CASE 38

A 70-year-old woman is brought to the emergency department with right flank pain, nausea, vomiting, and blood in her urine. She has no fever or urinary tract symptoms. She has recurrent kidney stones, vague abdominal pain, muscle weakness, and atrophy. On examination, she is in moderate distress secondary to her flank pain. She appears thin and fragile. Other than right back pain, her physical examination is normal. Urinalysis reveals large amounts of blood but no signs of infection. An intravenous pyelogram (IVP) is performed and reveals numerous kidney stones. A metabolic panel shows an extremely elevated calcium level. Further workup demonstrates that the patient has hyperparathyroidism from a parathyroid adenoma.

◆ How does parathyroid hormone (PTH) increase intestinal calcium absorption?

◆ What effect do elevated levels of PTH have on renal phosphate reabsorption?

◆ What are three factors that increase the activity of 1α-hydroxylase in the kidney?
ANSWERS TO CASE 38: CALCIUM METABOLISM

Summary: A 70-year-old woman who presents to the emergency department with kidney stones, abdominal pain, and muscle weakness is found to have hyperparathyroidism.

◆ **PTH and intestinal calcium absorption:** Increases absorption by increasing the production of 1,25-dihydroxycholecalciferol (1α-hydroxylase activity is increased).

◆ **Elevated levels of PTH and effect on phosphate:** Inhibits renal phosphate reabsorption in proximal tubule, resulting in phosphate excretion.

◆ **Three factors that increase 1α-hydroxylase activity:** Increased PTH, decreased serum calcium and phosphate levels.

CLINICAL CORRELATION

Hypercalcemia can be caused by a variety of conditions, including those which increase calcium absorption (milk-alkali syndrome), decrease calcium excretion (thiazide use), increase mobilization of the bone (hyperparathyroidism), and involve metastatic cancer (breast, prostate, etc.). A patient’s symptoms depend on the level of hypercalcemia. With a mild elevation, a patient may be asymptomatic. With increasing levels, patients may have constipation, anorexia, nausea, vomiting, abdominal pain, nephrolithiasis, renal failure, emotional lability, confusion, psychosis, or coma.

Objectives

1. Understand the synthesis, regulation, and secretion of PTH.
2. Understand the synthesis, regulation, and secretion of calcitonin.
3. Know about the role of vitamin D in calcium metabolism.

Definitions

**PTH:** A hormone that plays a critical role in controlling calcium and phosphate balance.

**1,25-dihydroxyvitamin D (calcitriol, 1,25-dihydroxycholecalciferol):** The most active form of vitamin D.

**25-hydroxyvitamin D (calcidiol, 25-hydroxycholecalciferol):** An inactive form of vitamin D.

**1α-hydroxylase:** The enzyme that converts the inactive form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D.
DISCUSSION

Calcium plays an essential role in many cellular processes, including muscle contraction, hormone secretion, cell proliferation, and gene expression. Hence, calcium balance is critical for the maintenance of normal body functions. Calcium balance is a dynamic process that reflects a balance among calcium absorption by the intestinal tract, calcium excretion by the kidney, and release and uptake of calcium by bone during bone formation and resorption (see the references at the end of this case). Most body calcium is stored in bone (~1000 g), which is a very dynamic site as bone is remodeled continuously, with only approximately 0.1% in the extracellular fluid (~1 g). Although only a small fraction of total body calcium (and phosphate) is located in the plasma, it is the plasma concentration of ionized calcium (and phosphate) that is tightly regulated, primarily under the control of PTH and vitamin D. Both of these hormones regulate calcium absorption by the intestine, bone formation and resorption, and urinary calcium excretion. Calcitonin and, to a smaller extent, estrogens also regulate calcium and phosphate homeostasis, although the mechanisms are not fully understood.

PTH, a peptide hormone, is synthesized and secreted by the chief cells of the parathyroid glands. In contrast to most secretory processes, low levels of extracellular calcium (ionized plasma calcium) induce secretion of PTH, whereas high levels inhibit secretion of PTH. The ionized calcium levels are sensed by a calcium-sensing receptor, CaSR, in the plasma membrane; this is a G protein–coupled receptor. Upon binding of calcium during periods of high calcium levels, phospholipase C (PLC) is activated, generating 1,4,5-triphosphate (IP₃) and diacylglycerol (DAG) and, in turn, inducing release of calcium from internal storage sites and activation of protein kinase C (PKC), respectively. Both the elevation of intracellular calcium levels and the activation of PKC inhibit the secretion (and synthesis) of PTH. In contrast, in the presence of low plasma calcium levels, less calcium is bound to the CaSR, leading to enhanced PTH secretion (and synthesis).

PTH is a potent regulator of plasma-ionized calcium levels, acting at three sites to increase plasma levels. First, PTH enhances intestinal calcium (and phosphate) absorption in the presence of permissive amounts of vitamin D (see below). Second, PTH stimulates bone resorption, resulting in the release of calcium phosphate. Third, PTH stimulates the active reabsorption of calcium from the kidney (see Case 26). The effects of PTH at the three sites lead to an elevation in ionized plasma calcium levels. In the presence of low PTH levels, these effects are reversed, resulting in a lowering of plasma calcium levels (see Figure 38-1).

Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels. Its role in calcium metabolism first was recognized in the childhood disease rickets, which is associated with a deficiency of a fat-soluble vitamin and is characterized by a hypocalcemia with various skeletal abnormalities. The disease is corrected by dietary vitamin
Figure 38-1. Regulation of plasma Ca^{2+} by PTH. PTH secretion from the chief cells of the parathyroid gland is regulated by plasma Ca^{2+} levels. High plasma Ca^{2+} levels are sensed by the chief cell calcium-sensing receptor to inhibit PTH synthesis and secretion, while low plasma Ca^{2+} levels have the opposite effect, stimulating PTH synthesis and secretion. In the presence of low plasma Ca^{2+}, PTH secretion works to increase plasma Ca^{2+} at three sites: the kidney, where PTH promotes Ca^{2+} reabsorption from the late distal tubule and connecting tubule and promotes conversion of 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D, in the proximal tubule; the intestine, where the elevated levels of 1,25-dihydroxyvitamin D (because of elevated PTH) stimulate calcium absorption; and bone, where PTH promotes net bone resorption. All three sites lead to an increase in plasma Ca^{2+} levels back toward normal values (see text for more details).
Vitamin D replacement therapy. Vitamin D is present in the diet and can be synthesized in the skin from 7-dehydrocholesterol in the presence of ultraviolet light. As this molecule passes through the liver, it is hydroxylated to 25-hydroxyvitamin D (25-hydroxycholecalciferol), the inactive form of vitamin D. 25-Hydroxyvitamin D travels by the circulation to the kidney, where proximal tubule cells contain the enzyme 1α-hydroxylase, which converts the molecule to 1,25-dihydroxyvitamin D, the most active form of vitamin D. The activity of the 1α-hydroxylase is tightly controlled by PTH and plasma phosphate levels. PTH and hypophosphatemia stimulate 1α-hydroxylase activity, resulting in elevated vitamin D levels and the maintenance of calcium (and phosphate) balance (see below). In contrast, low PTH levels and hyperphosphatemia inhibit the enzyme, reducing the production of vitamin D.

Although vitamin D has numerous actions, its two dominant actions appear to be to enhance the availability of calcium and phosphate for new bone formation and to prevent an abnormal rise or fall in plasma calcium and phosphate levels such as symptomatic hypocalcemia and hypophosphatemia. It does this by acting on all three primary sites of regulation of calcium balance. First, vitamin D increases the production of several intestinal proteins, including a luminal membrane calcium channel and a high-affinity cytosolic calcium-binding protein (calbindin), that enhance transepithelial absorption of calcium. PTH also is thought to stimulate intestinal calcium absorption, but this may be an indirect effect in which the PTH-induced increase in vitamin D formation in the kidney leads to enhanced intestinal calcium absorption. Second, in the kidney, vitamin D appears to act in a synergistic fashion with PTH to induce active calcium reabsorption in the distal convoluted tubule and connecting tubule (see Case 26) by increasing the synthesis of a distinct luminal membrane calcium channel and a cytosolic calcium-binding protein (calbindin). Third, vitamin D induces resorption of bone, mobilization of calcium, and bone mineralization after an elevation of plasma calcium levels. Hence, the actions of vitamin D on calcium metabolism are complex, but all point to control of the prevention of alterations in plasma calcium levels.

Calcitonin is a third hormone that is thought to underlie control of calcium balance, although its role in humans is not well defined. Calcitonin is synthesized and secreted by C cells in the thyroid gland. It is stored in secretory vesicles within the C cells and released after an elevation in extracellular calcium levels above normal. The role of calcitonin in calcium homeostasis, however, is questioned. With complete removal of calcitonin in thyroidectomized individuals or with overproduction of calcitonin in individuals with rare C-cell tumors, plasma calcium, vitamin D, and PTH levels are normal. Nonetheless, calcitonin may play a secondary role in calcium homeostasis in tissue that expresses a calcitonin receptor. The osteoclast bone cells appear to be a particular target of calcitonin; high levels of calcitonin are sensed and lead to inhibition of bone resorption, thereby slowing bone turnover and potentially
contributing to the generation of hypocalcemia. In the kidney, calcitonin causes mild natriuresis and calciuresis, which may contribute to the hypocalcemic (and hypophosphatemic) actions of calcitonin. Hence, a central role of calcitonin in regulating calcium metabolism in humans is not evident.

COMPREHENSION QUESTIONS

[38.1] Parathyroid hormone plays a critical role in regulating plasma calcium levels, as is evident in individuals with hyperparathyroidism, in which persistent hypercalcemia is evident. Under normal conditions, low plasma calcium stimulates PTH secretion, which in turn activates and/or inhibits calcium-handling processes at a number of different sites. High PTH levels stimulate and/or inhibit which of the following processes to return plasma calcium levels toward normal?

A. Inhibit calcium secretion by the gastrointestinal tract
B. Reduce the expression of plasma calcium-binding proteins
C. Stimulate bone resorption, leading to the release of calcium into the plasma
D. Stimulate calcium reabsorption by the renal proximal tubule
E. Stimulate the release of calcium from muscle cells

[38.2] A 50-year-old individual is admitted to the emergency room with a fractured tibia. The fracture occurred while this person was lifting light boxes. Bone scans of the spine and hip reveal low bone density. Laboratory tests show low plasma calcium, elevated PTH levels, and low vitamin D levels. The patient indicates that she is on a balanced diet with sufficient fruits and vegetables. However, the patient’s plasma creatinine and blood urea nitrogen (BUN) levels are elevated markedly. Which of the following is the most likely reason for the hypocalcemia and reduced bone mass?

A. Excessive urinary excretion of calcium
B. Impaired secretion of calcitonin
C. Low dietary calcium
D. A parathyroid gland tumor generating excessive amounts of PTH
E. Reduced renal activity of 1α-hydroxylase activity (which converts the inactive form of vitamin D to the active form)

[38.3] A 35-year-old woman undergoes a thyroidectomy for papillary serous thyroid cancer. The surgeon suspects that the parathyroid glands have been removed. Which of the following findings is most likely to be seen in the patient 1 week postoperatively?

A. Coma
B. Constipation
C. Esophagitis
D. Muscle spasms and tetany
Answers

[38.1] C. One of the major actions of PTH is on bone. Binding of PTH to receptors on bone cells stimulates bone resorption, particularly in the presence of permissive amounts of vitamin D. This leads to the release of calcium phosphate and the elevation of plasma levels of both calcium and phosphate. Separately, PTH can act on the gastrointestinal tract to stimulate calcium absorption and on the renal thick ascending limb and distal convoluted tubule to stimulate calcium reabsorption. Hence, PTH plays a major role in regulating plasma calcium levels through its actions on calcium handling by several organ systems.

[38.2] E. The key observation is that the patient has renal insufficiency or is in the early stages of chronic renal failure. This reduces the levels of \( 1\alpha \)-hydroxylase in the proximal tubule cells, thereby reducing the conversion of 25-hydroxyvitamin D, the inactive form of vitamin D, to 1,25-dihydroxyvitamin D, the most active form.

[38.3] D. Removal of the parathyroid glands may lead to hypocalcemia. Symptoms include nerve paresthesias, muscle spasms, and tetany. A physical sign is the Trousseau sign, the development of carpal spasm when the blood pressure cuff is inflated for about 2 to 3 minutes. The Chvostek sign is twitching of facial muscle when the facial nerve is percussed lightly anterior to the ear. Severe hypocalcemia can lead to seizures, laryngospasm, and lethargy. The other answers refer to symptoms or signs of hypercalcemia.

PHYSIOLOGY PEARLS

- The dominant site of calcium storage in the body is bone, which contains nearly 99.9% of body calcium.
- Calcium balance is regulated by three dominant processes: intestinal calcium absorption, bone mineral absorption and resorption, and kidney calcium reabsorption.
- Plasma calcium regulates the synthesis and secretion of PTH by the parathyroid glands. In contrast to most secretory processes, low calcium levels stimulate PTH secretion and high calcium levels inhibit PTH secretion.
- The active form of vitamin D, 1,25-dihydroxyvitamin D, is converted from the inactive form, 25-hydroxyvitamin D, by 1\( \alpha \)-hydroxylase in the kidney.
REFERENCES
