Chapter 6

Calcium Imbalances

Because many factors affect calcium regulation, there are a multitude of causes of disturbed calcium balance. For this reason, both hypocalcemia and hypercalcemia are relatively common imbalances. To facilitate understanding of calcium disturbances, it is helpful to review factors that affect calcium balance.

CALCIUM BALANCE

Distribution and Function

Calcium is the body's most abundant divalent cation.[1] More than 99% of the body's calcium is concentrated in the skeletal system, and approximately 1% is rapidly exchangeable with blood calcium (the remainder is more stable and exchanged only slowly). The small amount of calcium located outside the bone circulates in the serum, partly bound to protein and partly ionized. Calcium has a major role in transmission of nerve impulses. It helps regulate muscle contraction and relaxation, including normal heartbeat. Calcium has a vital role in the cardiac action potential and is essential for cardiac pacemaker automaticity. This ion is also involved in blood clotting and hormone secretion. Recommended adequate intake for calcium for both men and women aged 19 to 50 years is 1000 mg/day; some experts recommend increasing this amount to 1200 mg/day for those persons older than 50 years.[2]

Evidence suggests that calcium and vitamin D play important roles in the primary prevention of colorectal neoplasia.[3] It appears that calcium binds bile acids in the bowel lumen, inhibiting bile-induced mucosal damage.[4] Calcium is closely tied to magnesium and phosphorus regulation.[5]

Measurement of Calcium in Blood

The test most frequently performed in clinical settings to measure serum calcium is total calcium, with results normally ranging from 8.9 to 10.3 mg/dL (roughly equivalent to 2.23 to 2.57 mmol/L). The total calcium in serum is the sum of the ionized (47%) and non-ionized (53%) calcium components. In the non-ionized portion, calcium is primarily bound to albumin (and, to a lesser extent, to other anions such as citrate and phosphate). When serum albumin levels and pH are within normal ranges, readings from total calcium are generally useful. In contrast, when the serum albumin level is abnormal, corrections must be made in the reported total serum calcium levels. In noncritically ill patients, it is estimated that a 1.0 g/dL decrease in the serum albumin is accompanied by a 0.8 mg/dL decrease in the total calcium. The following is a convenient formula sometimes used to calculate the "corrected" calcium level when hypoalbuminemia is present:

$$\text{Corrected calcium (mg/dL)} = \text{measured serum calcium} + 0.8 \times (4.0 - \text{measured serum albumin g/dL})$$

For example, if the patient's serum albumin level is below normal by 1 g/dL (e.g., 3.0 g/dL rather than 4.0 g/dL), a measured total serum calcium concentration of 8.0 mg/dL should be adjusted upward to 8.8 mg/dL. In this situation, the ionized calcium level would be estimated at approximately half of the adjusted value. The direct relationship between albumin and total calcium often leads clinicians to ignore a low total serum calcium level in the presence of a similarly low serum albumin level.

The ionized calcium level in the bloodstream is affected by plasma pH. For example, when the arterial pH increases

(alkalosis), more calcium becomes bound to protein. Although the total serum calcium remains unchanged, the ionized portion decreases. Therefore, symptoms of hypocalcemia often occur when alkalosis is present (despite a normal total calcium level). Acidosis (low pH) has the opposite effect; that is, less calcium is bound to protein and, therefore, more exists in the ionized form. Signs of hypocalcemia will develop only rarely in the presence of acidosis, even when the total serum calcium level is lower than normal.

Direct measurement of ionized calcium by the laboratory is highly desirable, especially in critically ill patients. Recall that the ionized calcium concentration is the physiologically active and clinically important component.[6] Whole blood, heparinized plasma, or serum may be used for the measurement of calcium ionization.[7] Instructions from the laboratoy that is performing the analysis need to be carefully followed to assure accurate results. The normal value for urinary calcium is dependent on dietary calcium intake. Urine specimen collected for calcium analysis need to be appropriately acidified to prevent calcium salt precipitation.[8]

Regulation

Many biochemical and hormonal factors act to maintain a normal calcium balance. Among the most important are parathyroid hormone (PTH), calcitonin, and calcitriol (an active metabolite of vitamin D). PTH promotes transfer of calcium from the bone to the plasma, thereby raising the plasma calcium level. The bones and teeth are ready sources for replenishment of low plasma calcium levels. PTH also augments the intestinal absorption of calcium and enhances the net renal calcium reabsorption. Calcium is absorbed primarily in the duodenum and jejunum.[9]

Calcitonin (which is produced in the thyroid as well as several other tissues) is a physiological antagonist of PTH. Calcitonin secretion is directly stimulated by a high serum calcium concentration. At high levels, calcitonin inhibits bone resorption; the resultant reduced flux of calcium from bone causes a reduction in the serum calcium level.

Calcitriol (1,25-dihydroxyvitamin D) is a hormone that increases the extracellular calcium concentration by three main actions: promotion of calcium absorption from the intestine, enhancement of bone resorption of calcium, and stimulation of renal tubular reabsorption of calcium. Calcitriol has a synergistic effect with parathyroid hormone on bone resorption.

Osteoporosis

Osteoporosis is associated with prolonged low intake of calcium. It is characterized by loss of bone mass, which in turn causes bones to become porous, brittle, and susceptible to fracture. In the United States, osteoporosis is estimated to cause 1.5 million fractures annually, primarily of the hip and spine.[10] Although serum calcium levels are usually normal in individuals with osteoporosis, total body calcium stores are greatly diminished. Bone loss begins at an earlier age in women than in men and is accelerated by menopause. However, men also develop a negative calcium balance in later years, at which point they may become vulnerable to osteoporosis. A dual process is involved in osteoporosis: increased bone resorption and inadequate bone formation. Menopause leads to rapid bone loss in women because estrogen deficiency reduces calcium absorption and increases excretion; as a result, bone loss far outpaces bone deposition.

Risk of developing serious bone problems is greater in postmenopausal, physically inactive women who are elderly, thin and small-framed, and smokers, and in those who have a diet deficient in calcium.[11] Inactivity predisposes to bone loss by reducing the efficiency of calcium use. Conversely, regular physical exercise (such as running, walking, or bicycling) slows the rate of bone loss and improves calcium balance. Considering the magnitude of the problems associated with osteoporosis, prevention is the only cost-effective approach. Also important in the prevention of osteoporosis is elimination of bone toxins (such as cigarettes and heavy alcohol ingestion). Hypogonadal women who take estrogen have a reduced risk of developing osteoporosis; thus it is one factor to consider when deciding whether to take estrogen (hormone replacement therapy [HRT]).[12] It appears that low doses of estrogen are adequate to prevent postmenopausal osteoporosis; however, once osteoporosis has developed, it is not an effective treatment.[13]

Bisphosphonates are the most commonly used drugs for the treatment of osteoporosis. Since the first such agent was introduced, more than 190 million prescriptions have been written for their use.[14] All patients receiving bisphosphonates should have adequate calcium and vitamin D intake before and during therapy.[15] Some reports have described development of bisphosphonate-induced hypocalcemia in patients with unrecognized hypoparathyroidism, vitamin D deficiency, or impaired renal function.[16]

HYPOCALCEMIA

Hypocalcemia may be defined as a total serum calcium level of less than 8.9 mg/dL and an ionized calcium concentration of less than 4.6 mg/dL. However, it is important to recognize that reporting laboratories often have slightly differing values for normal calcium levels. Hypocalcemia is a common imbalance in critically ill patients. For example, the prevalence of ionized hypocalcemia is reported to range from 60% to 85% in medical, surgical, and trauma patients.[17] Hypocalcemia is a serious imbalance, in that it can potentiate cardiac arrhythmias and seizures.[18] Although mortality is greater in patients with hypocalcemia, this outcome does not appear to be independently associated with the imbalance.[19]

As discussed earlier, hypoalbuminemia can produce a falsely low total serum calcium test result (referred to as pseudohypocalcemia). In this situation, the ionized calcium level remains normal and the patient is asymptomatic and requires no treatment.

Causes

Causes of hypocalcemia vary, but are known to include surgical hypoparathyroidism, acute pancreatitis, magnesium imbalances, hyperphosphatemia, alkalosis, malabsorption syndromes, infusion of citrate in blood products, sepsis, and a variety of drugs (**Table 6-1**). However, hypocalcemia rarely results from decreased intake of calcium alone, as bone reabsorption can maintain normal levels for a prolonged period of time.[20]

Surgical Hypoparathyroidism

Primary hypoparathyroidism causes hypocalcemia, although surgical hypoparathyroidism following thyroidectomy or radical neck dissection is a more common cause. Postsurgical hypoparathyroidism may be either transient or permanent.

The frequency of surgical hypoparathyroidism is partially dependent on the technical skill of the surgeon, who strives to preserve the blood supply to the parathyroid glands. Much lower rates of hypoparathyroidism have been reported in endocrine surgical centers with a high volume of neck surgery than in other settings.[21] Transient hypocalcemia occurs 24 to 48 hours after thyroidectomy but frequently does not require treatment.[22] A recent study of 21 individuals who underwent thyroid surgery revealed that 18 developed hypocalcemia (although only 4 of the 18 were symptomatic).[23] The 4 patients who had symptomatic hypocalcemia had significantly lower intact parathyroid hormone

Table 6-1 Summary of Causes of Hypocalcemia

Cause	*Mechanism*
Hypoparathyroidism	Calcium shifted from the bloodstream into bone
Hyperphosphatemia	Phosphate binds ionized calcium and removes it from the bloodstream
Alkalosis	Increased binding of ionized calcium to albumin
Pancreatitis	Systemic endotoxins Saponification of fats Faulty PTH feedback loop
Hypomagnesemia	End-organ resistance to PTH Decreased production of PTH
Renal failure	Hyperphosphatemia Decreased active vitamin D
Sepsis	PTH suppression Elevated cytokines Elevated calcitonin
Long-term lack of sunlight	Inadequate vitamin D
Loop diuretics (furosemide)	Increased renal excretion
Phenytoin	Inhibits GI absorption of calcium
Citrate-buffered blood products	Citrate anions bind calcium
Edetate disodium	Chelation of calcium

(iPTH) levels than did the 14 patients without symptoms and the remaining 3 without hypocalcemia. The researchers concluded that a 1-hour postoperative iPTH level of 2.5 pmol/L or less can identify individuals at risk for developing symptomatic hypocalcemia.

The most likely mechanism in terms of causing hypocalcemia after radical neck dissection is ischemia to the parathyroid tissue following dissection and hemostatic maneuvers. It is also possible that trauma to the parathyroid glands precludes PTH from increasing to the level needed to elevate the low serum calcium concentration, thus contributing to the development of hypocalcemia. If permanent parathyroid damage has not occurred, parathyroid insufficiency resolves as edema at the surgical site lessens and revascularization occurs, allowing reestablishment of parathyroid gland integrity. Extensive neck surgery (as in radical neck dissection for cancer) is more likely to be associated with permanent hypoparathyroidism than are less involved surgical maneuvers.

Most patients who develop hypocalcemia after neck surgery are asymptomatic; however, some may develop paresthesias, laryngeal spasm, or tetany. It is common practice to check serum ionized calcium levels at regular intervals in the early postoperative period in patients who have undergone neck surgery.

With the emphasis on cost containment in the current healthcare environment, concerns have been raised that patients who have undergone thyroid or parathyroid gland surgery may be discharged before postoperative hypocalcemia becomes manifest. A retrospective study of 197 patients who had undergone such operations indicated that early postoperative calcium levels give a good indication of whether hypocalcemia is likely to occur.[24] In the study, postoperative calcium levels were plotted as a function of time, and the slope between the first two postoperative calcium levels was examined. The results indicated that an initial upsloping postoperative calcium curve based on these two early postoperative calcium measurements is a strong predictor of a stable postoperative calcium level; conversely, a steeply downsloping initial calcium curve is worrisome for eventual hypocalcemia.

Acute Pancreatitis

Hypocalcemia is not uncommon during acute pancreatitis and is associated with a poor outcome. While it is unclear precisely which mechanisms cause hypocalcemia in this setting, several possibilities have been identified. Inflammation of the pancreas causes release of proteolytic and lipolytic enzymes; it is believed that calcium ions combine with the fatty acids, forming soaps and thereby decreasing the serum calcium concentration.[25] In contrast, other researchers have concluded that systemic endotoxin exposure may play a significant role in the development of hypocalcemia in patients with acute pancreatitis.[26] Other investigators have found that there is an inadequate PTH response to the hypocalcemia caused by acute pancreatitis.[27] In any event, ionized hypocalcemia is a common problem, occurring in as many as 85% of patients with acute severe pancreatitis.[28] See Chapter 20 for a more extensive discussion of this topic.

Magnesium Abnormalities

The serum magnesium level influences both PTH secretion and action and, therefore, the serum calcium level. Severe hypomagnesemia (less than 1 mg/dL) inhibits PTH secretion. One study reported that 22% of the patients with hypocalcemia also had hypomagnesemia.[29] Hypomagnesemic hypocalcemia responds poorly to calcium therapy alone but can be resolved through concurrent calcium and magnesium replacement.

Hyperphosphatemia

Hyperphosphatemia that develops rapidly is associated with hypocalcemia. This condition might be seen in patients who receive excessive hypertonic sodium phosphate enemas. For example, as described in a recent report, a 13-year-old boy with chronic constipation developed severe hyperphosphatemia and hypocalcemia after receiving four hypertonic sodium phosphate pediatric enemas for severe constipation.[30] It is important for clinicians to recognize that these enemas are absorbable and can lead to potentially lethal complications if given improperly. See Chapters 8 and 13 for a more detailed discussion of this topic.

Alkalosis

Blood pH alters Ca^{++} binding to serum proteins. In alkalosis, a greater amount of calcium is bound to plasma proteins, resulting in a smaller percentage of ionized calcium. Thus patients with alkalosis are more susceptible to hypocalcemic tetany.

Inadequate Vitamin D

Inadequate consumption of vitamin D or insufficient exposure to the sun (ultraviolet radiation) can cause reduced calcium absorption, leading to hypocalcemia. Deficiency of vitamin D occurs in malabsorptive states, as described in the next subsection. It is not uncommon for elderly persons to have low vitamin D levels. Breastfed infants born to

mothers who are vitamin D deficient are at risk for developing vitamin D deficiency and hypocalcemia; unfortunately, maternal vitamin D deficiency is not uncommon.[31]

Malabsorption Syndromes

Intestinal malabsorptive disorders are likely to lead to hypocalcemia by decreasing the absorption of vitamin D, bile salts, and calcium. In a study involving 82 patients who underwent biliopancreatic bypass from 1988 to 2001, 26% were found to have hypocalcemia and 50% were found to have low vitamin D levels (despite the fact that most took multivitamins).[32]

Infusion of Citrate in Blood Products

Decreases in ionized Ca^{++} during blood transfusion correlate with speed of the transfusion and circulating citrate levels. Hypocalcemia is seen more commonly during the transfusion of plasma and platelets, which have high citrate concentrations.[33] Citrate is added to banked blood to act as an anticoagulant and to preserve the life of the blood. Usually the citrate in blood is rapidly metabolized by the liver as it is transfused and presents no problem for calcium balance. However, when blood is transfused faster than metabolism of the excess citrate can occur, hypocalcemia results. Recall that citrate is a negatively charged ion and that calcium is a positively charged ion; thus the two ions are attracted to each other. Therefore, transient hypocalcemia can occur with massive administration of citrated blood (as in exchange transfusions in neonates), as calcium ions combine with the citrate and are temporarily removed from the circulation (a process referred to as chelation). Citrate metabolism is hindered in patients with liver disease, shock, and hypothermia. Small children and osteoporotic adults are also at increased risk for citrate/calcium imbalances because they tend to have inadequate stores of bone calcium and, therefore, are less able to compensate for declining ionized calcium levels. When citrate intoxication occurs, it may be manifested as circumoral paresthesias, muscle tremors, or tetany.

The infusion of packed red blood cells (instead of whole blood) lowers the amount of citrate infused, thereby decreasing the already low risk for hypocalcemia after transfusions. However, there is sufficient citrate even in packed red blood cells to affect calcium balance. Two cases were reported in which the transfusion of small volumes of packed red blood cells proved sufficient to precipitate symptomatic hypocalcemia.[34] Subsequent investigation revealed that both of the patients had preexisting, untreated, and asymptomatic hypocalcemia (one following partial thyroidectomy years earlier and the other with documented hypocalcemia but without a definitive cause).

As indicated previously, hypocalcemia is more commonly observed during plasmapheresis than during blood transfusions. Ordinarily the citrate anticoagulant used during apheresis procedures is considered a safe medication because it is rapidly metabolized by the donor; however, life-threatening hypocalcemia can occur if the infusion rate of the citrate is too fast. A case was reported in which citrate was inadvertently administered too rapidly to a 54-year-old woman due to malfunction of the anticoagulant line of an apheresis instrument.[35] Seven minutes into the procedure the patient developed muscle spasm, chest pain, and hypotension; her serum ionized calcium level was 0.64 mmol/L (the normal level in the reporting laboratory was in the range of 1.18–1.38 mmol/L).

Drugs

A variety of medications can predispose to hypocalcemia. For example, loop diuretics increase renal excretion of calcium and phenytoin inhibits intestinal absorption of calcium. Phosphate-containing agents bind calcium in the intestinal tract and, therefore, interfere with its absorption. Edetate disodium (EDTA) is a chelating agent used in the treatment of toxic metal poisoning; three deaths were recently reported from hypocalcemia following the administration of this agent.[36]

Alcoholism

Alcoholics are at risk for hypocalcemia for many reasons. Among these are intestinal malabsorption, low levels of 25-hydroxyvitamin D, hypomagnesemia, hypoalbuminemia, respiratory and metabolic alkalosis, and pancreatitis. The most significant of these conditions is probably hypomagnesemia (caused by the toxic effects of alcohol). Magnesium replacement in alcoholics helps to correct hypocalcemia by increasing responsiveness to PTH.

Neonatal Hypocalcemia

Two types of hypocalcemia can occur in newborn infants. The first develops early, during the first 3 days of life. This type is attributed to parathyroid immaturity or maternal hyperparathyroidism (or both), resulting in neonatal parathyroid gland suppression; it most often resolves within the first week of life. Among the predisposing factors for this condition are prematurity, maternal insulin-dependent diabetes mellitus, and asphyxia at birth. A recent study of 381

calcium levels from 111 extremely low birthweight (ELBW) infants during the first 48 hours of life found that the majority (59.9%) had at least one hypocalcemic value.[37] The investigators concluded that serum calcium values are lower in ELBW infants and that the values may be inconsequential; they recommended that hypocalcemia be redefined for ELBW infants.

A second type of neonatal hypocalcemia occurs approximately 1 week after birth and is associated with hyperphosphatemia and hypomagnesemia. Hypocalcemia in infants with this "late-onset" condition can be caused by feeding them milk with a high phosphorus level, leading to hyperphosphatemia and then to hypocalcemia. Low serum calcium levels can persist until the child's parathyroid glands function well enough to respond.

Sepsis

Although hypocalcemia in critically ill, septic patients is common, the underlying basis for this condition is unclear. Researchers have postulated that calcium shifts from the extracellular compartment into the cells and that the hormonal response to the resultant hypocalcemia is inadequate. Possible causes for hypocalcemia in a group of patients with gram-negative sepsis described by Zaloga and Chernow included acquired parathyroid gland insufficiency, dietary vitamin D deficiency, and renal hydroxylase insufficiency.[38] Other sources have reported that hypocalcemia in septic critically ill patients may be related to an inflammatory response.[39]

In experimental settings, calcium administration in sepsis has been shown to increase or have no effect on mortality.[40] It is not known if sepsis-induced hypocalcemia is protective or harmful to the patient; there is no evidence that routine calcium replacement is needed but treatment is generally advocated for symptomatic patients.[41] A review of the literature by Forsythe et al. found no clear evidence that parenteral calcium supplementation affects the outcome of critically ill patients.[42]

Other Factors

Conditions commonly associated with low serum albumin levels (such as cirrhosis of the liver and the nephrotic syndrome) are frequently associated with a low total serum calcium concentration. Often, the ionized calcium concentration is normal and no symptoms of hypocalcemia appear. Medullary thyroid carcinoma may produce hypocalcemia if calcitonin (a calcium-lowering hormone) is secreted by the tumor.

Hypocalcemia was reported in almost 18% of 66 patients with acquired immune deficiency syndrome (AIDS).[43] The researchers postulated that intestinal malabsorption of vitamin D is the most likely cause of hypocalcemia in this patient population.

Clinical Signs

Clinical manifestations of hypocalcemia vary widely among patients and depend on the severity, duration, and rate of development of this condition (**Table 6-2**). The concurrent presence of hypomagnesemia and hypokalemia can potentiate the neurological and cardiac abnormalities associated with hypocalcemia.

Neuromuscular Manifestations

Tetany—the most characteristic manifestation of hypocalcemia—refers to the entire symptom complex induced by increased neural excitability. The increase in nerve mem-

Table 6-2 Summary of Clinical Signs of Hypocalcemia

Neuromuscular
• Numbness; tingling of fingers, circumoral region, and toes
• Muscle cramps, which can progress to muscle spasms, tremor, and twitching
• Hyperactive deep-tendon reflexes
• Trousseau's sign
• Chvostek's sign
• Convulsions (usually generalized, but may be focal)
• Spasm of laryngeal muscles
Cardiovascular
• Decreased myocardial contractility with a reduction in cardiac output
• ECG: prolonged QT interval
• Arrhythmias, ranging from bradycardia to ventricular tachycardia and asystole
Mental
• Impaired higher cerebral functioning, such as depression, emotional instability, anxiety, or frank psychoses
Laboratory
• Total serum calcium level less than 8.9 mg/dL
• Ionized calcium level less than 4.6 mg/dL

brane excitability causes fibers to discharge spontaneously, eliciting tetanic contractions. Findings may include sensations of tingling around the mouth (circumoral paresthesia) and in the hands and feet, as well as spasms of the muscles of the extremities and face. Although laryngeal spasms may occur, they rarely result in asphyxia.[44] Ordinarily, tetany occurs when the blood concentration of calcium falls from its normal value to about 6 mg/dL (approximately 35% below the normal calcium concentration).[45]

When hypocalcemic patients fail to show overt signs of tetany, latent tetany can be elicited in two ways. One involves placing a blood pressure cuff on the upper arm and inflating it to above systolic pressure for about 3 minutes and observing for carpal spasm (Trousseau's sign; see Figure 2-3). Trousseau's sign is not specific for hypocalcemia because it is negative in approximately 30% of individuals with latent tetany and positive for a small percentage of healthy individuals. Another test involves tapping over the facial nerve just anterior to the ear and observing for ipsilateral facial muscle contraction (Chvostek's sign). This sign is also not specific for hypocalcemia because it may occur in some healthy adults.

Cardiovascular Manifestations

In some patients, altered cardiovascular hemodynamics may be the most significant effect of hypocalcemia. This outcome is understandable given the important role that calcium ions play in the contraction of cardiac muscle. The cardiovascular effects of hypocalcemia include decreased myocardial contractility leading to reduced cardiac output, hypotension that is refractory to fluid replacement and vasoconstrictive agents, and decreased responsiveness to digitalis.[46] Dysrhythmias associated with hypocalcemia can range from bradycardia to ventricular tachycardia and asystole. Hypocalcemia prolongs the QT interval, predisposing the patient to life-threatening ventricular dysrhythmia. Often cardiac patients are already predisposed to both hypocalcemia and hypomagnesemia because they are taking potent loop diuretics.

Long-standing hypocalcemia can be complicated by reversible cardiomyopathy. In one case, a 46-year-old woman with chronic severe hypocalcemia (associated with untreated hypoparathyroidism) developed severe heart dysfunction.[47] After the hypocalcemia was corrected, near-normal cardiac function returned within a few months. Similar cases have been reported by other authors.[48]

Central Nervous System Manifestations

Convulsions may be the initial symptom of severe hypocalcemia.[49] Hypocalcemia may also cause impaired higher cerebral function, such as anxiety, depression, confusion, and frank psychoses.

Treatment

Treatment of hypocalcemia depends on the underlying cause, the magnitude of the serum calcium deficiency, and the severity of symptoms. Numerous etiological factors are associated with hypocalcemia. Ideally, treatment is directed at alleviating the cause.

Intravenous Calcium Replacement for Acute Hypocalcemia

Acute symptomatic hypocalcemia is a medical emergency, requiring prompt administration of intravenous (IV) calcium. Parenteral calcium salts include calcium gluconate, calcium chloride, and calcium gluceptate. Although calcium chloride produces a significantly higher ionized calcium level than does an equimolar amount of calcium gluconate, it is not used as often because it is more irritating to the vein and can cause tissue sloughing if allowed to infiltrate. Because calcium is very irritating, it should be administered through a central line whenever possible. For symptoms of severe hypocalcemia in an average-sized adult, the physician may prescribe 10 mL of 10% calcium gluconate (90 mg elemental calcium/10 mL), to be administered over a 10-minute period.[50] This dose may be followed by the infusion of additional calcium gluconate diluted in 500 or 1000 mL of 5% aqueous dextrose (D_5W) or 0.9% NaCl. (Calcium should not be mixed with any solution containing bicarbonate because of the possibility of precipitation.) Patients receiving digitalis should be monitored with an electrocardiogram (ECG) during the infusion because calcium administration may produce fatal arrhythmias if the infusion is given too rapidly. The serum calcium level should be monitored every 4 to 6 hours and the infusion rate adjusted to avoid recurrent symptomatic hypocalcemia.

Oral Calcium Replacement for Chronic Hypocalcemia

When oral calcium supplements are tolerated, the oral route of administration is preferred over the IV route because it is safer. Oral calcium can be provided as carbonate, gluconate,

lactate, or citrate salts. In some cases, long-term management may require the use of vitamin D preparations. These medications should be used with caution if severe hyperphosphatemia is present because of the danger of calcium phosphate precipitation in the soft tissues. If hyperphosphatemia is present, oral phosphate-binding medications (such as aluminum hydroxide) may be indicated.

Calcium carbonate is the least expensive and most frequently supplied oral calcium salt.[51] However, its rate of absorption is greatly reduced in patients with achlorhydria (unless taken with meals). Patients with achlorhydria, or hypochlorhydria, should be encouraged to take calcium carbonate with meals or to consider taking calcium citrate instead (at any time of the day).[52] Some experts recommend that patients taking proton pump inhibitors take calcium citrate instead of calcium carbonate. Unfortunately, calcium citrate costs approximately 50% more than calcium carbonate.[53]

Clinical Considerations

1. Be aware of patients at risk for hypocalcemia and monitor for its occurrence (see Table 6-2).
2. Be prepared to implement seizure precautions when hypocalcemia is severe.
3. Monitor the patient's airway closely because laryngeal stridor can occur.
4. Take safety precautions if confusion is present.
5. Be aware of factors related to the safe intravenous administration of calcium replacement salts (**Table 6-3**).
6. Educate individuals about recommended calcium dietary intake. Recommended adequate intake for calcium for both men and women aged 19 to 50 years is 1000 mg/day; the recommendation increases to 1200 mg/day for those older than 50 years.[54] The best way for healthy individuals to ensure an adequate calcium intake is to eat a wide variety of foods.
7. Calcium supplements may be necessary for individuals who are unable to consume sufficient calcium in their diets, such as those who do not tolerate milk or dairy products.
8. Individuals with a tendency to form renal stones should be encouraged to increase their fluid intake throughout the day and night. Fluids should be ingested during meals, several hours after meals, before bedtime, and during the night when awakened to void.
9. Inform individuals at risk for osteoporosis about the value of regular physical exercise in decreasing bone

Table 6-3 Considerations in the Administration of Intravenous Calcium

1. The dosage of calcium prescribed for a specific hypocalcemic patient depends on the severity of hypocalcemia as well as its cause.
2. The most commonly prescribed calcium preparations for IV use are as follows:
   - *Calcium gluconate*: 10 mL of a 10% solution contains 90 mg (4.5 mEq) of elemental Ca^{++} (suitable for either IV or IM use).
   - *Calcium chloride*: 10 mL of a 10% solution contains 270 mg (13.5 mEq) of elemental Ca^{++} (suitable only for IV use).
3. Calcium preparations may be given undiluted by slow IV push (if indicated) or—preferably—may be diluted with compatible parenteral fluids for slow infusion.
4. Calcium preparations are irritating to veins and may cause venous sclerosis; for this reason, administration through a central vein is recommended.
   - Because calcium gluconate is less irritating to veins than is calcium chloride, it is more frequently prescribed (although it contains only one-third as much elemental calcium as calcium chloride).
   - If a peripheral administration site is necessary, use the largest available vein. Do *not* use small hand veins.
   - Great care should be taken to avoid extravasation of calcium solutions (especially calcium chloride) because they can cause severe soft-tissue damage.
5. Calcium preparations should not be administered with bicarbonate or phosphate because a precipitate will form.
6. Calcium should be administered cautiously (with ECG monitoring) in patients taking digitalis because accidental hypercalcemia induced by too-rapid infusion of calcium could precipitate digitalis toxicity.
7. Frequent monitoring of the patient's response to calcium replacement therapy is indicated.
8. Serum calcium levels should be checked frequently (such as every 1 to 4 hours) and the dosage adjusted accordingly. Adequacy of treatment can also be monitored by observing Chvostek's and Trousseau's signs, the ECG, and hemodynamic parameters.

loss. Walking is well tolerated by all age groups and is an excellent form of exercise, as is bicycling.

10. Discuss the calcium loss associated with the use of alcohol and nicotine. Smoking lowers estrogen levels and interferes with the body's absorption of calcium; as a consequence, women who smoke are at greater risk of developing osteoporosis.

HYPOCALCEMIA CASE STUDIES

Case Study 6-1

A 46-year-old woman with end-stage renal disease was admitted with a secondary diagnosis of seizure activity and multi-infarct dementia. She required dialysis twice a week. On admission, laboratory data from a venous blood sample revealed the following: Na 138 mEq/L, BUN 41 mg/dL, K 5.8 mEq/L, serum creatinine 8.2 mg/dL, total Ca 7.0 mg/dL, albumin 3.0 g/dL, phosphorus 7.1 mg/dL, and HCO_3 13.5 mEq/L.

Commentary. Note the low total calcium level and the presence of hypoalbuminemia. With correction for the low serum albumin level, the serum calcium would be nearer to normal. (Recall that for every gram the serum albumin is below the normal level, 0.8 mg must be added to the reported calcium level.) Using the following equation:

$$\text{Corrected calcium (mg/dL)} = \text{measured serum calcium} + 0.8 \times (4.0 - \text{measured serum albumin g/dL})$$

The corrected total calcium is 7.8 mg/dL. Although the corrected total calcium level is still below normal, the ionized fraction of the calcium was normal; thus symptoms of hypocalcemia were not present. Note that this patient has metabolic acidosis (evidenced by the low serum bicarbonate level); both hypoalbuminemia and acidosis favor increased calcium ionization. Rapid correction, or over-correction, of acidosis in a patient with renal disease predisposes the patient to precipitation of hypocalcemic symptoms. Hyperphosphatemia was present, a major factor in explaining the hypocalcemia in this case.

Case Study 6-2

A hysterical young woman was admitted to the emergency department after an automobile accident in which she fractured her arm. She complained of circumoral paresthesia and then fainted. Arterial blood gas findings included a pH of 7.55 (alkalosis) and an arterial carbon dioxide pressure ($PaCO_2$) of 20 mm Hg (normal, 40 mm Hg), indicating respiratory alkalosis.

Commentary. Hyperventilation secondary to hysteria is a common cause of tetany in the hospital emergency department. In this situation, the tetany resulted from a reduction in the plasma ionized calcium level consequent to respiratory alkalosis. Fainting was due to cerebral ischemia caused by the low $PaCO_2$ (recall that a low $PaCO_2$ causes cerebral vasoconstriction). The total serum calcium level was probably normal, although the ionized fraction decreased. Correction of the hyperventilation (and thus of respiratory alkalosis) will restore the ionized calcium level to normal and alleviate symptoms.

Case Study 6-3

A case was reported in which a 40-year-old female was a first-time apheresis platelet donor.[55] Her history included hypertension, hyperlipidemia, and depression. Medications included bumetanide (a loop diuretic), pravastatin (a cholesterol-lowering drug), and paroxetine (a selective serotonin reuptake inhibitor [SSRI] antidepressant). Thirty minutes after the procedure started, the patient complained of tingling around her mouth, hands, and feet. Shortly thereafter, she developed acute-onset severe facial and extremity tetany. Treatment with intravenous calcium gluconate was started and the muscle contractions subsided over 10 to 15 minutes.

Commentary. These events are consistent with a severe reaction to calcium chelation by the sodium citrate anticoagulant used in the apheresis donation procedure. It is possible that the loop diuretic (bumetanide) contributed to the hypocalcemia. Authors of the reported case study concluded that careful screening is needed to help prevent severe reactions to citrate toxicity; it may be wise to measure pre-procedure calcium levels in selected donors to identify cases requiring extra vigilance. The authors also pointed out the need of maintaining preparedness for managing rare but serious reactions in volunteer apheresis blood donors.[56]

Case Study 6-4

A 32-year-old woman was admitted to an acute care facility with severe hypocalcemia and convulsions. She had undergone a subtotal thyroidectomy two weeks earlier. At the time of admission, her total serum calcium level was 3.2 mg/dL (normal for the reporting laboratory was 8.8 to 10.6 mg/dL).

Commentary. The hypocalcemia associated with thyroidectomy may occur weeks to months after surgery (as evidenced in this case). For this reason, patients should be taught about the symptoms of hypocalcemia and told to report signs early to their healthcare providers.

Case Study 6-5

A case was reported in which a 32-year-old mentally impaired man presented with a year-long history of loss of seizure control (after being seizure-free for 5 years on a regimen of phenytoin and phenobarbital).[57] Physical examination revealed a positive Chvostek's sign and a serum calcium level of 5.9 mg/dL (normal for the reporting laboratory was 8.8 to 10.4 mg/dL). An intravenous infusion of calcium was administered until the patient's serum calcium level reached 8.0 mg/dL. The method of calcium administration was then changed to the oral route. The patient's seizure activity diminished following calcium replacement.

Commentary. Phenytoin can interfere with vitamin D metabolism and impair calcium absorption for the intestinal and mobilization from the bone. The authors of the case report stated that vitamin D and calcium treatment should probably be maintained during the use of antiepileptic drugs.

Case Study 6-6

A case was reported in which a 43-year-old woman with a 20-year history of Crohn's disease presented to the emergency department with fatigue and weight loss.[58] For the past month, she had experienced tetany and muscle cramps as well as peripheral and perioral paresthesia. In addition, she experienced colicky abdominal pain. Upon examination, positive Chvostek's and Trousseau's signs were found. A serum calcium level of 1.3 mmol/L (corrected, 1.7 mmol/L) was found (normal, 2.23–2.57 mmol/L). Also present were hypomagnesemia and hypokalemia. Treatment consisted of electrolyte replacement with intravenous calcium, potassium, and magnesium. Vitamin D was replaced and a semi-elemental tube feeding was started. One month after discharge from the hospital, the patient continued to receive tube feedings and electrolyte replacement therapy. Plasma electrolyte levels normalized and the patient was gaining weight.

Commentary. Short bowel associated with severe Crohn's disease seriously impairs the ability of the bowel to absorb adequate amounts of carbohydrates, proteins, fats, vitamins, minerals, and electrolytes. Note that this patient required replacement of magnesium along with replacement of calcium to allow the serum calcium level to normalize.

HYPERCALCEMIA

Hypercalcemia occurs when calcium enters the extracellular fluid more rapidly than it can be excreted by the kidneys.[59] The incidence of this imbalance depends on the setting in which it occurs.[60] If allowed to become severe, hypercalcemia is associated with significant morbidity and mortality; therefore, it is important to detect this imbalance early.

Causes

Primary hyperparathyroidism and malignancy account for more than 90% of the cases of hypercalcemia in ambulatory and noncritically ill patients.[61] Only a small percentage of hypercalcemia cases are due to immobilization, vitamin A and D intoxication, lithium use, and thiazide diuretics.

Primary Hyperparathyroidism

Primary hyperparathyroidism accounts for more than half of the cases of hypercalcemia in ambulatory patients.[62] This disorder is far more common in women than in men.[63] Due to increased PTH production, hyperparathyroidism causes increased release of calcium from bone, augmented intestinal calcium absorption, and renal reabsorption of calcium. Mild hypercalcemia is found in approximately 10% of patients with thyrotoxicosis.[64]

Malignancies

Approximately 40% of the cases of hypercalcemia in hospitalized patients are associated with cancer.[65] Pathogenesis of the hypercalcemia of malignancy is complex and varies with the type of tumor. The malignancies most often associated with hypercalcemia include breast and lung cancers and hematologic malignancies such as multiple myeloma or lymphoma. Hypercalcemia is usually present only in patients with advanced cancer.[66] In a recent retrospective study, hypercalcemia was found to be a reliable indicator of impending death in cancer patients cared for in a hospice care setting.[67] Chapter 22 provides a more thorough discussion of tumors associated with hypercalcemia.

Immobilization

Bone mineral is lost during immobilization, sometimes causing an elevated total calcium concentration in the

bloodstream and resultant calciuria with the possibility of formation of renal stones. Hypercalcemia will result if the rate of bone resorption exceeds the kidneys' ability to excrete the excess calcium. In particular, patients with spinal cord injuries are at risk for immobilization-related hypercalcemia. Notable risk factors in this population include an age less than 21 years, male gender, and extensive cord injury.[68] Immobilization-related hypercalcemia has also been reported in individuals without spinal cord injury, such as those with prolonged illnesses in geriatric and critical care settings.[69, 70] The hypercalcemia of immobilization remits when activity is restored; if treatment is required, bisphosphonates may be the treatment of choice.[71]

Drugs

A variety of drugs can elevate calcium levels (**Table 6-4**). Thiazide-induced hypercalcemia may be partially mediated by volume contraction that increases renal reabsorption of calcium; also, it is thought that thiazides have a direct effect on distal tubular calcium reabsorption. Approximately 5% to 10% of patients treated with lithium develop hypercalcemia.[72] Vitamin D intoxication (with its associated hypercalcemia) is most commonly caused by too-aggressive treatment of hypoparathyroidism, rickets, or osteomalacia. Large doses of vitamin A analogues to treat acne may occasionally be associated with hypercalcemia.

Milk-alkali syndrome can occur in patients with peptic ulcers who are treated for a prolonged period with milk and alkaline antacids, particularly calcium carbonate. This syndrome is characterized by hypercalcemia, hyperphosphatemia, alkalosis, and progressive renal failure.[73] Patients who take large quantities of calcium-containing antacids may present with marked hypercalcemia. The milk-alkali syndrome should also be considered as a cause of hypercalcemia given the current popularity of calcium ingestion as a means to prevent osteoporosis.

Table 6-4 Summary of Hypercalcemia

Causes	*Clinical Signs*
Hyperparathyroidism	***Neuromuscular***
Malignant neoplastic disease: • Lung tumors, breast tumors, and multiple myeloma account for more than 50% of the cases	• Muscle weakness • Decreased deep-tendon reflexes
Prolonged immobilization	***Renal***
Drugs: • Thiazide diuretics • Lithium • Calcium supplements • Megadoses of vitamin A • Megadoses of vitamin D	• Polyuria (nephrogenic diabetes insipidus) • Hypercalciuria, perhaps leading to renal stones ***Gastrointestinal*** • Anorexia • Nausea • Vomiting • Constipation ***Cardiovascular*** • Arrhythmias • Heart block • ECG: shortened QT interval • Increased digitalis sensitivity • Hypertension ***Mental*** • Impaired higher cerebral functioning, such as confusion, emotional instability, anxiety, frank psychoses, lethargy, or coma

Clinical Signs

The magnitude of the serum calcium elevation and the time it takes to develop have major effects on clinical findings, as does the underlying cause of hypercalcemia. For example, acute hypercalcemia produces more symptoms than does chronic hypercalcemia. Also, malignancies can present with severe hypercalcemia (serum calcium level ≥ 14 mg/dL) more commonly than with other conditions.[74]

Clinical signs of hypercalcemia are summarized in Table 6-4. In some patients, mild hypercalcemia is found on routine examinations; other patients may present in hypercalcemic crisis. Although there are no firm diagnostic criteria for hypercalcemic crisis, it is generally thought to represent the presence of volume depletion, neurological manifestations, and cardiac arrhythmias in a patient with a serum calcium level greater than 14 mg/dL. As a rule, symptoms of hypercalcemia are proportional to the serum calcium level, although this is not always the case.

Serum calcium levels less than 11.5 mg/dL rarely produce symptoms. By comparison, levels between 11.5 and 13 mg/dL may be associated with lethargy, anorexia, nausea, and polyuria.[75] Further, calcium levels greater than 13 mg/dL constitute severe hypocalcemia and are associated with more severe symptoms (such as muscle weakness, impaired memory, emotional lability, stupor, and coma). A total calcium concentration greater than 14 mg/dL represents hypercalcemic crisis and is a medical emergency.[76]

Neuromuscular Changes

Hypercalcemia reduces neuromuscular excitability because it acts as a sedative at the myoneural junction. Symptoms such as muscular weakness and depressed deep-tendon reflexes may occur.

Gastrointestinal Symptoms

Constipation, anorexia, nausea, vomiting, and adynamic ileus are common symptoms of hypercalcemia. Constipation results from decreased GI motility caused by calcium's action on smooth muscle and nerve conduction, as well as from dehydration.[77] Delayed gastric emptying, nausea, and vomiting are also related to altered motility. Patients with hypercalcemia are predisposed to duodenal ulcer disease because of the increased gastric acid secretion, which is promoted by calcium's action on the parietal cells of the stomach. Pancreatitis is another potential complication of severe hypercalcemia and is probably related to calcium deposits in the pancreatic ducts.

Behavior Changes

Behavior changes associated with hypercalcemia may range from subtle alterations in personality to acute psychosis and may include confusion, impairment of memory, and bizarre behavior. Patients may become inattentive and lose their ability to concentrate; recent memory is affected more dramatically than is distant memory. Other mental status changes sometimes seen in patients with hypercalcemia include lethargy and drowsiness, as well as psychiatric disturbances such as irritability and depression; severe cases are associated with stupor or coma. Although the cause of these symptoms is not known, it has been suggested that increased calcium in the cerebrospinal fluid is involved. The more severe symptoms tend to occur when the serum calcium level approaches or exceeds 15 mg/dL. In a study of eight hypercalcemic inpatients with cancer during a period of 66 patient-days, Mahon found that the most evident changes were those affecting mental status.[78] For example, many subjects could not remember their home telephone numbers or perform simple mathematical computations. Some displayed inappropriate behaviors, such as pulling out a Foley catheter while the balloon was inflated. As serum calcium levels decreased toward normal, the mental symptoms gradually subsided.

Renal Changes

Disturbed renal tubular function produced by hypercalcemia can cause polyuria and polydipsia. More specifically, this disturbed function is a form of nephrogenic diabetes insipidus (NDI) that is usually reversible within 1 to 12 weeks after correction of the imbalance. The concentrating defect may become clinically apparent when the plasma calcium concentration exceeds 11 mg/dL. Renal colic may occur as a result of kidney stones, which may form from the excess calcium presented to the kidneys for excretion. Calcium salts deposited in the kidney can cause renal failure.

Cardiovascular Changes

Calcium is important in cardiac function; it exerts a positive inotropic effect on the heart and reduces heart rate in a way similar to the effect of cardiac glycosides. Calcium administration to patients receiving digitalis must be done with extreme care because it can precipitate severe arrhythmias.

Cardiac effects of hypercalcemia include QT-interval shortening and arrhythmias.[79] Bradycardia; first-, second-, and third-degree heart block; and bundle branch block may

occur. Hypercalcemia can also affect the systemic vasculature, perhaps leading to hypertension. The mechanism for the increase in blood pressure may be multifactorial. For example, serum levels of epinephrine and norepinephrine are higher in patients with hypercalcemia than in those with normocalcemia.

Treatment

Treatment should be directed at correcting the underlying cause of hypercalcemia whenever possible. For example, primary hyperparathyroidism is definitively managed by parathyroidectomy; further, when hypercalcemia is caused by malignant disease, treatment is directed at the underlying tumor.[80] When direct treatment of the underlying cause is not feasible, a number of medical treatments are available to treat severe symptomatic hypercalcemia. **Table 6-5** summarizes the treatments for hypercalcemia.

General Conservative Measures

When hypercalcemia is not life-threatening, treatment may be limited to simple actions such as a large fluid intake (unless contraindicated) and eliminating drugs that can contribute to hypercalcemia (such as thiazide diuretics, vitamin D preparations, and calcium-containing antacids). Whenever possible, the patient should be encouraged to be active, because immobility predisposes individuals to hypercalcemia.

0.9% Sodium Chloride and Loop Diuretics

Because most patients with severe hypercalcemia are volume depleted, isotonic saline (0.9% NaCl) is commonly administered to dilute the serum calcium, encourage renal excretion of calcium, and reduce the total serum calcium concentration (such as by 1.5 to 3 0 mg/dL).[81] In the early treatment phase, the rate of 0.9% NaCl and furosemide administration may be adjusted to keep the urine output between 200 and 300 mL/hr.[82] Plasma calcium levels usually will begin to decline within a few hours with the combination of furosemide and normal saline as long as the saline is administered at a sufficient rate.[83] Cardiovascular and renal function should be assessed before rapid saline infusion because fluid overload and congestive heart failure are potential complications. Furosemide should be used as necessary after the plasma volume has been expanded to prevent volume overload and to enhance calcium excretion. (A loop diuretic, such as furosemide, facilitates sodium and calcium excretion; conversely, the thiazide diuretics should not be used because they interfere with calcium excretion and may worsen hypercalcemia.) It may be necessary to monitor the central venous pressure to detect fluid overload, particularly in elderly patients or persons with marginal cardiac reserve; at the very least, breath sounds should be monitored at regular intervals. Hourly intake and output records should be maintained. Losses of potassium and magnesium will result from the large urinary output, which must be corrected as indicated by laboratory data.

Table 6-5 Summary of Treatments for Hypercalcemia

Agent	*Mechanism of Action*
0.9% sodium chloride solution, IV	Dilutes serum calcium concentration, increases glomerular filtration rate, and increases renal calcium excretion
Furosemide	Increases renal calcium excretion
Calcitonin	Inhibits bone resorption; inhibits renal reabsorption of calcium
Plicamycin	Inhibits bone resorption
Glucocorticoids	Inhibits calcium absorption in the intestine, inhibits bone resorption, inhibits cytokine release, and increases urinary calcium excretion
Phosphate salts	Inhibits bone resorption, interferes with GI absorption of calcium, and inhibits renal synthesis of 1,25-dihydroxyvitamin D
Bisphosphonates	Inhibit bone resorption
Gallium nitrate	Inhibits bone resorption

Bisphosphonates

Bisphosphonates, such as pamidronate and etidronate, inhibit bone resorption and, therefore, can treat hypercalcemia. The bisphosphonate dosage is determined by the severity of the hypercalcemia. Bisphosphonates are the mainstay of treatment for hypercalcemia associated with malignancy. They normalize calcium in more than 70% of patients, although it may take as long as 48 to 72 hours before the full therapeutic effect becomes evident.[84] Serum calcium levels may remain in the normal range for weeks to months after bisphosphonate therapy.

Plicamycin

Plicamycin (an antineoplastic agent) lowers serum calcium by blocking bone resorption. Because of the potential for nephrotoxicity and hepatotoxicity, long-term use of plicamycin is limited; use of this agent should be avoided in patients with underlying renal or liver dysfunction. Since the advent of the bisphosphonates, plicamycin has been used much less often than in the past.[85]

Calcitonin

By inhibiting bone resorption, salmon calcitonin has a slight and short-term effect on plasma calcium levels. The efficacy of calcitonin is largely limited to the first 48 hours after its administration (which limits its use in the control of long-term hypercalcemia).[86] Calcitonin is used largely as adjunctive therapy in controlling hypercalcemia in acute care settings until more powerful (but slower-acting) drugs take effect.[87]

Glucocorticoids

Glucocorticoids can reduce the serum calcium level by inhibiting cytokine release, inhibiting absorption of calcium in the intestine, and increasing urinary calcium excretion.[88] They are effective in reducing serum calcium in hypercalcemia due to sarcoidosis, vitamin D intoxication, multiple myeloma, or other hematologic malignancies. A drawback of glucocorticoids is that clinically significant reductions in serum calcium may not occur until at least 5 to 10 days after therapy is initiated.[89] Possible complications associated with glucocorticoids include hyperglycemia and sodium and water retention.

Gallium Nitrate

Gallium nitrate lowers the serum calcium level by inhibiting bone resorption. It has a delayed action onset of 2 days. This agent carries a significant risk of nephrotoxicity and is contraindicated when the serum creatinine is greater than 2.5 mg/dL.[90]

Phosphate Salts

When ingested orally, phosphate produces a small reduction in the serum calcium level by inhibiting bone resorption, interfering with the GI absorption of calcium, and inhibiting renal synthesis of 1,25-dihydroxy vitamin D. Because of its modest effect on the serum calcium level, oral phosphate use is limited to long-term treatment of mild hypercalcemia. It is important to remember that increasing the serum phosphate concentration alters the extracellular calcium–phosphate equilibrium to promote the formation of calcium-phosphate precipitates, which are then deposited in various body tissues including bone, soft tissues, blood vessels, lung, myocardium, and kidneys. Because of the risk of soft-tissue calcification, phosphate therapy is limited primarily to patients with low serum phosphate levels (less than 3.0 mg/dL) and adequate renal function.

Clinical Considerations

1. Be aware of patients at risk for hypercalcemia and monitor for its presence. (See Table 6-4.)
2. Increase patient mobilization when feasible; recall that immobilization favors hypercalcemia. Hospitalized patients at risk for hypercalcemia should be ambulated as soon as possible; outpatients should be told the importance of frequently moving about.
3. Encourage the oral intake of sufficient fluids to keep the patient well hydrated. Sodium-containing fluids should be given, unless contraindicated by other conditions, because sodium favors calcium excretion. Always consider the patient's preferences when encouraging oral fluids.
4. Encourage adequate bulk in the diet to offset the tendency toward constipation.
5. Take safety precautions if confusion or other mental symptoms of hypercalcemia are present. Explain to the patient and family that the mental changes associated with hypercalcemia are reversible with treatment.
6. Be aware that cardiac arrest can occur in patients with severe hypercalcemia; be prepared to deal with this emergency situation.
7. Be aware that bones may fracture more easily in patients with chronic hypercalcemia because bone resorption has been excessive, weakening the bony structure. Transfer patients cautiously.

8. Educate home-bound oncology patients with a predisposition for hypercalcemia, as well as their families, regarding symptoms that occur with this condition. Instruct them to report symptoms to healthcare providers before they become severe. In a study reported by Mahon, constipation, confusion, anorexia, increasing bone pain, weight loss, and weakness were the symptoms that most frequently caused readmission of patients with cancer. In a study of 22 hospitalized and 18 ambulatory cancer patients,[91] Coward reported that 90% were unaware that hypercalcemia might be a complication of their cancer.[92] Furthermore, only one of the patients knew the symptoms of cancer-induced hypercalcemia. Almost 70% of the patients did not recall being told of measures that might prevent hypercalcemia.
9. Be alert for signs of digitalis toxicity when hypercalcemia occurs in digitalized patients.
10. Be familiar with the treatment modalities for hypercalcemia and associated nursing functions (see the treatment section in this chapter and in Chapter 22).

HYPERCALCEMIA CASE STUDIES

Case Study 6-7

A 47-year-old woman who appeared thin and dehydrated was admitted to the hospital with abdominal pain, weight loss, and a history of vomiting for 3 months. Her body weight of 38 kg was only 84% of her ideal body weight; her mid-arm circumference was 60% of standard. On examination, a nodule was felt near the right lobe of the thyroid gland and was later found to be an adenoma. A serum calcium level was obtained and was found to be high (13.8 mg/dL).

The patient was rehydrated with 0.9% NaCl solution; however, saline diuresis did not represent a long-term solution to this woman's problem of severe hypercalcemia. Thus the right upper parathyroid gland was surgically removed. At the time of discharge from the hospital, the patient's calcium concentration had normalized to 8.7 mg/dL.

Commentary. This patient had hypercalcemia due to a parathyroid adenoma, which is one of the most common causes of hypercalcemia. She received the usual treatment for this disorder—rehydration with isotonic saline and surgical removal of the tumor.

Case Study 6-8

A 49-year-old woman with a history of breast cancer and metastases to the bone and liver was admitted to the hospital with polyuria and polydipsia; her total serum calcium level was 3.08 mmol/L (12.3 mg/dL). A single IV infusion of pamidronate was administered. The serum calcium level returned to normal and did not change until 6 weeks later. Several subsequent recurrences of hypercalcemia were also treated with single infusions of pamidronate given in the outpatient department. The patient was able to continue receiving palliative therapy at home, but died 6 months later from other complications.

Commentary. The polyuria associated with hypercalcemia occurs as a result of a renal concentrating defect; although the precise cause of this abnormality is not certain, a defect in the action of antidiuretic hormone in the collecting ducts and damage to the concentrating segments of the nephrons play a role. Provided the patient is not too nauseated to drink fluids, fluid intake will increase as the patient becomes more thirsty. Treatment of this woman's intermittent bouts of hypercalcemia allowed her to be more comfortable during her remaining months of life.

Case Study 6-9

A 59-year-old woman with carcinoma of the left breast underwent a radical mastectomy and adjuvant chemotherapy. She was later admitted to the hospital for management of hip pain, confusion, and hypercalcemia (corrected serum calcium, 15.2 mg/dL). Isotonic saline was administered IV, and she was given calcitonin subcutaneously every 8 hours. She also received pamidronate IV. The patient remained confused after the serum calcium level normalized. No further treatment was administered when the hypercalcemia recurred, and she died 1 month later from a pulmonary embolus.

Commentary. Because hypercalcemia can impair mental function, it is not unusual to observe confusion in patients with hypercalcemia. However, the behavior changes usually gradually subside once the hypercalcemia is resolved. Therefore, it was concluded that the confusion was due to something other than hypercalcemia.

Case Study 6-10

A 50-year-old man with dysphagia due to an adenocarcinoma in the gastroesophageal junction became acutely confused and

reported recent nausea, anorexia, and polyuria. Because of his nausea, he was unable to consume fluids; his skin turgor was poor and his mucous membranes were dry. The ionized serum calcium level was elevated (8.7 mg/dL). Isotonic saline and a single dose of pamidronate were administered IV. The serum calcium level normalized within 3 days and the patient's confusion improved. Later, the confusion returned and he was found to have multiple metastases to the lung, bone, and brain. After consultation with his family, treatment of hypercalcemia was withdrawn, and he was treated palliatively at home until he died 10 days later.

Commentary. Nausea and vomiting are classic symptoms of hypercalcemic states, as is constipation. High serum calcium levels cause slowed GI motility and delayed gastric emptying; these conditions contribute to anorexia, nausea, and vomiting. The polyuria associated with hypercalcemia is related to a renal concentrating defect; inability to replace the large urinary losses with increased oral fluid intake results in fluid volume depletion. Although this patient's confusion was partially alleviated by correction of the serum calcium level, other causes were present that caused it to recur (namely, metastases to the brain).

Case Study 6-11

A case was reported in which a 40-year-old woman was admitted to the emergency department with eclampsia.[93] During her examination, she was found to have profound hypercalcemia and metabolic alkalosis (pH 7.57) secondary to milk-alkai syndrome. The corrected calcium level was 4.71 mmol/L (normal range is 2.23 to 2.57 mmol/L). The patient revealed that she had self-medicated with multiple antacid tablets for dyspepsia. Treatment consisted of aggressive rehydration, bisphosphonates, and discontinuation of antacid tablets. The patient made a full recovery and delivered a normal infant.

Commentary. It is possible to consume enough calcium and alkali with over-the-counter antacids to induce milk-alkali syndrome. Upon questioning, it was learned that the patient had taken approximately 24 antacid tablets per day, in addition to an unknown multivitamin preparation.

Case Study 6-12

A case was reported in which a 32-year-old man had a 3-day history of nausea, vomiting, and constipation.[94] In addition, he complained of muscular weakness and polyuria/polydipsia. Laboratory analysis revealed a serum calcium level of 6.9 mmol/L (equivalent to about 27.6 mg/dL), a hematocrit of 52%, and an extremely high parathyroid hormone concentration (70.2 pmol/L (reference range, 1.6 to 6.8 pmol/L). A parathyroid adenoma was identified and removed.

Commentary. Parathyroid adenoma accounts for 96% of the cases of primary hyperparathyroidism.

Case Study 6-13

A 50-year-old woman with breast cancer and metastases to the bone and liver was admitted with polyuria and polydipsia. Laboratory results showed that her total calcium level was 12.3 mg/dL. Following treatment with a bisphosphonate, her serum calcium level returned to normal for almost 2 months. Several recurrences of hypercalcemia were managed the same way. The patient was able to continue palliative therapy at home before ultimately dying from complications other than hypercalcemia.

Commentary. The polyuria and polydipsia noted in this case were attributable to nephrogenic diabetes insipidus secondary to hypercalcemia. Fortunately, this condition was corrected when the hypercalcemia was treated. The value of bisphosphonates in treating hypercalcemia is immense in that they provide relief from the multiple symptoms of severe hypercalcemia.

Case Study 6-14

A case was reported in which a 69-year-old woman with squamous cancer of the anus was admitted to the hospital in an unresponsive state.[95] She had a 3-day history of lethargy, weakness, obstipation, and emesis of feculent material. A fecal impaction of the transverse and ascending colon was identified. Laboratory results showed a total calcium level of 14.7 mg/dL (corrected for a low albumin level) and a BUN level of 33 mg/dL. The patient was treated with hydration, calcitonin, and a bisphosphonate. The lethargy and bowel dysfunction were ultimately corrected.

Commentary. This case demonstrates the profound effect that hypercalcemia can have on the bowel (slowed bowel function due to smooth muscle depression).

Case Study 6-15

A 70-year-old man presented with progressive weakness over a period of 3 weeks. He had experienced nausea, vomiting, and constipation. The patient had a history of heartburn and self-medicated with 200 antacid (calcium carbonate) tablets per week; in addition, he drank three quarts of milk per day. Laboratory results showed a serum calcium level of 15 mg/dL. Also evident were signs of renal damage (serum creatinine 5.9 mg/dL and BUN 60 mg/dL).

Commentary. This patient presented with evidence of milk-alkali syndrome. A typical calcium carbonate antacid table may contain 200 mg of elemental calcium (as calcium carbonate). Multiplying this number by 200 tablets and adding the amount of calcium consumed in three quarts of milk per day shows the extremely high calcium intake consumed by this patient. (One quart of milk contains approximately 1200 mg of calcium.)

Also see Case Studies 14-2, 14-5, and 22-3 for a discussion of other patients with calcium problems.

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