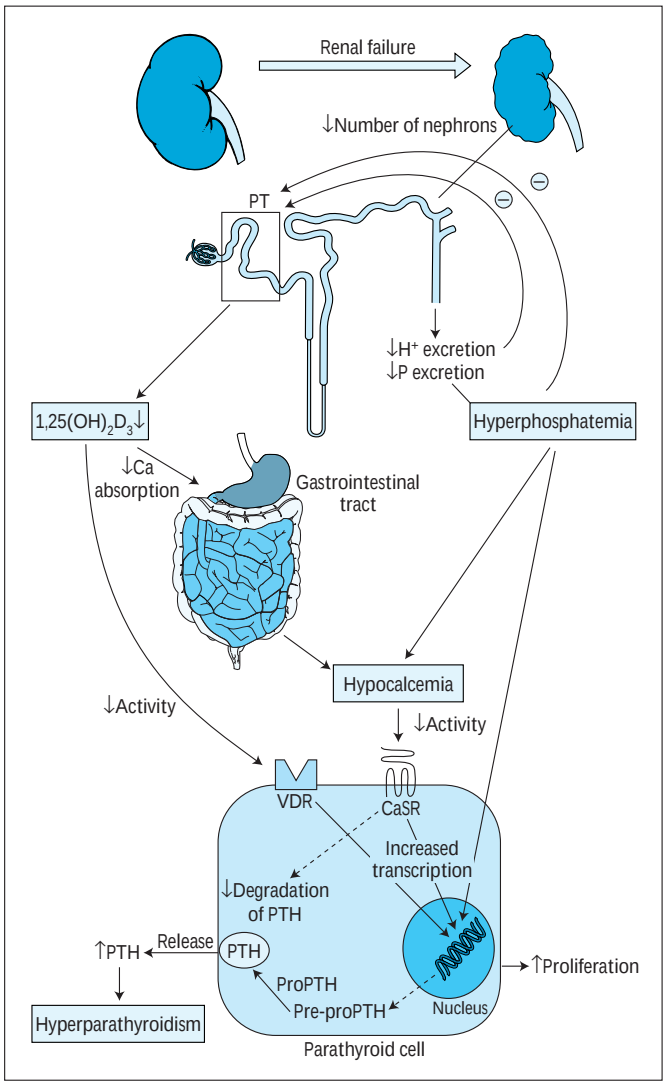

FIGURE 5-22
Pathogenesis of secondary hyperparathyroidism (HPT) in chronic renal failure (CRF). Decreased numbers of proximal tubular (PT) cells, owing to loss of renal mass, cause a quantitative decrease in synthesis of 1,25-dihydroxy-vitamin D_3 ($1,25(OH)_2D_3$). Loss of renal mass also impairs renal phosphate (P) and acid (H^+) excretion. These impairments further decrease the activity of the 1-α-hydroxylase enzyme in the remaining PT cells, further contributing to the decrease in levels of $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ deficiency decreases intestinal absorption of calcium (Ca), leading to hypocalcemia, which is augmented by the direct effect of hyperphosphatemia. Hypocalcemia and hyperphosphatemia stimulate PTH release and synthesis and can recruit inactive parathyroid cells into activity and PTH production. Hypocalcemia also may decrease intracellular degradation of PTH. The lack of $1,25(OH)_2D_3$, which would ordinarily feed back to inhibit the transcription of prepro-PTH and exert an antiproliferative effect on parathyroid cells, allows the increased PTH production to continue. In CRF there may be decreased expression of the Ca-sensing receptor (CaSR) in parathyroid cells, making them less sensitive to levels of plasma Ca. Patients with the b allele or the bb genotype vitamin D receptor (VDR) may be more susceptible to HPT, because the VDR-$1,25(OH)_2D_3$ complex is less effective at suppressing PTH production and cell proliferation. The deficiency of $1,25(OH)_2D_3$ may also decrease VDR synthesis, making parathyroid cells less sensitive to $1,25(OH)_2D_3$. Although the PTH receptor in bone cells is downregulated in CRF (*ie*, for any level of PTH, bone cell activity is lower in CRF patients than in normal persons), the increased plasma levels of PTH may have harmful effects on other systems (*eg*, cardiovascular system, nervous system, and integument) by way of alterations of intracellular Ca. Current therapeutic methods used to decrease PTH release in CRF include correction of hyperphosphatemia, maintenance of normal to high-normal levels of plasma Ca, administration of $1,25(OH)_2D_3$ orally or intravenously, and administration of a Ca-ion sensing receptor (CaSR) agonist [14–16,19–22].