Chapter 69: Disorders of Calcium and Phosphorus Homeostasis

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UPDATE SUMMARY

Update Summary

July 10, 2023

The following sections were updated:

- Acute treatment of hypocalcemia: Updated elemental calcium description to include mg and mEq
- Pharmacologic therapy of hypercalcemia: Clarified availability of calcitonin

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 77, Electrolyte Homeostasis.

KEY CONCEPTS

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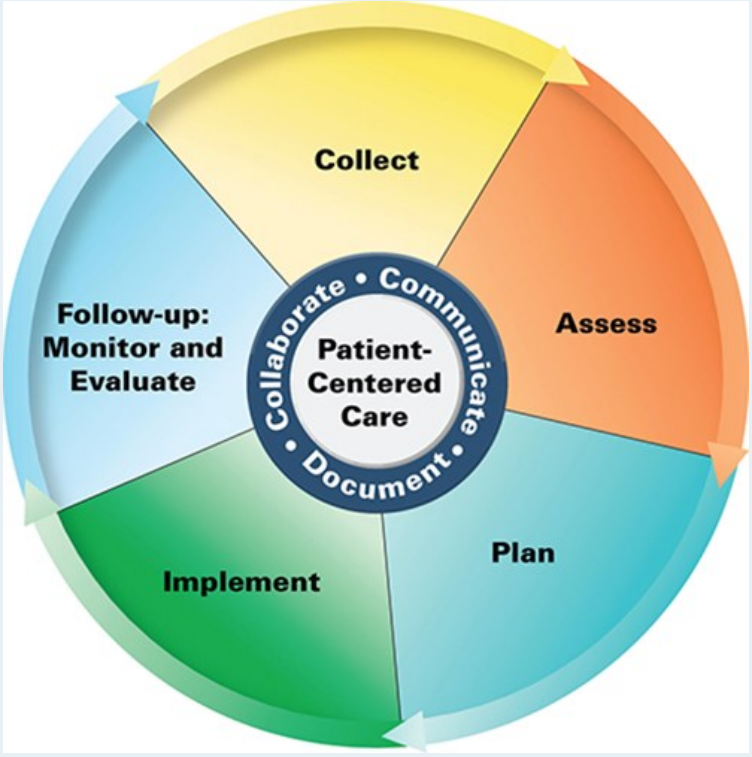
1. Severe acute hypercalcemia can result in cardiac arrhythmias, whereas chronic hypercalcemia can lead to calcium deposition in soft tissues including blood vessels and the kidney.
2. The correction of hypercalcemia can include multiple pharmacotherapeutic modalities such as hydration, diuretics, bisphosphonates, and corticosteroids, depending on the etiology and acuity of the hypercalcemia.
3. Hypocalcemia is typically associated with an insidious onset; however, some medications such as cinacalcet are associated with rapid decreases in serum calcium.
4. Acute treatment of hypocalcemia requires calcium supplementation, whereas chronic management may require other therapies such as vitamin D to maintain serum calcium concentrations.
5. Hyperphosphatemia occurs most frequently in patients with chronic kidney disease (CKD).
6. Treatment of nonemergent hyperphosphatemia includes the use of phosphate binders to decrease absorption of phosphorus from the gastrointestinal (GI) tract.
7. Hypophosphatemia is a relatively common complication among critically ill patients.
8. Treatment of acute hypophosphatemia usually requires intravenous (IV) phosphorus supplementation.

PATIENT CARE PROCESS

Patient Care Process for the Management of Hypercalcemia



Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, family, social—dietary habits)
- Evaluate symptoms (see the "Clinical Presentation: Hypercalcemia" section)
- Current medications, including over-the-counter medications, herbal products, nutritional supplements
- Objective data (see the "Clinical Presentation: Hypercalcemia" section)
  - Blood pressure, heart rate, height, weight
  - Labs (serum calcium and albumin, ionized calcium when available)
  - Other diagnostic tests when indicated (eg, ECG)

Assess

- Plausible etiology for hypercalcemia (see Table 69-1)
- Acuity of symptoms and urgency for treatment (see Fig. 69-2)
- Current medications and dietary intake that may contribute to or worsen hypercalcemia
- Kidney function (eg, serum creatinine, creatinine clearance)
- Serum calcium goal

Plan*

- Pharmacotherapy based on etiology of hypercalcemia including specific dose, route of administration, frequency of administration, and anticipated duration of treatment (see Table 69-2)
- Monitoring parameters include efficacy (eg, reduction in serum calcium, resolution of symptoms), safety (adverse medication reactions), and timeframe (see Table 69-2)
- Patient education (eg, purpose of treatment, medication therapy, expected time to reduce calcium, need for future medications)

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up based on acuity and symptoms

Follow-up: Monitor and Evaluate

- Measure serum calcium to determine response
- Presence of adverse medication reactions
- Consider alternative medication management if desired reduction in calcium is not achieved

Collaborate with patient, caregivers, and other healthcare professionals.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled "Skeletal Endocrine Control" in Khan Academy by Tracy Kim Kovach. This ~8-minute video provides a brief overview of calcium and phosphorus homeostasis. The video is useful to enhance students' understanding regarding the COLLECT and ASSESS steps in the patient care process: <https://www.khanacademy.org/test-prep/mcat/organ-systems/the-skeletal-system/v/skeletal-endocrine-control>.

INTRODUCTION

Disorders of calcium and phosphorus are common complications of multiple acute and chronic diseases. These disorders are frequently seen in the acute care setting; however, they are also often present in ambulatory patients, usually in a less severe state. The consequences of electrolyte disorders can range from asymptomatic to life-threatening, requiring hospitalization and emergent treatment. The maintenance of fluid and electrolyte homeostasis requires adequate functioning and modulation by multiple hormones on tissues of multiple organ systems.

Many common medication therapies can disturb the normal homeostatic mechanisms that maintain calcium and phosphorus balance. In addition, with some medication therapies, toxicity is enhanced when underlying electrolyte disorders are present. Medication-induced disorders typically respond well to discontinuation of the offending agent(s); however, additional therapies are sometimes required to correct the disorder. This chapter reviews the etiology, classification, clinical presentation, and therapy for the most common disorders of calcium and phosphorus homeostasis.

DISORDERS OF CALCIUM HOMEOSTASIS

The maintenance of physiologic calcium concentrations in the intracellular and extracellular spaces is vital for the preservation and function of cell membranes, propagation of neuromuscular activity, regulation of endocrine and exocrine secretory functions, blood coagulation cascade, platelet adhesion process, bone metabolism, muscle cell excitation/contraction coupling, and mediation of the electrophysiologic slow-channel response in cardiac and smooth-muscle tissues.

The disorders of calcium homeostasis are related to the calcium content of the extracellular fluid (ECF), which is tightly regulated and comprises less than 0.5% of the total body stores of calcium. Skeletal bone contains more than 99% of total body stores of calcium.[1] ECF calcium is moderately bound to plasma proteins (40%-50%), primarily albumin.[1] Ionized or free calcium is the biologically active form and is the fraction that is homeostatically regulated.[1] Extracellular calcium, however, is most commonly measured as the total serum calcium concentration, which includes both bound and unbound calcium. The normal total calcium serum concentration range is 8.6 to 10.2 mg/dL (2.15-2.55 mmol/L).[1]

Proper assessment of total serum calcium concentration includes measurement of the patient's serum albumin concentration. Hypoalbuminemia, which can be associated with many chronic disease states, is probably the most common cause of "laboratory hypocalcemia." Patients remain asymptomatic because the unbound or ionized fraction of serum calcium remains normal (normal range, 4.48-5.2 mg/dL [1.12-1.30 mmol/L]).[1] A corrected total serum calcium concentration can be calculated based on the measured total serum calcium and the difference between a patient's measured albumin concentration and the normative value of 4 g/dL (40 g/L) by the following equations:

$$\text{Corrected serum calcium (mg/dL)} = \text{Measured serum calcium (mg/dL)} + (0.8 \times [4\,\text{g/dL} - \text{measured albumin (g/dL)}])$$

or

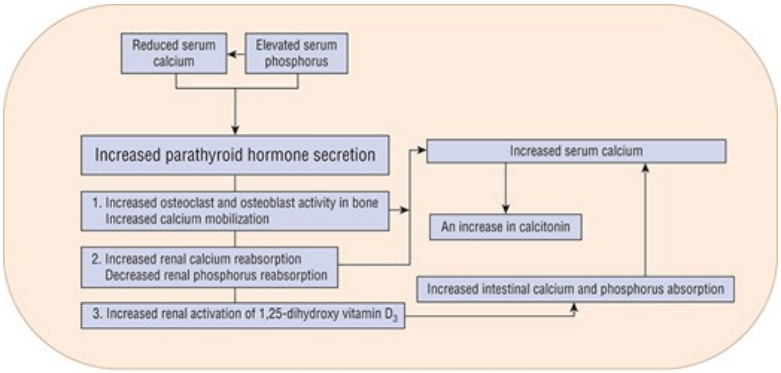
$$\text{Corrected serum calcium (mmol/L)} = \text{Measured serum calcium (mmol/L)} + (0.02 \times [40\,\text{g/L} - \text{measured albumin (g/L)}])$$

The concentration of ionized calcium is closely regulated by the interactions of parathyroid hormone (PTH), phosphorus, vitamin D, and calcitonin (Fig. 69-1). PTH increases serum calcium concentrations by stimulating calcium release from bone, increasing renal tubular reabsorption, and

enhancing absorption in the GI tract secondary to increased kidney production of 1,25-dihydroxyvitamin D_3. Vitamin D directly increases serum calcium, as well as phosphorus concentrations, by increasing GI absorption. Indirectly, it can also lead to calcium release from bone and reduced renal excretion. Calcitonin inhibits osteoclastic bone resorption. Calcitonin plasma concentrations are increased when ionized calcium concentrations are high as the body attempts to return the serum calcium concentration to the normal range. Disruption of these homeostatic mechanisms results in the clinical manifestations of hypercalcemia or hypocalcemia.

FIGURE 69-1

Homeostatic mechanisms to maintain serum calcium concentrations.



Total serum calcium and ionized calcium are poorly correlated in patients with hypoalbuminemia, critical illness, and acid-base disorders.[1] Alteration of the concentration of albumin or its binding of calcium can be expected to change the unbound fraction of total serum calcium. Each 1 g/dL (10 g/L) drop in the serum albumin concentration below 4 g/dL (40 g/L) will result in a decrease of total serum calcium concentration by 0.8 mg/dL (0.20 mmol/L).[1] This approach to calculating an albumin-adjusted calcium concentration has been found to overestimate the degree of hypercalcemia and usually fails to identify hypocalcemia in critically ill patients, because the ionized calcium concentration may be normal despite a low total serum calcium concentration in the setting of hypoalbuminemia. Therefore, ionized calcium values should be used to assess calcium status in critically ill patients.[1] Change in ECF pH is the most significant cause of changes in calcium binding to albumin. In the presence of acute metabolic alkalosis the fraction of calcium bound to albumin is increased, thus reducing the plasma concentration of ionized calcium. This can result in symptomatic hypocalcemia with manifestations such as tetany, paresthesia, muscle cramping, heart block, and seizures.[1] Conversely, metabolic acidosis decreases calcium binding to albumin and results in increased ionized calcium.

HYPERCALCEMIA

There are numerous causes of hypercalcemia (total serum calcium more than 10.2 mg/dL [2.55 mmol/L]) (Table 69-1). The most common causes of hypercalcemia are primary hyperparathyroidism and cancer.

TABLE 69-1

Etiologies of Hypercalcemia

Neoplasms
- Bone metastasis
  - Breast
  - Multiple myeloma
  - Lymphoma
  - Leukemia
- Humoral induced
  - Ovary
  - Kidney
  - Pheochromocytoma
  - Multiple endocrine neoplasia
  - Lung
  - Head and neck
  - Esophagus
  - Cervix
  - Lymphoproliferative disease

Hyperparathyroidism
- Primary
- Tertiary

Miscellaneous
- Immobilization
- Paget's disease
- Familial hypocalciuric hypercalcemia
- Adolescence
- Rhabdomyolysis

Medications
- Thiazides
- Lithium
- Vitamin D
- Vitamin A
- Calcium
- Aluminum/magnesium antacids
- Theophylline
- Tamoxifen
- Ganciclovir

Granulomatous disease
- Sarcoidosis
- Tuberculosis
- Cryptococcus
- Berylliosis
- Histoplasmosis
- Coccidioidomycosis
- Leprosy

Endocrine disease
- Adrenal insufficiency
- Hyperthyroidism
- Acromegaly

Epidemiology and Etiology

Primary hyperparathyroidism occurs predominantly after the age of 50 years and affects women 3 to 4 times more than men.[2] Hypercalcemia associated with malignancy occurs in approximately 10% to 30% of patients with cancer at some time during the course of their disease and is dependent on tumor type.[3] Cancer-associated hypercalcemia is predominantly encountered in hospitalized patients, whereas primary hyperparathyroidism accounts for the vast majority of cases in the outpatient setting.[3,4]

Pathophysiology

Hypercalcemia is the result of one or a combination of three primary mechanisms: increased bone resorption, increased GI absorption, or increased tubular reabsorption by the kidneys (see Fig. 69-1).

Many tumors secrete PTH-related protein (PTHrP), which binds to the PTH receptors in bone and kidney tissue, leading to increased bone resorption and tubular reabsorption.[5] Tumors can also secrete substances such as vitamin D, transforming growth factor, interleukins, prostaglandins, interferon, tumor necrosis factor, and granulocyte-macrophage colony-stimulating factor, which are associated with the development of hypercalcemia.[3] Hypercalcemia of malignancy is generally associated with bone metastases and is a common complication of squamous cell

carcinomas of the lung, head, and neck, hematologic malignancies such as multiple myeloma and T-cell lymphomas, and carcinomas of ovary, kidney, bladder, and breast. The most frequent types of malignancy associated with hypercalcemia are multiple myeloma, breast, renal, and squamous carcinomas.[3] Breast and squamous cell lung carcinomas secrete PTHrP which binds to the type I PTH receptor (PTHR1) and enhances bone resorption.[5] In contrast, patients with multiple myeloma often develop hypercalcemia principally as the result of osteoclast-mediated bone destruction.[3]

Primary hyperparathyroidism is the most common cause of chronic hypercalcemia in the general population. Benign parathyroid adenomas account for 80% to 85% of these cases of hyperparathyroidism, parathyroid hyperplasia accounts for 15%, and parathyroid carcinoma is the cause in less than 1% of cases.[4]

Other causes of chronic hypercalcemia include medications, endocrine and granulomatous disorders, physical immobilization, high bone-turnover states (eg, adolescence and Paget's disease), and rhabdomyolysis. Increased GI absorption can be the result of excessive ingestion of vitamin D analogs, calcium supplements, and lithium. Lithium and vitamin A therapy can increase bone resorption, whereas increased renal tubular reabsorption of calcium can occur with thiazide and lithium therapy. The exact mechanism of lithium-induced hypercalcemia is unknown but may include competitive inhibition of calcium influx into cells, increasing the threshold sensitivity of the calcium-sensing receptor (CaSr) and subsequent inhibition of PTH gene transcription.[6] Addison's disease, acromegaly, and thyrotoxicosis are endocrine disorders that can lead to hypercalcemia because of increased renal tubular reabsorption and increased bone resorption. Milk-alkali syndrome is the term applied to those situations where an individual develops hypercalcemia following the ingestion of calcium and absorbable alkali (eg, calcium carbonate) and is a frequent cause of hypercalcemia in patients who are not undergoing hemodialysis.[7,8] Finally, the granulomatous disorders (eg, sarcoidosis, tuberculosis, histoplasmosis, leprosy) are associated with hypercalcemia secondary to an increase in GI and renal tubular absorption as the result of granuloma production of 1,25-dihydroxyvitamin D_2.[9]

Clinical Presentation: Hypercalcemia

CLINICAL PRESENTATION: Hypercalcemia

General

- The signs and symptoms of hypercalcemia depend on the severity and rapidity of onset.

Symptoms

- Symptoms include fatigue, weakness, anorexia, depression, anxiety, cognitive dysfunction, vague abdominal pain, and constipation. Renal symptoms can include polyuria, polydipsia, and nocturia. Rarely, severe hypercalcemia leads to acute pancreatitis.

Signs

- Kidney: Nephrolithiasis; renal tubular dysfunction, particularly decreased concentrating ability; and acute and chronic kidney disease
- Cardiovascular: Hypercalcemia also directly shortens the myocardial action potential, which is reflected in a shortened QT interval and coving of the ST-T wave. Spontaneous ventricular tachyarrhythmias and elevations in blood pressure have also been reported. Chronic hypercalcemia can lead to cardiac calcification
- Musculoskeletal: Rheumatologic complaints related to hyperparathyroidism include gout, pseudogout, and chondrocalcinosis

Laboratory Tests

- Serum calcium concentrations of more than 10.2 mg/dL (2.55 mmol/L) are considered to represent hypercalcemia. Patients with values up to 13 mg/dL (3.25 mmol/L) are generally considered to have mild or moderate hypercalcemia, whereas those with values greater than this indicate the presence of severe hypercalcemia

Patients with mild-to-moderate hypercalcemia, that is, total serum calcium concentrations above the upper threshold of normal but less than 13 mg/dL (3.25 mmol/L) or ionized calcium concentrations less than 6 mg/dL (1.50 mmol/L) can often be asymptomatic. This is typically the case for the vast majority of patients who have medication-induced hypercalcemia or primary hyperparathyroidism.[9,10]

1 The presenting signs and symptoms of severe hypercalcemia that occur if the total serum calcium concentration is more than 13 mg/dL (3.25 mmol/L) may differ depending on the acuity of onset.[1] Hypercalcemia of malignancy usually develops quickly and is accompanied by a classic symptom complex of anorexia, nausea and vomiting, constipation, polyuria, polydipsia, and nocturia.[3] Polyuria and nocturia secondary to a urinary-concentrating defect constitute some of the most frequent renal effects of hypercalcemia.[9] Hypercalcemic crisis is characterized by an acute elevation of total serum calcium to a value more than 15 mg/dL (3.75 mmol/L), acute kidney injury (AKI), and obtundation (inability to arouse).[11] If untreated, hypercalcemic crisis can progress to oliguric AKI, coma, and life-threatening ventricular arrhythmias.[9] The primary complications associated with chronic hypercalcemia (hyperparathyroidism) include metastatic calcification, hypercalciuria, and CKD secondary to interstitial nephrocalcinosis.[9]

Calcium and/or calcium–phosphorus complex deposition in blood vessels and multiple organs is a complication of chronic hypercalcemia and/or concomitant hyperphosphatemia and hyperparathyroidism. Calcium deposits in atherosclerotic lesions contribute to cardiac disease.[12] Intracardiac and arterial calcifications have been found in patients with Paget's disease who have normal kidney function. It is hypothesized that similar calcification processes occur in both bone and vascular tissue, leading to cardiovascular diseases including heart failure, systolic hypertension, and ischemic heart disease.[13]

The electrocardiographic changes associated with hypercalcemia include shortening of the QT interval and coving of the ST-T wave.[9] Very high serum calcium concentrations can cause T-wave widening, indicating a repolarization defect that may be associated with spontaneous ventricular tachyarrhythmias.[9] Hypertension and arrhythmias have occurred in the setting of hypercalcemia. The effects of digoxin on cardiac conduction including lowering of the excitation threshold, shortening of the effective refractory period, and increased atrioventricular refractoriness can be potentiated by hypercalcemia.[14]

Nephrolithiasis

Nephrolithiasis (ie, kidney stones) and nephrocalcinosis (ie, calcium deposits in the kidney) are the primary renal complications arising from long-standing hypercalcemia, as the result of primary hyperparathyroidism. Stone formation is dependent on a favorable milieu within the kidney or urinary tract, such as oversaturation of the urine and/or reduced concentrations of endogenous inhibitors of crystal formation (eg, citrate or pyrophosphate). About 20% to 30% of patients with primary hyperparathyroidism exhibit nephrolithiasis.[15,16] Of note, in those patients with low glomerular filtration rates (GFRs), the 24-hour urinary calcium will actually diminish secondary to decreased production of 1,25-dihydroxyvitamin D_2. However, the fractional excretion of calcium might increase.[16] Sarcoidosis is the other hypercalcemic condition frequently associated with calcium stones.[9] Other causes of nephrolithiasis with calcium-containing stones include hypocitraturia, renal tubular acidosis, hyperoxaluria, and hyperuricosuria, which are conditions that are prevalent among bariatric surgery patients.[17,18] Stone formers who have primary hyperparathyroidism are more likely to be women, older than 50 years, and have a family history of multiple endocrine disorders.[15] High dietary sodium intake can also raise urinary calcium concentrations, perhaps due to a reduction in calcium reabsorption in the kidney, thus predisposing patients to calcium stones. Although CKD can be the ultimate result of persistent stones, it is the primary cause of kidney disease in less than 2% of the end-stage kidney disease population.

Treatment

Desired Outcome

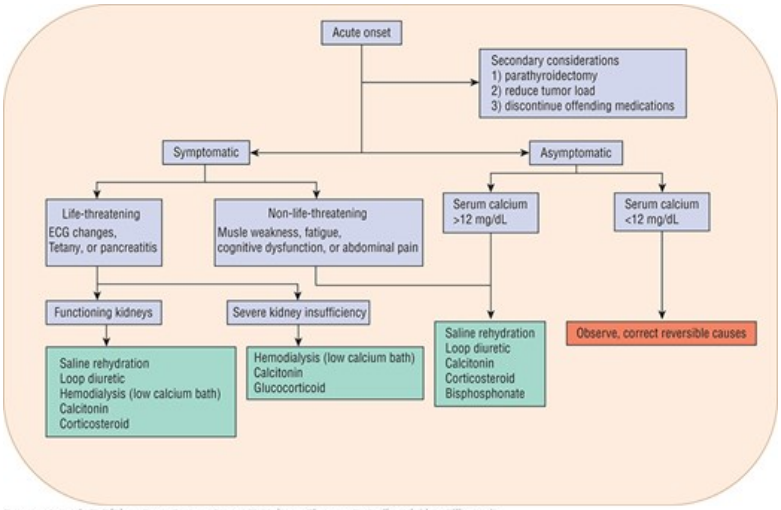
The indications for the treatment of acute hypercalcemia are dependent on the severity of hypercalcemia, acuity of its development, and the presence or absence of symptoms requiring emergent treatment (eg, necrotizing pancreatitis). The therapeutic intervention plan should be crafted to reverse signs and symptoms, restore normocalcemia within hours to days depending on acuity, and correct or manage the underlying cause of hypercalcemia.

General Approach

Chronic hypercalcemia is usually caused by an underlying medical condition or prescribed pharmacotherapies that can be resolved by successful treatment of the condition or withdrawal of the offending agent resulting in a decrease in serum calcium within days or weeks. Acute hypercalcemic episodes induced by malignancies may be mitigated by chemotherapy and/or radiation treatment. Effective surgical or medication treatment of primary hyperparathyroidism should reduce serum calcium concentrations as well as reduce the development of long-term complications such as vascular complications, CKD, and kidney stones. For treatment of nephrolithiasis, the goal in management of serum calcium is prevention of stone formation and diameter. The reduction of serum calcium should be targeted at the underlying disease state causing hypercalcemia (eg, using cinacalcet for primary hyperparathyroidism). Hypercalcemic crisis and acute symptomatic severe hypercalcemia are medical emergencies and require immediate treatment (Fig. 69-2).

FIGURE 69-2

Pharmacotherapeutic options for the acutely hypercalcemic patient. Serum calcium of 12 mg/dL is equivalent to 3 mmol/L.



These patients may require immediate-acting interventions to promptly reduce the serum calcium concentration if electrocardiogram (ECG) changes, neurologic manifestations, or pancreatitis are present. Pharmacologic therapy consisting of volume expansion and enhancement of urinary calcium excretion with loop diuretics is usually the initial management strategy. Hemodialysis against a zero- or low-calcium dialysate solution should be considered for patients with severely impaired kidney function (CKD stage 4 or 5) who cannot tolerate large fluid loads and in whom diuretics have limited efficacy.[9]

Effective treatment of moderate-to-severe hypercalcemia in the absence of life-threatening symptoms begins with attention to the underlying disorder and correction of associated fluid and electrolyte abnormalities. Patients with primary hyperparathyroidism may require surgery, particularly if they have systemic manifestations.

Patients with malignancy often require surgical or chemotherapeutic reduction of tumor load to control the exogenous supply of cytokines and hormones (eg, PTHrP) that cause hypercalcemia. In contrast, patients with medication-induced hypercalcemia generally respond to discontinuation of the offending agent.

Pharmacologic Therapy

Symptomatic Patient Management

2 For those patients with normal to moderately impaired kidney function (CKD stages 3a, 3b, and 4), the cornerstone of initial first-line treatment of severe, acute hypercalcemia or hypercalcemic crisis is volume expansion with normal saline to increase natriuresis and ultimately urinary calcium excretion (Table 69-2). Patients with symptomatic hypercalcemia are often extracellular volume depleted secondary to vomiting and polyuria; thus, rehydration with saline-containing fluids is necessary to interrupt the stimulus for sodium and calcium reabsorption in the renal tubule.[19] Rehydration

can be accomplished by the rapid infusion of 1 to 2 L of normal saline followed by a maintenance infusion at 250 to 300 mL/hr, until the patient is fluid resuscitated and serum calcium approaches the upper limit of the normal range.[19] The precise rate depends on concomitant conditions (primarily cardiovascular and kidney) and magnitude of hypercalcemia. The saline infusion rate can be decreased to a rate that approximates the patient's intake of oral or IV fluids. See Chapter 68 for a thorough discussion of how to calculate water deficit and monitor patient's response to saline infusion. Loop diuretics such as furosemide (40-80 mg IV every 1-4 hours) have been used to increase urinary calcium excretion.[19] Loop diuretics block calcium (and sodium) reabsorption in the thick ascending limb of the loop of Henle and augment the calciuric effect of saline alone. Rehydration prior to loop diuretic use is critical because if dehydration persists or becomes worse, the serum calcium can actually increase because of enhanced proximal tubule calcium reabsorption.[20] The primary role for loop diuretics in the setting of hypercalcemia is to minimize the development of volume overload from the administration of saline (Fig. 69-2 and Table 69-2). Furosemide should not be used first-line as there is little evidence that supports the efficacy of furosemide in treatment of hypercalcemia.[20] Potassium chloride, 10 to 20 mEq/L (10-20 mmol/L), should be considered for addition to the saline infusion after rehydration is accomplished to prevent the development of hypokalemia that is a common adverse medication reaction of aggressive diuretic therapy. Serum magnesium concentrations should also be monitored, and magnesium replacement initiated if magnesium concentrations fall below 1.8 mg/dL (0.74 mmol/L). Rehydration with saline and administration of furosemide may result in normalization total serum calcium within 24 to 48 hours; however, patients should be monitored closely for fluid overload.[19,20] Hemodialysis with low or zero calcium dialysate is a treatment option in the case of failure or when calcium concentrations are life-threatening.[20] It should be noted that preparing a patient for hemodialysis takes time to achieve vascular access; thus, this approach is best suited for patients already receiving hemodialysis chronically.

TABLE 69-2

Medication Dosing Table for Hypercalcemia

Medication/Brand Name	Starting Dosage	Time Frame to Initial Response	Monitoring and Special Population Considerations
0.9% Saline ± electrolytes	200-300 mL/hr	24-48 hr	Electrolyte abnormalities, fluid overload CI in kidney disease, heart failure
Loop diuretics • Furosemide/Lasix® • Bumetanide/Bumex® • Torsemide	40-80 mg IV q 1-4 hr of furosemide or equivalent	N/A	Electrolyte abnormalities (potassium and magnesium), CI in patients with allergy to sulfas (use ethacrynic acid)
Calcitonin/Miacalcin® (Discontinued Drug Product List)	4 units/kg q 12 hr SC/IM	1-2 hr	Facial flushing, nausea/vomiting, allergic reaction, CI in patients with allergy to calcitonin
Pamidronate/Aredia®	30-90 mg IV over 2-24 hr	2 days	Fever, fatigue, skeletal pain, CI in kidney disease
Zoledronic acid/Reclast®	4 mg IV over 15 minutes	1-2 days	Fever, fatigue, skeletal pain, CI in kidney disease
Corticosteroids	40-60 mg oral prednisone equivalents daily	3-5 days	Diabetes mellitus, osteoporosis, infection, CI in patients with serious infections, hypersensitivity

CI, contraindicated; SC, subcutaneous.

Asymptomatic Patient Management

Calcitonin

In those patients in whom saline hydration therapy is contraindicated (eg, severe heart failure, moderately-to-severely impaired kidney function), short-term therapy with calcitonin is a viable alternative agent to initiate reduction of serum calcium concentrations within 24 to 48 hours. In fact, calcitonin begins to reduce serum calcium concentrations within a few hours; however, the degree and extent of serum calcium concentration reduction are often unpredictable.[1]

Subcutaneous or Change IV to IM administration of salmon calcitonin, 4 to 8 international units/kg every 12 hours, has been used to manage hypercalcemia in patients with malignancy.[3] The intranasal formulation of calcitonin has been used in doses of 200 to 400 international units daily; unfortunately, this has resulted in only mild decreases in serum calcium. The lack of significant efficacy of the synthetic intranasal formulation is the result of the lower potency and shorter duration of action as compared to salmon calcitonin. In February 2023, the FDA communicated that Miacalcin® injection was not withdrawn from sale for reasons of safety or effectiveness; therefore, the FDA could approve abbreviated new drug applications for calcitonin injection if legal and regulatory requirements are met.

Pharmacology

Calcitonin decreases serum calcium concentrations, primarily by inhibiting bone resorption. It can also reduce renal tubular reabsorption of calcium, thus promoting calciuresis.[3] Calcitonin from salmon sources is most commonly administered subcutaneously or intramuscularly (for larger volumes), which may rapidly lower calcium concentrations initially, but the effect can be transient.[3]

Adverse Medication Reactions

The adverse medication reactions from calcitonin (facial flushing, nausea, and vomiting) may limit patient acceptability. Allergic reactions, although rare, do occur; therefore, a test dose can be given prior to starting therapy. If marked erythema and/or wheal formation does not occur within 15 minutes after administration, then therapy can be initiated. Salmon calcitonin therapy is associated with tachyphylaxis caused by antibody formation to foreign proteins or molecules resembling the calcitonin polypeptide.[21] The addition of corticosteroid therapy increases effectiveness.[3]

Bisphosphonates

Bisphosphonates block bone resorption efficiently, render the hydroxyapatite crystal of bone mineral resistant to hydrolysis by phosphatases, and also inhibit osteoclast precursors from attaching to the mineralized matrix, thus blocking their transformation into mature functioning osteoclasts.[3,9] The antiresorptive properties of this class of agents can provide long-term control of serum calcium and are the first-line therapy for cancer-associated hypercalcemia.

Pharmacology

The first-line bisphosphonates to treat hypercalcemia are pamidronate and zoledronic acid.[22] The usual dose of pamidronate is 30 to 90 mg as an IV infusion given over no less than 2 hours and up to 24 hours.[22] Pamidronate also has the advantage of single-day therapy.[22] Zoledronic acid is a high-potency bisphosphonate with demonstrated effectiveness in the treatment of hypercalcemia of malignancy. Complete response has been reported in 88.4% to 86.7% of zoledronic acid-treated versus 69.7% of pamidronate-treated patients.[23] Zoledronic acid IV doses of 4 to 8 mg given over 15 minutes have resulted in normalization of serum calcium concentrations.[3] IV infusions of 0.02 or 0.04 mg/kg diluted in 5% dextrose (given over 20-50 minutes) have also been effective.[24] The onset of serum calcium concentration decline is slower with bisphosphonate therapy (concentrations begin to decline in 2 days and reach a nadir in 7 days); thus calcitonin therapy or other interventions may be necessary if more rapid serum calcium reduction is required.[22] Duration of normocalcemia after treatment is variable and dependent on the severity and treatment response of the underlying malignancy, but usually does not exceed 2 to 3 weeks.

Adverse Medication Reactions

Fever is a common adverse medication reaction of IV bisphosphonate therapy. The safety of continuous bisphosphonate therapy in treating hypercalcemia of malignancy is unclear; however, zoledronic acid has been associated with atrial fibrillation.[25] Kidney function monitoring (eg, serum

creatinine) is advised with the use of bisphosphonates, as kidney function declines and acute tubular necrosis occurs rarely.[26,27] It is advisable to evaluate serum creatinine within a week after the infusion and just prior to the next scheduled dose.[22] Osteonecrosis of the jaw is a rare, but serious adverse medication reaction. With osteonecrosis of the jaw, there is an area of exposed bone in the maxillofacial or mandibular region that does not heal within 8 weeks after diagnosis.[22] Higher potency bisphosphonates and longer durations of therapy are associated with increased risk.[28]

Denosumab

Pharmacology

Denosumab is a monoclonal antibody that inhibits the receptor activator of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) ligand (RANKL), a principal mediator of osteoclast survival. Denosumab is FDA-approved for the treatment of patients with hypercalcemia of malignancy.[3] The medication is effective in treatment of patients with hypercalcemia of malignancy (with or without bone metastases) who are refractory to IV bisphosphonate therapy, that is, their corrected serum calcium remains above 12.5 mg/dL (3.13 mmol/L) after more than 7 days of therapy.[3] Denosumab has also been reported to successfully treat hypercalcemia after successful stem cell transplantation and restitution of osteoclast function in patients with osteopetrosis, a heritable disorder associated with defective osteoclast function.[2,29]

Adverse Medication Reactions

Denosumab has been associated with osteonecrosis of the jaw.[30] Although advanced kidney disease has not been shown to affect the pharmacodynamics and pharmacokinetics of denosumab, severe, symptomatic hypocalcemia has been reported in CKD patients receiving the medication.[31] Close monitoring of serum calcium is recommended for patients with creatinine clearance (CrCl) <30 mL/min (0.5 mL/s).[22] This may be due to induction of a hungry bone-like syndrome and warrants careful monitoring.[32]

Corticosteroids

Prednisone or an equivalent agent is usually effective in the treatment of hypercalcemia resulting from multiple myeloma, leukemia, lymphoma, sarcoidosis, and hypervitaminoses A and D.[9,33,34] Corticosteroids are effective because they reduce GI calcium absorption.[34] Corticosteroids may also prevent tachyphylaxis to salmon calcitonin.[35] Daily doses of 40 to 60 mg of prednisone or the equivalent have effectively normalized serum calcium values within 3 to 5 days followed by a reduction in urinary calcium excretion within 7 to 10 days. The disadvantages of corticosteroid therapy are its relatively slow onset of action and the potential for diabetes mellitus, osteoporosis, and increased susceptibility to infection.[36]

Cinacalcet

The calcimimetic agent cinacalcet is approved for management of parathyroid carcinoma, primary hyperparathyroidism where parathyroidectomy is indicated but cannot be undertaken, and secondary hyperparathyroidism in patients with CKD on dialysis.[3,37] Cinacalcet is an allosteric modulator of the CaSr, and increases the sensitivity for receptor activation by extracellular calcium. This results in reduced PTH and serum calcium concentrations.[3,37] Cinacalcet administered at a starting dose of 30 mg orally twice daily has been used for the treatment of hypercalcemia secondary to parathyroid carcinoma. The dosage is titrated every 2 to 4 weeks in 30 mg increments until the desired serum calcium concentration is achieved. The maximum approved dosage is 90 mg four times daily.[3] Hypocalcemia is a common adverse medication reaction and patients with specific CaSR polymorphisms may be particularly susceptible.[37] Patients should have serum calcium measured within 1 week after starting or increasing the dose of this agent. The role of cinacalcet in the management of nephrolithiasis is still controversial, but it has shown benefits in patients with primary hyperparathyroidism.[38] Etelcalcetide is the first IV calcimimetic that is structurally different from cinacalcet but also acts as an allosteric modulator of the CaSR. Etelcalcetide is only approved to treat secondary hyperparathyroidism in hemodialysis patients (see Chapter 64).[39]

Pharmacoeconomic Considerations

Corticosteroids are inexpensive for treatment of asymptomatic hypercalcemia from a pharmacoeconomic standpoint; however, the low cost of the medication may be offset by the multitude of long-term adverse medication reactions and potential need for additional treatment. Calcitonin is only suitable for short-term therapy and thus the long-term pharmacoeconomic benefits are unknown. Use of bisphosphonates for the management of

bone metastases of malignancy is associated with lower morbidity and health gains (quality of life) well below the typical cost-effectiveness threshold.[40] Due to calcitonin's faster onset of action, it may be added to bisphosphonate treatment for rapid serum calcium reduction. However, combination treatment with a bisphosphonate plus calcitonin likely results in similar outcomes and higher costs for moderate-to-severe hypercalcemia of malignancy.[41] The introduction of denosumab and its demonstrated efficacy in preventing and delaying skeletal-related adverse medication reactions while reducing hypocalcemia have prompted questions regarding its cost-effectiveness.[40] Although denosumab is associated with additional health gains compared to zoledronic acid, it may not offer economic advantages.[40] Additional considerations for choice of therapy include co-pay costs and patient assistance program availability for these agents.[42]

Nephrolithiasis from Chronic Hypercalcemia and Hypercalciuria

Patients who develop nephrolithiasis from hypercalciuria are most often treated with sodium citrate to prevent stone formation, thiazide diuretics to decrease urinary calcium excretion, or shock wave lithotripsy (Table 69-3). There are multiple approaches to treating and preventing future nephrolithiasis issues which include stone removal or disintegration, using medications to dissolve or prevent stone formation as well as dietary interventions to prevent stone formation.[18] Procedures such as shockwave lithotripsy are effective in disintegrating stones and subsequently allowing for their urinary removal; however, the procedure is painful and expensive. Urinary alkalinizing agents such as potassium or sodium citrate prevent growth of stone diameter, increasing the likelihood of spontaneous passage. These agents are available in liquid form, but must be taken consistently multiple times per day to maintain an alkaline urine.[15] Thiazide diuretics decrease urinary calcium excretion and reduce the potential for crystal formation and are commonly used for prevention.[18] Other agents such as calcium binding resins, natural plant extracts (*Phyllanthus niruri*), and reduction of dietary calcium offer little benefit.

TABLE 69-3

Treatment of Nephrolithiasis Associated with Chronic Hypercalcemia and Hypercalciuria

Intervention	Indications	Comments
Extracorporeal Shock Wave Lithotripsy		
Uses sound waves to break up stones, which then can pass spontaneously	Obstruction of the urinary tract, especially with stones >5 mm	Consider adjunctive use of potassium citrate to inhibit aggregation of residual fragments
Prevention of Stone Formation		
Alkalinizing agents	Prevention; Treatment for nonemergent active stones	Potassium citrate is preferred over sodium citrate as it decreases urinary calcium, inhibits calcium oxalate precipitation, and increases urinary citrate more
Potassium citrate PO 20 mEq three times daily or 30 mEq twice daily		
Sodium citrate PO 20-30 mEq twice daily		
Decrease Urinary Calcium Excretion		

Thiazide diuretics	Prevention	Medication of choice in patients with low bone density
Hydrochlorothiazide PO 50 mg daily		
Indapamide PO 2.5 mg daily		
Chlorthalidone PO 25 mg daily		
Binding Intestinal Calcium		
Cellulose sodium phosphate PO 10 g daily in three divided doses with meals	Prevention for those with absorptive hypercalciuria	Restrict dietary intake of oxalate-containing foods, concomitant magnesium therapy recommended, alternative to thiazides if intolerant or ineffective, initial dose dependent on urinary calcium excretion, monitor bone density
Inhibition of Crystal Formation		
Phyllanthus niruri plant extract PO 2 g daily	Prevention, after shock wave lithotripsy	Commercial preparations with *P. niruri* as the sole ingredient can be difficult to obtain, variable dosages reported
Low-Calcium Diet		
Less than 400 mg/day	Prevention	Monitor bone density prior to and periodically during treatment, limit oxalate restriction, can increase hyperoxaluria, high calcium intake may actually be more beneficial

HYPOCALCEMIA

3 Hypocalcemia (total serum calcium less than 8.6 mg/dL [2.15 mmol/L] or ionized calcium less than 4.4 mg/dL [1.10 mmol/L]) occurs infrequently in the outpatient setting and is most common in older adults, malnourished patients, and those who have received sodium phosphate as a bowel preparation agent.

Epidemiology

Hypocalcemia occurs in 15% to 88% of adult hospitalized patients.[1] Emergent treatment of hypocalcemia is rarely warranted unless life-threatening symptoms are present (eg, frank tetany or seizures).

Pathophysiology

Hypocalcemia is the result of alterations in the effect of PTH and vitamin D on the bone, gut, and kidney (see Fig. 69-1). The primary causes of hypocalcemia are vitamin D deficiency and postoperative hypoparathyroidism. Other causes include magnesium deficiency, critical illness, medications, hypoalbuminemia, blood transfusions, peripheral blood progenitor cell harvesting, tumor lysis syndrome, and mutations in the CaSr.[37,43-47] PTH concentrations are elevated in conditions of hypocalcemia, except hypoparathyroidism and hypomagnesemia.[48]

Vitamin D Deficiency

Vitamin D and its metabolites play an important role in the maintenance of extracellular calcium concentrations and in normal skeletal structure and

mineralization. Vitamin D is necessary for the optimal absorption of calcium and phosphorus. On a worldwide basis, the most common cause of chronic hypocalcemia is nutritional vitamin D deficiency. In malnourished populations, manifestations include rickets and osteomalacia. Nutritional vitamin D deficiency is uncommon in Western societies because of the fortification of milk with ergocalciferol. The most common cause of vitamin D deficiency in Western societies is GI disease.[9] Gastric surgery, chronic pancreatitis, small-bowel disease, intestinal resection, and bypass surgery are associated with decreased concentrations of vitamin D and its metabolites.[9] Vitamin D replacement therapy might need to be administered by the IV route if poor oral bioavailability is noted. Decreased production of 1,25-dihydroxyvitamin D_3 can occur as a result of a hereditary defect leading to vitamin D-dependent rickets.[48] Polymorphisms of the vitamin D receptor have been identified, and these genetic variations can contribute to increased risk of rickets associated with vitamin D and calcium-deficient diets.[49] It also can occur secondary to CKD if there is insufficient production of the 1-α-hydroxylase enzyme for the production of the 1,25-dihydroxyvitamin D_3. Treatment of hypocalcemia associated with CKD is reviewed in Chapter 62.

Hypoparathyroidism

Hypoparathyroidism can be caused by autoimmune disease, congenital defects, or iatrogenically by inadvertent removal of some or all of the parathyroid glands during thyroidectomy or from damage with radiation therapy. Surgery is the most common cause of chronic hypoparathyroidism, but only occurs in about 3% of patients who have undergone total thyroidectomy.[48] Chronic hypoparathyroidism that persists for more than 6 months may insidiously lead to hypocalcemia and thus most patients remain asymptomatic.[48] The chronic hypocalcemia may ultimately present as visual impairment secondary to cataracts.[50]

Hungry Bone Syndrome

An acute, symptomatic rapid fall in total serum calcium concentration (to values less than 7 mg/dL [1.75 mmol/L]) is common in patients who have recently had a parathyroidectomy or thyroidectomy. Hypocalcemia in these postsurgical patients is generally transient in nature.[48] The “hungry bone syndrome” is a condition of profound hypocalcemia whereby the bone avidly incorporates calcium and phosphorus from the blood in an attempt to recalcify bone.[51] Serum calcium concentrations should be monitored every 6 hours during the 24 to 48 hours following such surgeries, and pharmacologic doses of calcium can be necessary to prevent or minimize the decrease in serum calcium.

Hypomagnesemia

Hypomagnesemia of any cause can be associated with severe symptomatic hypocalcemia that is unresponsive to calcium replacement therapy (see Chapter 70). Reduced serum magnesium concentrations can impair PTH secretion and induce resistance of target organs to the actions of PTH.[48] Normalization of serum calcium concentrations in these patients is thus dependent on appropriate replacement of magnesium.

Critical Illness

During critical illness or postoperatively, hypocalcemia is common but usually mild. It is hypothesized that cytokines impair PTH secretion, decrease production of 1,25-dihydroxyvitamin D_3, and cause PTH end-organ resistance.[48]

Medication-Induced Hypocalcemia

Medication-induced hypocalcemia has been reported due to chelation of calcium (eg, oral sodium phosphate solutions, ethylenediaminetetraacetate, foscarnet), increased enzymatic processing of vitamin D (eg, phenobarbital, phenytoin, ketoconazole), decreased PTH sensitivity (eg, calcitonin), increased sensitivity of the CaSr (eg, cinacalcet), increased excretion of calcium (eg, furosemide), blocked bone resorption (eg, denosumab, bisphosphonates, fluoride), and induction of hypomagnesemia (eg, aminoglycosides).[31,48,52,53]

Chelating agents in blood (citrate) and in radiographic contrast media (ethylenediaminetetraacetate) can cause transient hypocalcemia.[43,44,48] Concentrated citrate is often used in hemodialysis catheter locks and to anticoagulate the dialysis circuit during continuous kidney replacement therapy.[54] Symptomatic hypocalcemia has been reported in patients exposed to citrate solutions, which is related to both the concentration of the citrate solution and capacity to metabolize citrate (ie, impaired metabolism with severe liver failure and tissue hypoperfusion).[55] Injection of citrate

solutions greater than the volume of the dead space of the catheter lumen or accidental injection of citrate catheter lock solutions that are not intended for systemic administration has been associated with serious cardiovascular problems such as hypotension or cardiac arrest.[56] Oral phosphorus therapy, commonly used to treat patients with malabsorption syndromes caused by GI diseases, can also result in hypocalcemia by chelation.

The anticonvulsants phenobarbital and phenytoin cause hypocalcemia by increasing catabolism of vitamin D and thereby impairing calcium release from bone and reducing intestinal calcium absorption.[43] By decreasing PTH sensitivity, calcitonin can lead to hypocalcemia.[48] Cinacalcet increases the sensitivity of the CaSr potentially inducing hypocalcemia.[48] Loop diuretics such as furosemide can induce hypocalcemia by increasing calcium excretion.[48] Denosumab and bisphosphonates block bone resorption and can lead to hypocalcemia, especially in the presence of vitamin D deficiency, insufficient calcium intake, or PTH imbalance.[48] Medications that cause hypomagnesemia (eg, aminoglycosides, amphotericin B, cyclosporine, diuretics, foscarnet, and cisplatin) are also associated with an increased risk of hypocalcemia.[57]

Clinical Presentation: Hypocalcemia

CLINICAL PRESENTATION: Hypocalcemia

General

- Acute hypocalcemia may result in rapid decreases in serum ionized calcium. Parathyroidectomy and thyroidectomy are also associated with a rapid reduction in serum calcium. In chronic hypocalcemia, vitamin D deficiency should be considered.

Symptoms

- The symptoms of hypocalcemia include tetany, paresthesia, muscle cramps, and laryngeal spasms. Chronic hypocalcemia is usually associated with depression, anxiety, memory loss, and confusion.

Signs

- Neurologic: The hallmark of acute hypocalcemia is tetany, which is characterized by neuromuscular irritability including seizure potential. Extrapyramidal disorders, mainly parkinsonism but also dystonia, hemiballismus, choreoathetosis, and oculogyric crises occur in 5% to 10% of patients with idiopathic hypoparathyroidism. Chvostek and/or Trousseau signs can be elicited during physical examination.
- Dermatologic: The skin can be dry, puffy, and coarse. Other dermatologic manifestations can include hyperpigmentation, dermatitis, eczema, and psoriasis. Hair and skin signs including coarse, brittle, and sparse hair with patchy alopecia and brittle nails can also appear.
- Ophthalmologic: Cataract development has been reported to occur with hypocalcemia.
- Dental manifestations: These are usually associated with the presence of chronic hypocalcemia in early development. Signs include dental hypoplasia, failure of tooth eruption, defective enamel and root formation, and abraded carious teeth.
- Cardiovascular: Hypotension, decreased myocardial performance, and heart failure have been reported. A prolonged QT interval, arrhythmias, and bradycardia can also occur but are more common with acute or severe hypocalcemia.
- GI: Steatorrhea can be associated with chronic hypocalcemia.
- Musculoskeletal: Myopathy has been reported.
- Endocrine: Hypocalcemia alone can impair insulin release. In addition, idiopathic hypoparathyroidism can be associated with polyglandular autoimmune syndromes.

Laboratory Tests

- Serum calcium concentrations of less than 8.6 mg/dL (2.15 mmol/L) are considered to represent hypocalcemia if ionized calcium values are also less than 4.4 mg/dL (1.1 mmol/L).

The clinical manifestations of hypocalcemia are quite variable. The more acute the decrease in ionized calcium concentration, the more likely the patient will develop symptoms.[48] Increases in plasma pH enhance the binding of calcium to albumin and thus alkalosis can result in rapid decreases in ionized calcium. Concomitant hypomagnesemia, hypokalemia, hyponatremia, and additive adverse medications reactions also increase the likelihood of symptomatic presentation.

Hypocalcemia can manifest as neuromuscular, central nervous system (CNS), dermatologic, and cardiac sequelae.[1] Acute hypocalcemia is more likely to manifest as neuromuscular (paresthesia, muscle cramps, tetany, and laryngeal spasm), and cardiovascular symptoms, whereas chronic hypocalcemia often presents as CNS (eg, depression, anxiety, memory loss, confusion, hallucinations, tonic–clonic seizures) and dermatologic (eg, hair loss, grooved and brittle nails, eczema) symptoms.[43] The hallmark sign of acute hypocalcemia is tetany caused by enhanced peripheral neuromuscular irritability.[1] Tetany manifests as paresthesia around the mouth and in the extremities, muscle spasms and cramps, carpopedal (hands and feet) spasms, and rarely as laryngospasm and bronchospasm.[9] Chvostek and/or Trousseau signs can be elicited during physical examination.[48]

Chvostek sign is elicited by tapping the facial nerve anterior to the ear and eliciting twitching of facial muscles. The sensitivity and specificity of Chvostek sign for hypocalcemia are limited; a positive Chvostek sign is observed in 25% of healthy individuals and 29% of patients with hypocalcemia are negative.[48] Trousseau sign is elicited by inflating a blood pressure cuff above systolic blood pressure for 3 minutes and observing whether a carpal spasm is induced. With only 1% of healthy individuals with a positive Trousseau, this sign has greater specificity for hypocalcemia.[48]

The cardiovascular manifestations of hypocalcemia result in ECG changes characterized by a prolonged QT interval and symptoms of decreased myocardial contractility often associated with heart failure.[43] Both acute and chronic hypocalcemia can result in a reversible syndrome characterized by acute myocardial failure or refractory heart failure. Other cardiovascular manifestations include arrhythmias, bradycardia, and hypotension that are unresponsive to fluid and vasopressor administration.[43]

Treatment

Desired Outcome

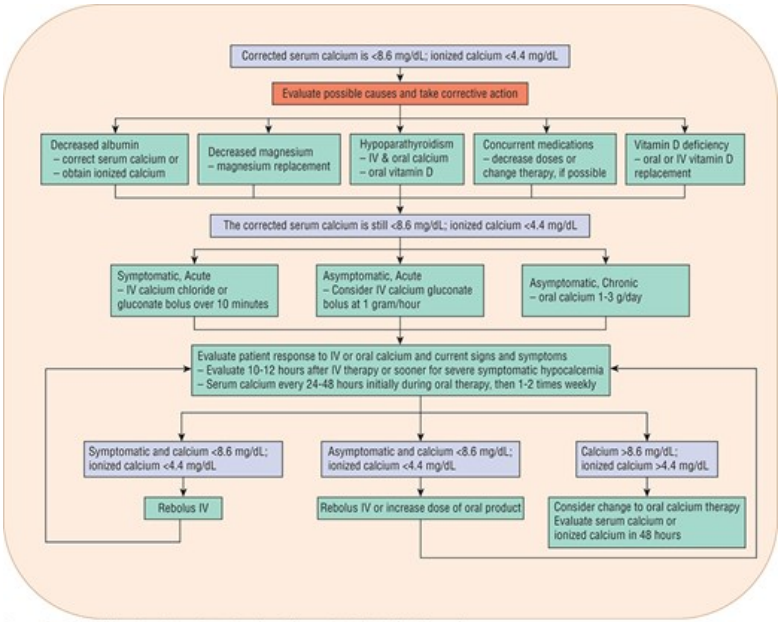
The goals of therapy for patients with normal kidney function are the resolution of signs and symptoms of hypocalcemia, restoration of normocalcemia, management of associated electrolyte abnormalities, and treatment of the underlying cause of hypocalcemia. The goals for patients with CKD are different and are discussed in Chapter 62. Asymptomatic hypocalcemia associated with hypoalbuminemia requires no treatment because ionized (biologically active) plasma calcium concentrations are normal. Treatment of hypocalcemia is dependent on identification of the pathogenesis of the underlying disorder, acuteness of onset, and presence and severity of symptoms.

Pharmacologic Therapy

Treatment of hypocalcemia is driven by acuity of onset and how significant the ionized calcium is below the normal range. The first approach to treatment is to evaluate causes that will dictate corrective action. Acute symptomatic hypocalcemia will nearly always require parenteral administration of soluble calcium salts (Fig. 69-3).

FIGURE 69-3

Hypocalcemia diagnostic and treatment algorithm. Serum calcium of 8.6 mg/dL is equivalent to 2.15 mmol/L and 4.4 mg/dL is equivalent to 1.10 mmol/L.



Acute Treatment

The initial therapeutic intervention for patients with severe, symptomatic hypocalcemia (ionized calcium <4 mg/dL [1 mmol/L]) is to administer 0.5 to 1 g of calcium chloride (1 g calcium chloride = 13.6 mEq calcium [273 mg calcium]) or up to 3 g of calcium gluconate (1 g calcium gluconate = 4.56 mEq calcium [91 mg calcium]) IV slowly over 10 minutes.[1] The treatment of asymptomatic hypocalcemia is controversial, but many practitioners will supplement calcium to avoid negative consequences of hypocalcemia and progression to clinical manifestations.[1] For mild-moderate asymptomatic hypocalcemia (ionized calcium 1-4.48 mg/dL or 1-1.12 mmol/L), 1 to 2 g IV calcium gluconate is recommended, and in the case of severe, asymptomatic hypocalcemia, up to 3 g IV calcium gluconate is indicated as in symptomatic patients.[1] For critically ill patients who are asymptomatic with a serum total calcium less than 7 mg/dL (1.75 mmol/L), 1 to 2 g IV calcium gluconate may be empirically administered with follow-up measurement of ionized calcium.[1] In non-emergent, asymptomatic cases, calcium retention and safety are optimized by infusing calcium gluconate at a rate of 1 g/hr.[1] Since calcium chloride delivers three times more elemental calcium than an equivalent amount of calcium gluconate, clinicians must carefully review dosing to ensure medication errors do not occur. Calcium gluconate is generally preferred over calcium chloride for peripheral venous administration because calcium gluconate is less irritating to veins. To prevent tissue necrosis, calcium chloride should be administered via central venous access. Calcium should not be infused at a rate greater than 60 mg elemental calcium per minute because severe cardiac dysfunction, including ventricular fibrillation, can result, thus ECG monitoring is recommended.[57] IV calcium administration should be used with caution in patients receiving digitalis glycosides because of the possibility of bradycardia or atrioventricular (AV) block.[50] In severe hypokalemia, an acute rise in serum calcium from IV calcium administration can result in cardiac arrhythmias. Bolus doses of calcium are only effective for 1 to 2 hours; therefore, repeat doses should be given hourly as needed until severe, symptomatic patients are stabilized.[1,57] Ionized calcium should be reevaluated approximately 10 to 12 hours after supplementation or sooner for severe, symptomatic hypocalcemia.[1] Calcium should not be added to bicarbonate- or phosphate-containing solutions or infused in the same IV line because of the possibility of precipitation.[57]

Chronic Treatment

Once acute hypocalcemia is corrected by parenteral administration, further treatment modalities should be individualized according to the cause of hypocalcemia. If hypomagnesemia is present, then magnesium supplementation is indicated until concentrations normalize, which will promote successful calcium supplementation regardless of route (see Chapter 70). Hypocalcemia secondary to hungry bone syndrome following parathyroidectomy has been attenuated by pretreatment with bisphosphonates, especially with longer duration use and normalization of alkaline phosphatase prior to surgery.[58] Asymptomatic and chronic hypocalcemia associated with hypoparathyroidism and vitamin D-deficient states can be managed by oral calcium and vitamin D supplementation. Therapy is initiated with 1 to 3 g/day of elemental calcium.[57] Average maintenance doses range from 2 to 8 g of elemental calcium per day in divided doses. If serum calcium does not normalize, a vitamin D supplement may need to be added. In patients with achlorhydria a solution of 10% (1-30 mL) calcium chloride orally every 8 hours can raise serum calcium.[57] Treatment of chronic hypoparathyroidism with PTH formulations such as teriparatide has been shown to better maintain serum calcium concentrations and normalize urinary calcium.[59]

Treatment of chronic asymptomatic hypocalcemia associated with vitamin D-deficient states should be individualized. The optimal 25-hydroxyvitamin D concentration is controversial, but the Endocrine Society defines vitamin D sufficiency as a concentration of at least 30 ng/mL (75 nmol/L).[60] In patients with malabsorption, vitamin D requirements vary markedly, and large doses can be required. In contrast, vitamin D deficiency associated with anticonvulsant medication can be corrected with smaller doses of vitamin D. The usual oral dose of ergocalciferol is 50,000 international units once weekly for 8 weeks followed by decreased maintenance dosing as needed to achieve the goal 25-hydroxyvitamin D concentration.[60] The treatment of vitamin D deficiency associated with CKD generally requires the administration of 1,25-dihydroxyvitamin D_3 or another synthetic vitamin D_2 analog such as paricalcitol or doxercalciferol (see Chapter 61). Patients who have reduced 25-hydroxylase activity (eg, hepatic disease) can also require treatment with calcitriol (1,25-dihydroxyvitamin D_3). Oral doses of 1,25-dihydroxyvitamin D_3 usually range from 0.5 to 2 µg daily. Vitamin D_3 (cholecalciferol) may be more efficacious at raising serum 25-hydroxyvitamin D concentrations compared with plant source vitamin D_2 (ergocalciferol). However, higher loading and maintenance doses of cholecalciferol may be required to maintain serum 25-hydroxyvitamin D concentrations. In selected cases, increasing calcium ingestion can be required if vitamin D replacement alone is ineffective in returning serum calcium concentrations to normal.

Adverse Medication Reactions

Adverse medication reactions of oral calcium and vitamin D supplementation include hypercalcemia and hypercalciuria, especially in patients with hypoparathyroidism, in whom the renal calcium-sparing effect of PTH is absent. Hypercalciuria can increase the risk of calcium stone formation and nephrolithiasis in susceptible patients. One maneuver to help prevent calcium stones is to maintain the urine calcium excretion below 300 mg/day. Intermittently monitoring of 24-hour urine collections for total calcium excretion can help minimize the occurrence of hypercalciuria. The addition of thiazide diuretics for patients at risk for stone formation can increase tubular calcium reabsorption and reduction of vitamin D requirements (see Table 69-3).[57]

DISORDERS OF PHOSPHORUS HOMEOSTASIS

Inorganic phosphorus in the form of phosphate is an essential element in phospholipid cell membranes, nucleic acids, and phosphoproteins, which are required for mitochondrial function.[61] Phosphorus regulates the intermediary metabolism of carbohydrates, fats, and proteins. Phosphorus also regulates enzymatic reactions including glycolysis, ammoniagenesis, and the 1-hydroxylation of 25-hydroxyvitamin D_3.[61] In addition, phosphorus is required for the generation of 2,3-diphosphoglycerate (2,3-DPG) in red blood cells, which is required for normal oxygen–hemoglobin dissociation and delivery of oxygen to the tissues.[61] Phosphorus is the source of the high-energy bonds of adenosine triphosphate (ATP), thus fueling a wide variety of physiologic processes, including muscle contractility, electrolyte transport, neurologic function, and other important biochemical reactions.[61] Considering its diverse biologic importance, it is not difficult to appreciate the clinical implications of disorders of phosphorus homeostasis.

Phosphate, the major intracellular anion, is present in living organisms mainly as organic phosphate esters such as 2,3-DPG, adenosine, guanosine triphosphate, and fructose 1,6-diphosphate.[61] Only a small fraction of intracellular phosphorus exists as inorganic phosphate; however, this fraction is critical because it is the source from which ATP is resynthesized.[61] The majority of inorganic phosphate is located in the extracellular space where it is the prime determinant of intracellular phosphate; thus, small increments in the organic phosphate concentrations can profoundly alter both the extracellular and intracellular phosphate concentrations. Metabolic disturbances (acidosis, alkalosis, and ketoacidosis), hydrogen ion shifts, and hormones (PTH, calcitonin, cortisol, and vitamin D) all can cause transcellular shifts in phosphorus concentrations. Because of these phenomena, the serum phosphorus concentration does not accurately reflect total body stores.[62]

The typical Western diet provides a daily intake of 800 to 1,600 mg of phosphorus. Approximately 60% to 80% of this is absorbed in the GI tract by passive and active transport (vitamin D-mediated). Phosphorus absorption is increased directly by 1,25-dihydroxyvitamin D_3 and low phosphate diets and indirectly by PTH. Decreased absorption occurs under conditions of increased dietary intake of phosphorus and magnesium, glucocorticoid therapy, and hypothyroidism. The normal serum phosphorus concentration in adults is 2.7 to 4.5 mg/dL (0.87-1.45 mmol/L) and for children younger than 12 years it is 4 to 5.6 mg/dL (1.29-1.81 mmol/L). Influx via the GI tract and bone and tubular reabsorption by the kidney are the most important regulators of steady-state serum phosphorus concentrations. Renal excretion of phosphorus is a two-step process: glomerular filtration and proximal tubular reabsorption by passive transport coupled to sodium. Under normal conditions, 85% to 90% of filtered phosphate is reabsorbed, the majority in the early proximal tubule. Renal tubular reabsorption of phosphate is directly inhibited by PTH.[62] Fibroblast growth factor 23 (FGF23) also is a key regulator of phosphate homeostasis.[63] FGF23 acts principally to decrease tubular reabsorption of phosphate and inhibit 1-α-hydroxylase, thereby reducing the concentration of active vitamin D. FGF23-mediated receptor activation requires klotho, a transmembrane protein. The tissue specificity for FGF23 effects is defined by klotho–FGF23 coexpression. Conversely, phosphate reabsorption in the renal tubule is increased by growth hormone, insulin, and insulin-like growth factor 1.[61] Internal phosphorus balance (ie, transcellular phosphate distribution) is also of importance in the maintenance of normal serum phosphate. The serum phosphate concentration can vary by as much as 2 mg/dL (0.65 mmol/L) throughout the day, primarily as the result of changes in carbohydrate intake, insulin secretion, and diurnal variation.[61]

HYPERPHOSPHATEMIA

Hyperphosphatemia typically results from either CKD, AKI, or endogenous intracellular phosphate release. Hyperphosphatemia occurs frequently in patients with AKI and is a nearly universal finding in those with advanced CKD (eg, stages 4 and 5). Tumor lysis syndrome, a complication of chemotherapy associated with massive lysis of cells and release of intracellular contents, is also associated with hyperphosphatemia. The incidence of tumor lysis syndrome is highest among patients treated for acute lymphoblastic leukemia, acute myeloid leukemia, and Burkitt's lymphoma (see

Chapter 155).[46] Other causes of hyperphosphatemia include hemolysis and rhabdomyolysis.

Pathophysiology

5 The most common cause of hyperphosphatemia is a reduction in renal tubular excretion of phosphate despite elevations in PTH and FGF23 when GFR is markedly impaired (eg, GFR less than 25 mL/min/1.73 m^2 [0.24 mL/s/m^2]).[62,64] Retention of phosphate decreases vitamin D synthesis and induces hypocalcemia, which leads to an increase in PTH, a finding that can be seen in those with stage 2 to 5 CKD. This physiologic response inhibits further tubular reabsorption of phosphorus as the kidney attempts to correct hyperphosphatemia and normalize serum calcium concentrations. Patients with excessive exogenous phosphate administration or who experience massive tissue breakdown or cell lysis in the setting of AKI can rapidly develop moderate-to-severe hyperphosphatemia (serum phosphate more than 6.5 mg/dL [2.10 mmol/L]).[62] Severe hyperphosphatemia (serum phosphate more than 7 mg/dL [2.26 mmol/L]) is commonly encountered in patients with CKD, especially those with GFRs less than 15 mL/min/1.73 m^2 (0.14 mL/s/m^2) (see Chapter 61).

Hyperphosphatemia caused by an increase in renal tubular reabsorption associated with hypoparathyroidism and associated decreases in PTH, is usually less severe than that observed in patients with advanced kidney disease or excessive exogenous or endogenous introduction of phosphate into the ECF. Acromegaly (mediated by growth hormone) and thyrotoxicosis (mediated by catecholamines) can also cause hyperphosphatemia by increasing tubular phosphate reabsorption.

Exogenous Phosphate Loads

Iatrogenic causes of hyperphosphatemia have been widely reported, and clinicians should be aware of the phosphorus content of IV, oral, and rectally administered products.[65] Although less-well recognized, oral and rectal administration of phosphate-containing solutions such as sodium phosphate (Fleet® Phospho-Soda) can also result in severe and life-threatening hyperphosphatemia, especially in patients with moderate-to-severe CKD.[53,65] The risk of mortality is dependent on the amount of phosphorus absorbed from the administered product; however, fatalities have occurred at low phosphate concentrations.[65] Acute phosphate nephropathy and kidney failure have also been reported with the use of oral sodium phosphate bowel preparations. The FDA issued a safety warning regarding the use of these products in patients at risk (ie, older adults, patients with CKD) or on medications known to affect kidney hemodynamics (eg, diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], or renin–angiotensin–aldosterone system inhibitors).[66] Acute phosphorus poisoning as a result of ingestion of laundry detergents is a rare and often unrecognized cause of elevated phosphate concentrations.

Rapid Tissue Catabolism

Any disorder that results in necrosis of skeletal muscle (ie, rhabdomyolysis) can generate the release of large amounts of intracellular phosphate into the systemic circulation. This condition is frequently associated with AKI (see Chapter 61) and thus severe hyperphosphatemia can develop because of increased endogenous phosphate release coupled with the impaired renal excretion because phosphaturic hormones (eg, PTH, FGF23) become ineffective. Bowel infarction, malignant hyperthermia, and severe hemolysis are also conditions that can increase endogenous release of phosphate.

Moderate hyperphosphatemia is also commonly observed in patients undergoing treatment for acute leukemia and lymphomas.[46] Chemotherapeutic treatment of acute lymphoblastic leukemia can result in the release of large amounts of phosphate into the systemic circulation secondary to lysis of lymphoblasts. Initiation of chemotherapy for Burkitt lymphoma results in tumor lysis syndrome, a rapid lysis of malignant cells that results in hyperphosphatemia, hyperuricemia, hyperkalemia, and hypocalcemia.[46]

Acid–Base Disorders

Lactic acidosis and diabetic ketoacidosis (DKA) can trigger the transcellular shift of endogenous intracellular phosphate into the extracellular space and thereby dramatically increases serum phosphorus concentrations.[67] After the institution of treatment, serum phosphate concentrations should be checked hourly as they can decrease rapidly, and patients can ultimately develop hypophosphatemia.

Clinical Presentation: Hyperphosphatemia

CLINICAL PRESENTATION: Hyperphosphatemia

General

- Serum phosphate concentration is primarily determined by the ability of the kidneys to reabsorb phosphate; therefore, hyperphosphatemia is uncommon in patients with normal kidney function.

Symptoms

- Acute symptoms include GI disturbances, lethargy, obstruction of the urinary tract, and rarely seizures. Symptoms associated with chronic hyperphosphatemia include "red eye" and pruritus.

Signs

- The elevated calcium-phosphate product results in precipitation in arteries, joints, soft tissues, and the viscera. This can result in tissue necrosis, termed calciphylaxis or calcemic uremic arteriopathy.

Laboratory Tests

- Serum phosphate concentrations more than 4.5 mg/dL (1.45 mmol/L) represent hyperphosphatemia.

The severe acute onset of hyperphosphatemia can result in calcium and phosphate complexation and lead to the precipitation of calcium phosphate crystals in soft tissues, and within the kidney that can result in nephrolithiasis or obstructive uropathy. Extravascular calcification can result in band keratopathy, "red eye," pruritus, and periarticular calcification, especially in patients with CKD. In addition, soft-tissue calcifications in the conjunctiva, skin, heart, cornea, lung, gastric mucosa, and kidney have been observed, primarily in patients with CKD and chronic disordered mineral metabolism.[62] Extracellular phosphate can form insoluble nanoparticles with both calcium and fetuin-A which are referred to as calciprotein particles.[61] Calcium-phosphate crystals are likely to form in vivo when the product of the serum calcium and phosphate concentrations exceeds 50 to 60 mg^2/dL^2 (4-4.8 $mmol^2/L^2$). Serum phosphate concentrations greater than 6.5 mg/dL (2.10 mmol/L) have been independently associated with increased morbidity and mortality in patients on maintenance hemodialysis.[68] Other symptoms associated with moderate-to-severe hyperphosphatemia include nausea, vomiting, diarrhea, lethargy, and seizures. The major effects of long-term hyperphosphatemia are related to the development of hypocalcemia (caused by phosphate inhibition of renal 1-α-hydroxylase) and its related consequences, as well as vascular and organ damage resulting from the deposition of calcium-phosphate crystals. Hyperphosphatemia associated with CKD can result in renal osteodystrophy because of overproduction of PTH. This condition is discussed in detail in Chapter 62.

Treatment

Desired Outcome

Management of patients with acutely elevated serum phosphorus concentrations should be directed at avoiding GI and neurologic symptoms and preventing deposition in the urinary tract to avoid the development of AKI. The treatment of hyperphosphatemia is focused on returning serum phosphorus concentrations to the normal or near normal (for patients with CKD) range, with the goal to minimize the long-term cardiovascular consequences of calcium-phosphate deposition in the vasculature. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines suggest that for patients with CKD stages 3 to 5, serum phosphorus should be maintained in the normal range. In hemodialysis-dependent patients with stage 5 CKD, KDIGO suggests lowering elevated phosphorus concentrations toward the normal range (see Chapter 62).[69]

Pharmacologic Therapy

Severe symptomatic hyperphosphatemia manifesting as hypocalcemia and tetany may be treated by the IV administration of calcium. Although this can seem counterintuitive and many consider it controversial, for a patient with phosphate of 16 mg/dL (5.17 mmol/L) and calcium of 7 mg/dL (1.75 mmol/L), for example (the calcium–phosphorus product is 112 mg^2/dL^2 [9 $mmol^2/L^2$]), correction of severe hypocalcemia is of primary importance

because of the critical nature of this disorder. If serum calcium concentrations are not critically low, the initial management strategy should include limitation of all exogenous sources of phosphate and efforts to block further absorption should be initiated. Hemodialysis can be initiated if the patient remains symptomatic despite these interventions.[57]

6 In general, the most effective way to treat nonemergent hyperphosphatemia is to decrease phosphate absorption from the GI tract by implementing phosphate-binding therapy and altering the dietary content of phosphate.[62] Phosphate binding agents containing divalent and trivalent cations (calcium, lanthanum, magnesium, iron, and aluminum), or sevelamer are the agents most frequently used in the prevention and treatment of hyperphosphatemia (see Chapter 62).[70] Long-term treatment with aluminum hydroxide and aluminum carbonate should be avoided because the use of these agents has been associated with anemia, CNS disorders, and bone disease.[70] Calcium and magnesium agents are available in oral suspension formulations, which can aid administration in acutely ill patients who are receiving enteral nutrition. The most frequent adverse medication reaction from phosphate-binding agents (especially calcium) is constipation. Typically, calcium salts are the preferred initial phosphate-binding agents except when there is concomitant hypercalcemia or evidence of vascular calcification. For long-term therapy with phosphate binders, it is recommended to avoid hypercalcemia and to limit use of calcium-based phosphate binders, and this may require additional non-calcium agents such as sevelamer.[69] Calcium-based phosphate binders may increase vascular calcification, but there is no difference in cardiovascular events for hyperphosphatemia treated with lanthanum carbonate versus calcium carbonate in patients undergoing hemodialysis.[71] The iron-based binders offer the potential advantage of enhancing iron absorption (ferric citrate coordination complex) or reduced pill burden (sucroferric oxyhydroxide).[72] Other mechanistic approaches are being evaluated to manage hyperphosphatemia. Tenapanor is an investigational drug that blocks paracellular absorption of phosphate in the GI tract and may eventually be FDA-approved for hyperphosphatemia treatment in adult patients with CKD undergoing hemodialysis.[73]

HYPOPHOSPHATEMIA

Mild-to-moderate hypophosphatemia is usually asymptomatic and associated with serum phosphate concentrations of 1.5 to 2.7 mg/dL (0.48-0.87 mmol/L), whereas severe hypophosphatemia that is frequently symptomatic is correlated with serum phosphorus concentrations of less than 1.5 mg/dL (0.48 mmol/L).[1]

Incidence

Hypophosphatemia has been observed in approximately 1% to 3% of the laboratory screening panels of patients who have been admitted to a hospital.[74] The incidence in hospitalized critically ill patients is 18% to 28%.[74] Unlike its severe form, mild or moderate hypophosphatemia seldom causes recognizable signs and symptoms.[1]

Pathophysiology

7 Hypophosphatemia can be the result of decreased GI absorption, reduced tubular reabsorption, or extracellular to intracellular redistribution.[61] Although mild-to-moderate hypophosphatemia is common and can occur in inpatients and outpatients, severe hypophosphatemia is predominantly encountered in the acute care setting and can be associated with life-threatening symptoms, including seizures, coma, and rhabdomyolysis (Table 69-4).

TABLE 69-4

Conditions Associated with the Development of Hypophosphatemia

Decreased GI absorption
Phosphate-binding drugs
• Sucralfate

• Calcium carbonate
• Aluminum/magnesium antacids
• Sevelamer
• Lanthanum carbonate
• Ferric citrate
• Sucroferric oxyhydroxide
Decreased dietary phosphorus intake
Glucocorticoids
Vitamin D deficiency/resistance
Hyperparathyroidism
Chronic diarrhea
Steatorrhea
Reduced tubular reabsorption
Hyperparathyroidism (primary and secondary)
Elevated FGF23
Recovery from burns
Rickets
Malignant neoplasms
Fanconi syndrome
Acute volume expansion
Metabolic acidosis
Renal transplantation
Vitamin D deficiency and/or resistance
Diuretics

• Loop diuretics
• Thiazide diuretics
• Osmotic agents
• Carbonic anhydrase inhibitors (acetazolamide)
Glucocorticoids
Sodium bicarbonate
Internal redistribution
Refeeding syndrome
Nutrition support
Parathyroidectomy (hungry bone syndrome)
Alcohol use disorder
Respiratory alkalosis
Diabetic ketoacidosis (correction)
Dextrose solutions
Insulin
Catecholamines
Anabolic steroids
Glucagon
Calcitonin
Erythropoietin

Decreased GI Absorption

Phosphate-binding substances such as sucralfate, calcium carbonate, sevelamer, lanthanum carbonate, sucroferric oxyhydroxide, ferric citrate coordination complex, and aluminum- or magnesium-containing antacids have the potential to bind large amounts of phosphorus in the gut, thereby preventing absorption. If phosphate-binding agents are ingested on a chronic basis in conjunction with a dietary phosphorus deficiency, hypophosphatemia can result.[1] Patients who are receiving long-term phosphate-binding agents, those with peptic ulcer disease or CKD, and those who may be predisposed to moderate hypophosphatemia (eg, alcohol use disorder) are at highest risk for the development of severe hypophosphatemia. Hyperparathyroidism can cause hypophosphatemia as a result of decreased GI absorption of dietary phosphorus.

Decreased Tubular Reabsorption

Reduced tubular reabsorption of phosphate can occur in patients with hyperparathyroidism (primary and secondary) with normal kidney function and those with vitamin D deficiency or elevated FGF23 concentrations. Elevated PTH concentrations lead to an increase in serum calcium concentrations and decreased serum phosphate concentrations. Serum phosphorus is decreased as the result of a reduction in renal tubular reabsorption.[67] Recovery from extensive third-degree burns is associated with development of an anabolic state as stress levels decrease and nutritional therapies take effect as well as a marked diuretic phase associated with an impressive renal loss of phosphate.[75] Because phosphate is rapidly incorporated into the new cells, this can contribute to the severity of the hypophosphatemia. Medications that cause increased renal elimination of phosphate include diuretics (eg, loop diuretics, thiazide diuretics, osmotic diuretics), carbonic anhydrase inhibitors (eg, acetazolamide), glucocorticoids, and sodium bicarbonate.[1] The IV iron formulation ferric carboxymaltose has been associated with the development of hypophosphatemia in 51% of patients treated, and 13% of cases were severe (serum phosphorus less than 1 mg/dL [0.32 mmol/L]) and prolonged.[76] The mechanism is unclear, however, iron deficiency itself is associated with elevated FGF23.[77]

Internal Redistribution

Rapid refeeding of malnourished patients with high-carbohydrate, high-calorie diets with inadequate amounts of supplemental phosphate can result in severe symptomatic hypophosphatemia. This phenomenon is especially prevalent in patients with other underlying risk factors for the development of hypophosphatemia, such as alcohol use disorder.[75] The etiology of severe hypophosphatemia associated with nutrition support can be separated into two phases: acute, rapid hypophosphatemia secondary to intracellular shifts of phosphate resulting from glucose-induced insulin secretion; and the gradual decrease in serum phosphate concentration over 5 to 10 days secondary to tissue repair in the presence of phosphate deprivation.[78] The development of severe hypophosphatemia secondary to nutrition support can be prevented by appropriate phosphate supplementation. Adult patients with normal kidney function receiving parenteral nutrition require approximately 10-15 mmol of phosphorus per 1,000 kcal (2.4-3.6 mmol per 1,000 kJ) (see Chapter 165).[1] The Recommended Dietary Allowance of phosphorus for healthy adults is provided in one liter of most enteral nutrition formulations (see Chapter 166).[1] In severely malnourished patients, the phosphorus requirements are higher with the initiation of nutrition support.[1] Phosphorus requirements are also typically increased in patients with critical illness, thermal injury, traumatic brain injury, and liver resection.[1] Transcellular shifts in phosphate also occur after parathyroidectomy, causing severe hypocalcemia and hypophosphatemia because of hungry bone syndrome (deposition of phosphate and calcium in the bone).

Severe and prolonged respiratory alkalosis (a result of hyperventilation, pain, anxiety, and sepsis) can cause hypophosphatemia.[74] Respiratory alkalosis is thought to contribute significantly to the hypophosphatemia observed during alcohol withdrawal syndrome.[62] Although patients with DKA may present with hyperphosphatemia, the initiation of therapy to correct it can cause serum phosphate concentrations to decrease rapidly as phosphate shifts back into the intracellular compartment. In addition, the acidosis associated with the DKA state can cause a decomposition of organic compounds inside the cell and a release of inorganic phosphate into the plasma and subsequently into the urine.[79] The combination of intracellular phosphate breakdown and the shift of phosphate into cells on initiation of treatment can lead to severe hypophosphatemia. Medications associated with transcellular shifts in phosphate include dextrose solutions, glucagon, insulin, catecholamines, calcitonin, erythropoietic agents, and anabolic steroids.

Patients with alcohol use disorder are prone to a variety of serum electrolyte disorders including hypocalcemia, hypomagnesemia, hypokalemia, and hypophosphatemia. The etiology of hypophosphatemia in patients with alcohol use disorder is multifactorial. Malnutrition, poor dietary intake, diarrhea, vomiting, and the use of phosphate-binding antacids can all contribute to hypophosphatemia related to alcohol use disorder.[80] In addition, serum phosphate concentrations may decrease after hospitalization in patients with alcohol use disorder with the institution of dextrose-containing IV fluids as a result of an intracellular shift of phosphate.[78,80] Hyperventilation associated with the alcohol withdrawal syndrome can also contribute to the development of hypophosphatemia.[78] Patients with alcohol use disorder are particularly susceptible to the complications of hypophosphatemia such as rhabdomyolysis, which is often seen during withdrawal or refeeding.[78] Thus, serum phosphate concentrations should be routinely monitored in this patient population.

Clinical Presentation: Hypophosphatemia

CLINICAL PRESENTATION: Hypophosphatemia

General

- Major conditions associated with symptomatic hypophosphatemia are chronic alcohol use disorder, nutrition support without adequate phosphate supplementation, and the chronic ingestion of antacids. Severe hypophosphatemia can also be seen during treatment of DKA and with prolonged hyperventilation.

Symptoms

- Except for the effects on mineral metabolism, the symptoms of hypophosphatemia are caused by two consequences (reduction of red cell 2,3-DPG and reduction of intracellular ATP concentrations), and can impact virtually all organ systems. The symptoms are predominantly neurological and can include irritability, apprehension, weakness, numbness, paresthesia, and confusion. Severe acute development of hypophosphatemia can result in seizures or coma.

Signs

- The initial response of bone to hypophosphatemia contributes to hypercalcemia and hypercalciuria. Prolonged hypophosphatemia can also result in rickets and osteomalacia.
- Neurologic: Severe hypophosphatemia can lead to a metabolic encephalopathy.
- Cardiopulmonary: Impaired myocardial contractility, respiratory failure secondary to ATP depletion, heart failure, new onset or worsening of an existing condition.
- Musculoskeletal: Proximal myopathy, dysphagia, and ileus have been reported. Acute hypophosphatemia superimposed on preexisting severe phosphate depletion can lead to rhabdomyolysis.
- Hematologic: Alterations in the hematopoietic system can also occur, resulting in hemolysis, reduction in phagocytotic and granulocyte chemotactic ability, as well as defective clot retraction and thrombocytopenia.

Laboratory Tests

- Serum phosphate concentrations less than 2.7 mg/dL (0.87 mmol/L) are indicative of hypophosphatemia; however, symptomatic hypophosphatemia typically is not evident until serum phosphate less than 1.5 mg/dL (0.48 mmol/L).

The clinical manifestations of severe hypophosphatemia are diverse and many organ systems can be affected. It is likely that two primary biochemical abnormalities are responsible for most of the clinical manifestations of severe hypophosphatemia.[74] First, intracellular energy stores may be decreased secondary to depletion of intracellular ATP. This can result in disruptions in cellular function. Second, reduced red blood cell 2,3-DPG concentrations are associated with a shift to the left of the oxyhemoglobin saturation curve. This shift is associated with a decrease in the release of oxygen to peripheral tissues (secondary to increased oxygen affinity for hemoglobin) and may result in tissue hypoxia.[74] These metabolic disorders can be seen in a wide variety of organ systems.

Neurologic manifestations of severe hypophosphatemia can result in a metabolic encephalopathy syndrome characterized by irritability, apprehension, weakness, numbness, paresthesia, dysarthria, confusion, obtundation, seizures, and coma has been described in patients with severe hypophosphatemia.[75,78] Neuropsychiatric disturbances include apathy, delirium, hallucinations, and paranoia. Peripheral neuropathy and symptoms resembling Guillain–Barré syndrome have also been reported.[78]

Severe hypophosphatemia can result in significant dysfunction of skeletal muscle ranging from myalgia, bone pain, and weakness, with chronic hypophosphatemia, to potentially fatal rhabdomyolysis with severe acute hypophosphatemia.[75] Laboratory evaluations can help distinguish between chronic and acute on chronic hypophosphatemia. Elevated alkaline phosphatase, normal creatine phosphokinase, and normal to low phosphate and

calcium are present in cases of chronic hypophosphatemia. In contrast, hyperkalemia, hyperuricemia, elevated blood urea nitrogen and creatinine, hypercalcemia, and myoglobinuria are often present in cases in which rhabdomyolysis complicates the acute or chronic hypophosphatemia.[68] Hypophosphatemia can result in acute respiratory failure secondary to respiratory muscle weakness and diaphragmatic contractile dysfunction. Thus, frequent assessment of serum phosphate concentration is indicated in patients at risk for respiratory failure.[74] Likewise, adequate treatment of hypophosphatemia in respiratory failure can aid in successful weaning from the ventilator.[74] Dysphagia and ileus have also been attributed to hypophosphatemia.[74]

Myocardial dysfunction may be impaired in the setting of hypophosphatemia and can result in congestive cardiomyopathy. This has been observed in patients with alcohol use disorder, and postoperative and critically ill patients. Depletion of cardiac ATP stores may be the cause of this syndrome.[81] Arrhythmias have also been reported in patients with hypophosphatemia. Because hypophosphatemia is a potentially reversible cause of heart failure, it should be considered in patients who experience an acute deterioration in ventricular function.

Hematologic manifestations of hypophosphatemia include decreased concentrations of 2,3-DPG, decreased red blood cell ATP, and membrane rigidity.[81] When red blood cell ATP decreases, cells become spherocytic and rigid, and are trapped and destroyed in the spleen.[81] Therefore, hemolysis can be a manifestation of severe hypophosphatemia. Reduction in ATP content of white blood cells can result in mobility, chemotaxis, phagocytosis, and bactericidal dysfunction.[78,81] These changes can contribute to an increased risk of infection in patients with hypophosphatemia.

Finally, prolonged hypophosphatemia may result in osteopenia and osteomalacia because of enhanced osteoclastic resorption of bone and limited crystallization constituents (phosphate), respectively.[80]

Treatment

Desired Outcomes

The goals of therapy are the reversal of signs and symptoms of hypophosphatemia, normalization of serum phosphate concentrations, and management of underlying conditions. Awareness of the clinical situations in which hypophosphatemia is anticipated (eg, alcohol use disorder, DKA, initiation of nutrition support in severely malnourished) is of vital importance in preventing and managing hypophosphatemia.

Pharmacologic Therapy

Pharmacologic treatment for hypophosphatemia will typically involve phosphorus salt supplementation. The acuity and other electrolyte conditions dictate the salt, formulation, and route of administration (Table 69-5).

TABLE 69-5

Oral Phosphorus Replacement Therapy with Phosphate, Potassium, and Sodium Content Per Packet or Tablet

Product	Phosphate Content	Potassium Content	Sodium Content
Packet			
Phos-NaK®	250 mg (8 mmol)	280 mg (7.1 mEq)	160 mg (6.9 mEq)
Tablet			
Av-Phos 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
K-Phos Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
K-Phos No. 2®	250 mg (8 mmol)	88 mg (2.3 mEq)	134 mg (5.8 mEq)
Phospha 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
Phospho-Trin 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)
Virt-Phos 250 Neutral®	250 mg (8 mmol)	45 mg (1.1 mEq)	298 mg (13 mEq)

Phosphorus 31 mg = 1 mmol; potassium 39 mg = 1 mEq = 1 mmol; sodium 23 mg = 1 mEq = 1 mmol.

Mild-to-Moderate Hypophosphatemia

Mild-to-moderate (1.5-2.7 mg/dL [0.48-0.87 mmol/L]) or asymptomatic hypophosphatemia can generally be treated by the administration of oral phosphate salts. Fixed-dose and weight-based phosphate supplementation may be used.[1] Oral phosphate salts in divided doses of 1 to 2 g (32-64 mmol) daily can be provided for mild-to-moderate hypophosphatemia (see Table 69-5). Phosphate concentrations should be monitored daily, with the goal of correcting the reduced phosphate concentration in approximately 7 to 10 days. The primary dose-limiting adverse medication reaction associated with oral phosphate replacement is the development of osmotic diarrhea. For patients who are unable to receive oral supplements, IV phosphorus supplementation may be required. A graduated dosing scheme for IV treatment of hypophosphatemia may be used in patients with normal kidney function.[1] For mild hypophosphatemia (2.3-2.7 mg/dL [0.74-0.87 mmol/L]), an IV phosphate dose of 0.08-0.16 mmol/kg is recommended.[1] In moderate hypophosphatemia (1.5-2.2 mg/dL [0.48-0.71 mmol/L]), an IV phosphate dose of 0.16-0.32 mmol/kg is recommended.[1] Patients with mild-to-moderate hypophosphatemia and impaired kidney function should receive reduced doses, typically ≤50% of the initial empiric dose, with careful monitoring of serum phosphate concentration because they are predisposed to phosphate retention.[1] In the setting of obesity (weight >130% IBW or BMI ≥30 kg/m^2), an adjusted body weight may be used to calculate phosphorus requirements to avoid overdosing. The maximum rate of IV phosphorus infusion is 7.5 mmol/hr.[1] Potassium and sodium are the available salts for IV phosphorus administration. For patients with concomitant hypokalemia, potassium phosphate can be used (1 mmol potassium phosphate = 1.47 mEq K).[1] Patients with hypophosphatemia and normal or elevated serum potassium concentrations should be treated with sodium phosphate (1 mmol sodium phosphate = 1.33 mEq Na).[1] In addition to phosphate supplementation for hypophosphatemia, dipyridamole can decrease renal phosphate leaking and increase serum phosphate. Doses of 75 mg four times daily have resulted in increases in serum 1,25-dihydroxyvitamin D_3 and decreases in serum calcium and urolithiasis events.[82]

Severe Hypophosphatemia

Patients with severe (less than 1.5 mg/dL [0.5 mmol/L]) or symptomatic hypophosphatemia should be treated with parenteral phosphate

replacement. Thus, dosage and infusion recommendations, as well as response to parenteral phosphate replacement, are highly variable.[83] For severe symptomatic hypophosphatemia (<1.5 mg/dL [0.48 mmol/L]), an IV phosphate dose of 0.32 to 0.64 mmol/kg is recommended for patients with normal kidney function.[1] In critically ill trauma patients, doses up to 1 mmol/kg have been used.[84] IV phosphate therapy produces the desired increase in serum phosphate at 24 hours in 20% to 80% of patients. Response is dependent on the degree of phosphate depletion and replacement dose administered.[80] The initial success is often followed in 48 to 72 hours by recurrent hypophosphatemia, necessitating close monitoring of serum phosphate and repeat administration of phosphate products as warranted.

Adverse Medication Reactions of Parenteral Phosphate

Parenteral phosphate supplementation is associated with risks of hyperphosphatemia, metastatic soft tissue deposition of calcium-phosphate product, hypomagnesemia, hypocalcemia, hyperkalemia or hypernatremia (dependent on which IV phosphate formulation is administered), and thrombophlebitis from potassium phosphate. Inappropriate administration of large doses of parenteral phosphate over relatively short time periods has resulted in symptomatic hypocalcemia and soft-tissue calcification.[61] The rate of infusion and choice of initial dosage should therefore be based on severity of hypophosphatemia, presence of symptoms, and coexistent medical conditions. Patients should be closely monitored with frequent serum phosphate determinations for 48 to 72 hours after starting IV therapy. Opinions are mixed regarding the optimal time to reevaluate serum phosphorus after supplementation. Monitoring serum phosphorus 12 to 24 hours after supplementation or daily may be sufficient.[1] However, for patients with severe hypophosphatemia, more frequent monitoring may be warranted.[1] It can be necessary to continue administration of IV phosphate for several days in some patients, although other patients may be able to tolerate an oral maintenance regimen. Monitoring should also include assessment of serum potassium, calcium, and magnesium concentrations. Hypomagnesemia secondary to intracellular shifts occurs frequently (27%-80%) in patients with severe hypophosphatemia.[70] Therapy with parenteral phosphate should be undertaken with great caution and at reduced dosage for patients with hypercalcemia or impaired kidney function.[78]

CONCLUSION

Initial treatment strategy should be based on acuity of onset and severity of symptoms. Because the etiologies of calcium and phosphate disorders are diverse, it is important to integrate the known or anticipated consequences of concomitant diseases into the treatment strategy. The patient's medication history should be comprehensively assessed to determine whether the electrolyte abnormality may be medication induced. After resolution or treatment of the acute calcium or phosphate disorder, the medication regimen should be evaluated periodically. This proactive interventional approach will facilitate the management of mild disorders in the community and can reduce the need for hospitalization.

ABBREVIATIONS

2,3-DPG	2,3-diphosphoglycerate
AKI	acute kidney injury
ATP	adenosine triphosphate
AV	atrioventricular
CaSr	calcium-sensing receptor
CNS	central nervous system
CKD	chronic kidney disease
CrCl	creatinine clearance
DKA	diabetic ketoacidosis
ECF	extracellular fluid
ECG	electrocardiogram
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GFR	glomerular filtration rate
GI	gastrointestinal
IV	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
NSAID	nonsteroidal anti-inflammatory drug
PTH	parathyroid hormone
PTHrP	PTH-related protein
PTHR1	PTH receptor (type I)

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SELF-ASSESSMENT QUESTIONS

1. A malignancy associated with hypercalcemia from PTH-related protein is:

   A. Breast

   B. Prostate

   C. Leukemia

   D. Cervical

2. An adult female was found at home obtunded. Upon arriving to the hospital, she was diagnosed with rhabdomyolysis and acute kidney injury. Laboratory data include serum calcium 8.3 mg/dL (2.08 mmol/L), serum albumin of 1.2 g/dL (12 g/L), and serum phosphorus 2.3 mg/dL (0.74 mmol/L). Which of the following electrolyte disorders is *most likely* from this patient's rhabdomyolysis-induced acute kidney injury?

   A. Hypocalcemia

   B. Hypercalcemia

C. Hyperphosphatemia

D. Hypophosphatemia

3. CP, an adult female with stage 4 renal cell carcinoma, presents to the emergency department with profound weakness, abdominal pain with nausea and vomiting, and dehydration. Laboratory data include: sodium 135 mEq/L (mmol/L), potassium 4.5 mEq/L (mmol/L), chloride 101 mEq/L (mmol/L), bicarbonate 24 mEq/L (mmol/L), serum creatinine 1.2 mg/dL (106 µmol/L), BUN 40 mg/dL (14.3 mmol/L), and serum calcium 14.2 mg/dL (3.55 mmol/L). What is the *most likely* cause of CP's hypercalcemia?

A. Primary hyperparathyroidism

B. Secondary hyperparathyroidism associated with kidney disease

C. Bone metastases

D. Excessive endogenous Vitamin D production

4. Which of the following is the *most appropriate initial* therapy for CP?

A. Hemodialysis with a low calcium bath

B. High-dose IV loop diuretic

C. Saline hydration

D. Intravenous bisphosphonate

5. An adult female with asymptomatic hypercalcemia secondary to metastatic lung cancer presents with a serum calcium of 12.2 mg/dL (3.05 mmol/L). Her serum creatinine is 0.9 mg/dL (80 µmol/L) and estimated glomerular filtration rate >60 mL/min/1.73 m^2. The decision is made to initiate therapy with an agent that inhibits bone resorption. Based on the efficacy and toxicity profile of the following agents, which would be the *most appropriate* to initiate in this patient?

A. Prednisone

B. Pamidronate

C. Calcitonin

D. Denosumab

6. Which treatment is *most appropriate* to reduce stone number and diameter in an adult patient with primary hyperparathyroidism?

A. Cinacalcet

B. Calcium-restricted diet

C. Lithotripsy

D. Etelcalcitide

7. An adult female with chronic kidney disease stage 3b (estimated GFR 40 mL/min/1.73 m^2) is scheduled to have a colonoscopy. Her oral medications include: ramipril 10 mg once daily, furosemide 80 mg twice daily, and metoprolol succinate 50 mg once daily. Prior to her colonoscopy, she is advised to use a sodium phosphate bowel preparation. All but which of the following put her at increased risk for phosphate nephropathy or acute kidney injury?

A. Chronic kidney disease

B. Ramipril

C. Metoprolol succinate

D. Furosemide

8. A critically ill adult male is asymptomatic with a serum calcium of 8.1 mg/dL (2.03 mmol/L). Ionized calcium and albumin have not been evaluated. What is the *most appropriate* recommendation regarding this patient's serum calcium concentration?

A. Check an ionized calcium concentration

B. Administer calcium chloride 1 g IV over 10 minutes

C. Administer calcium gluconate 2 g IV over 2 hours

D. Administer calcium gluconate 3 g IV over 3 hours

9. An adult female presents with asymptomatic hypocalcemia secondary to vitamin D deficiency. She has no kidney or hepatic impairment. Which of the following is the *most appropriate* therapy to initiate at this time?

A. Calcitriol

B. Doxercalciferol

C. Ergocalciferol

D. Paricalcitol

10. What mechanism may cause drug-induced hypocalcemia from bisphosphonates?

A. Blocked bone resorption

B. Increased sensitivity to CaSr

C. Decreased PTH sensitivity

D. Induction of hypomagnesemia

11. An adult female with stage 4 chronic kidney disease is treated for iron deficiency anemia with ferric carboxymaltose 750 mg IV. She reports significant myalgias and weakness one week after the infusion. Which of the following electrolyte disorders is the *most likely* the cause of her symptoms?

A. Hypercalcemia

B. Hypocalcemia

C. Hyperphosphatemia

D. Hypophosphatemia

12. An adult female with chronic disease-related malnutrition who underwent surgery for esophageal cancer is initiated on enteral nutrition. Laboratory data prior to enteral nutrition included: serum phosphorus 4 mg/dL (1.29 mmol/L) and serum potassium 4.1 mEq/L (mmol/L). Laboratory data 24 hours after initiation of enteral nutrition included: serum phosphorus 0.8 mg/dL (0.26 mmol/L) and serum potassium 2.6 mEq/L (mmol/L). Which of the following *best* describes the pathogenesis of her hypophosphatemia?

A. Decreased gastrointestinal absorption

B. Decreased tubular reabsorption

C. Increased internal redistribution

D. Increased renal excretion

13. An adult hospitalized male (93 kg, 6 ft 1 in.' [185 cm]) has the following current laboratory data: magnesium 2.1 mEq/L (0.86 mmol/L), phosphorus 1.2 mg/dL (0.39 mmol/L), sodium 136 mEq/L (mmol/L), potassium 5.9 mEq/L (mmol/L), blood urea nitrogen 10 mg/dL (3.6 mmol/L), and serum creatinine 0.9 mg/dL (80 µmol/L). What is the *most appropriate* electrolyte replacement at this time?

A. K-Phos No. 2® 250 mg tablet orally every 6 hours

B. Phos-NaK® 250 mg packet orally every 6 hours

C. Sodium phosphate 45 mmol IV once

D. Potassium phosphate 45 mmol IV once

14. An older male who resides in a nursing home develops hypophosphatemia (serum phosphorus 1.7 mg/dL [0.55 mmol/L]) secondary to limited oral intake associated with advanced dementia. His other laboratory data include: serum potassium 3.4 mEq/L (mmol/L) and total corrected calcium 8.5 mg/dL (2.13 mmol/L). Which of the following is the *best* therapy to initiate in this patient?

A. Neutra-Phos-K®

B. K-Phos Neutral®

C. Neutra-Phos®

D. Potassium phosphate IV

15. Hemolysis related to hypophosphatemia is *most likely* caused by which of the following?

A. Altered cardiac conduction

B. Depletion of ATP stores

C. Myocardial cell apoptosis

D. Vitamin D deficiency

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Rationale: Many tumors secrete PTH-related protein, which binds the PTH receptors on bone and in kidney tissues, inducing bone resorption and increasing tubular reabsorption of calcium. Breast cancer is associated with hypercalcemia from PTH-related protein. See the "Pathophysiology" (Hypercalcemia) section.

2. **B.** Rationale: Rhabdomyolysis can induce hypercalcemia due to mobilization of calcium from calcium phosphate deposits in the injured muscles. Severe, rapidly developing hypercalcemia can result in obtundation. See the "Pathophysiology" (Hypercalcemia) section.

3. **C.** Rationale: Cancers that metastasize to bone can cause hypercalcemia. See the "Pathophysiology" (Hypercalcemia) section.

4. **C.** Rationale: First-line therapy for patients with relatively intact kidney function is volume expansion with normal saline to induce calciuresis. See the "Pharmacologic Therapy" (Hypercalcemia) section.

5. **B.** Rationale: Bisphosphonates are first-line for treating hypercalcemia of malignancy. Calcitonin is associated with tachyphylaxis, and prednisone has a slow onset and extensive adverse medication reaction profile. Denosumab is a good option for patients with impaired kidney function. See

the "Pharmacologic Therapy" (Hypercalcemia) section.

6. **A.** Rationale: Cinacalcet reduces stone number and diameter. Etelcalcitide is also a calcimimetic; however, it is only approved to treat secondary hyperparathyroidism in patients undergoing hemodialysis. See the "Pharmacologic Therapy" (Hypercalcemia) section.

7. **C.** Rationale: Metoprolol succinate does not affect renal hemodynamics whereas ramipril causes dilation of the efferent arteriole and furosemide can induce volume depletion. Chronic kidney disease will impair her ability to excrete phosphorus. See the "Pathophysiology" (Hyperphosphatemia) section.

8. **A.** Rationale: The serum calcium is not low enough to warrant treating without evaluating the ionized calcium first. Ionized calcium is the gold standard for calcium monitoring in critically ill patients. See the "Disorders of Calcium Homeostasis" and "Acute Treatment" (Hypocalcemia) sections.

9. **C.** Rationale: Ergocalciferol is an appropriate therapy for an adult patient with asymptomatic hypocalcemia secondary to vitamin D deficiency and no kidney or hepatic impairment. See the "Chronic Treatment" in Hypocalcemia section.

10. **A.** Rationale: Bisphosphonates may cause hypocalcemia by the mechanism of blocked bone resorption. While the other answer choices are mechanisms that may cause hypocalcemia, they are associated with other medications. See the "Medication-induced Hypocalcemia" section.

11. **D.** Rationale: Based on her history of ferric carboxymaltose administration one week ago, hypophosphatemia is the most likely cause of her symptoms. See the "Pathophysiology" (Hypophosphatemia) section.

12. **C.** Rationale: Hypophosphatemia in the setting of refeeding syndrome occurs as a result of internal redistribution or intracellular shifts of phosphate. See the "Pathophysiology" (Hypophosphatemia) section.

13. **C.** Rationale: In the setting of severe hypophosphatemia and normal kidney function, parenteral phosphate replacement with 0.32 to 0.64 mmol/kg is recommended (30-60 mmol based on the patient's weight of 93 kg). Oral replacement is inappropriate because of the severity and the patient should not receive potassium phosphate in the setting of hyperkalemia. See the "Severe Hypophosphatemia" (Treatment) section.

14. **A.** Rationale: Since the patient has asymptomatic hypokalemia and hypophosphatemia, treatment with an oral agent including potassium is the best choice. See the "Mild-to-Moderate Hypophosphatemia" (Treatment) section.

15. **B.** Rationale: When red blood cell ATP decreases, cells become spherocytic and rigid, and are trapped and destroyed in the spleen. See the "Pathophysiology" (Hypophosphatemia) section.