12

ELECTROLYTES, OTHER MINERALS, AND TRACE ELEMENTS

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OBJECTIVES

After completing this chapter, the reader should be able to

- Describe the homeostatic mechanisms involved in sodium and water balance, hyponatremia, and hypernatremia
- Describe the physiology of intracellular and extracellular potassium regulation as well as the signs and symptoms of hypokalemia and hyperkalemia
- List common causes of serum chloride abnormalities
- List common conditions resulting in serum magnesium abnormalities and describe signs and symptoms of hypomagnesemia and hypermagnesemia
- Describe the metabolic and physiologic relationships among the metabolism of calcium, phosphate, parathyroid hormone, and vitamin D
- List common conditions resulting in serum calcium abnormalities and describe signs and symptoms of hypocalcemia and hypercalcemia
- List common conditions resulting in altered copper, zinc, manganese, and chromium homeostasis and describe the signs and symptoms associated with their clinical deficiencies
- Interpret the results of laboratory tests used to assess sodium, potassium, chloride, calcium, phosphate, magnesium, copper, zinc, manganese, and chromium (in the context of a clinical case description, including history and physical examination)

Serum or plasma electrolyte concentrations are among the most commonly used laboratory tests by clinicians for assessment of a patient's health status, clinical conditions and disease progression. The purpose of this chapter is to present the physiological basis of the need to assess serum concentrations of common electrolytes and minerals. The interpretation of these laboratory results and the clinical significance of abnormal results are addressed.

Serum sodium, potassium, chloride, and total carbon dioxide content (often referred to *as serum bicarbonate concentration*) are among the most commonly monitored electrolytes in clinical practice. Magnesium, calcium, and phosphate are also monitored as determined by the patient's disease states and clinical indication. The homeostasis of calcium and phosphate is frequently discussed in the context of the endocrine system because of the effects of vitamin D and parathyroid hormone (PTH) on the regulation of these minerals. Serum total carbon dioxide content, often measured in conjunction with electrolytes, is discussed in Chapter 13 because of its significance for the assessment of acid–base status. Listed in **Table 12-1** are the current dietary reference intake for electrolytes, minerals, and trace elements.

TABLE 12-1. Recommended Dietary Reference Intake of Electrolytes and Minerals for Healthy Adults According to the Dietary Guidelines 2015–2020

NUTRIENT	DIETARY REFERENCE INTAKE[a]	
	Male	Female
Sodium	2300 mg (100 mEq)	
Potassium	4700 mg (~120 mEq)	
Chloride	Varies with potassium and sodium intakes	
Magnesium	19–30 yo: 400 mg	19–30 yo: 310 mg
	31+ yo: 420 mg	31+ yo: 320 mg
Calcium	19–70 yo: 1000 mg	19–50 yo: 1000 mg
	71+ yo: 1200 mg	51+ yo: 1200 mg
Phosphorus	700 mg	
Copper	900 mcg	
Zinc	11 mg	8 mg
Manganese	2.3 mg	1.8 mg
Chromium[b]	19–50 yo: 35 mcg	19–50 yo: 25 mcg
	51+ yo: 30 mcg	51+ yo: 20 mcg

yo = years old.

[a]According to the Recommendations from 2015–2020 Dietary Guidelines for Americans. http://health.gov/dietaryguidelines/2015/ (accessed 2016 Feb 8).

[b]Adequate intakes according to Institute of Medicine (U.S.) Food and Nutrition Board. Dietary Reference Intakes. Washington, DC: National Academies Press (U.S.); 2001.

ELECTROLYTES

The traditional units, International System (SI) units, and their conversion factors for electrolytes, minerals, and trace elements discussed in this chapter are listed in **Table 12-2**. Although the normal ranges of serum concentrations for each of the electrolytes are listed below, clinicians should always confirm with the institutional clinical laboratory department for their institutional reference range due to the variance introduced by equipment, analytical technique, and quality assurance data.

Sodium

Normal range: 135–145 mEq/L (135–145 mmol/L)

Sodium is the most abundant cation in the extracellular fluid and is the major regulating factor for bodily fluid and water balance. Extracellular (i.e., intravascular and interstitial) and intracellular sodium contents are closely affected by body fluid status. Thus, an accurate interpretation of serum sodium concentration must include an understanding of body water homeostasis and the interrelationship between the regulation of sodium and water.[1]

Physiology

Sodium is essential for maintaining the optimal transmembrane electric potential for action potential and neuromuscular functioning as well as regulating serum osmolality and water balance. Serum osmolality is an estimate of the water-solute ratio in the vascular fluid. It can be measured in the laboratory or estimated using the following equation:

$$\begin{aligned}&\text{Estimated serum osmolality (mOsm/kg)}\\&= (2 \times \text{serum [Na]}) + [\text{glucose, in mg/dL}]/18\\&\quad + [\text{blood urea nitrogen, in mg/dL}]/2.8\end{aligned}$$

The normal range of serum osmolality is 285–295 mOsm/kg. The measured osmolality should not exceed the estimated value by more than 10 mOsm/kg. A difference of 10 mOsm/kg or more is considered an increased osmolal gap, which may suggest the presence of other unmeasured solutes (e.g., organic solvents, alcohol) and is useful to providing assessments in clinical toxicology. Decreased serum osmolality usually suggests a water excess, whereas increased serum osmolality suggests a water deficit. Although serum osmolality may be helpful in assessing water status, especially the intravascular volume, it should not be the primary and only parameter in assessing fluid status. The results also should be interpreted in the context of the ability of the solute to cross cellular membranes (e.g., uremia causing hyperosmolality without relative intracellular depletion) and the patient's symptoms and signs of disease. **Figure 12-1** summarizes the inter-relationship and regulation between water and sodium.

Changes in body water and plasma volume can directly or indirectly affect the serum sodium concentration. For example, as the result of changes in effective circulating volume, baroreceptors and osmoreceptors will respond accordingly to restore an isovolemic state of the body. Baroreceptors are located in the carotid sinus, aortic arch, cardiac atria, hypothalamus, and the juxtaglomerular apparatus in the kidney. Stimulation of these receptors will promote urinary loss of water and sodium. Osmoreceptors are present primarily in the hypothalamus. The three major effectors in response to the stimulation of the osmoreceptors include vasopressin or antidiuretic hormone (ADH), the renin-angiotensin-aldosterone system, and natriuretic peptides. The resultant renal effects from these three distinct pathways collectively regulate the homeostasis of water and sodium.

The kidneys are the primary organ responsible for the retention and excretion of body sodium and water. The glomeruli receive and filter about 180 L of plasma fluid daily. On average, fewer than 2 L of water and between 0.1–40 g of sodium are excreted in the urine, depending on the fluid status of the individual. Although almost 100% of the plasma sodium is filtered by the glomeruli, <1% is excreted in the urine under normal circumstances. The proximal tubule and the loop of Henle collectively account for up to 90% of sodium reabsorbed from the kidneys.

The homeostatic mechanism for water and sodium also involves the equilibrium among intravascular, interstitial, and intracellular fluids.[3] Net movement of water occurs from areas of low osmolality to areas of high osmolality. This effect can be readily observed in patients with a low serum osmolality due to a deficit of serum sodium or excess of plasma water. In patients with hyponatremia, water moves from the plasma to the higher osmolality in the interstitial space.[3] In the presence of high hydrostatic and oncotic pressure gaps across capillary walls, the net effect is excessive interstitial water accumulation and edema formation.[2,3]

Antidiuretic hormone (vasopressin). ADH, also known as *arginine vasopressin*, is a nine amino acid peptide hormone that regulates renal handling of free water. By altering the amount of water reabsorbed by the kidney, ADH has an indirect but pivotal effect in changing or maintaining serum sodium concentration. ADH is secreted by the magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus, where both osmoreceptors and baroreceptors are present to detect fluid changes in the vasculature.

TABLE 12-2. Conversion Factors to SI Units

NUTRIENT	TRADITIONAL UNITS	CONVERSION FACTORS TO SI UNITS	SI UNITS
Sodium	mEq/L	1	mmol/L
Potassium	mEq/L	1	mmol/L
Chloride	mEq/L	1	mmol/L
Magnesium	mEq/L	0.5	mmol/L
Calcium	mg/dL	0.25	mmol/L
Phosphate	mg/dL	0.3229	mmol/L
Copper	mcg/dL	0.1574	µmol/L
Zinc	mcg/dL	0.153	µmol/L
Manganese	mcg/L	18.2	nmol/L
Chromium	mcg/L	19.2	nmol/L

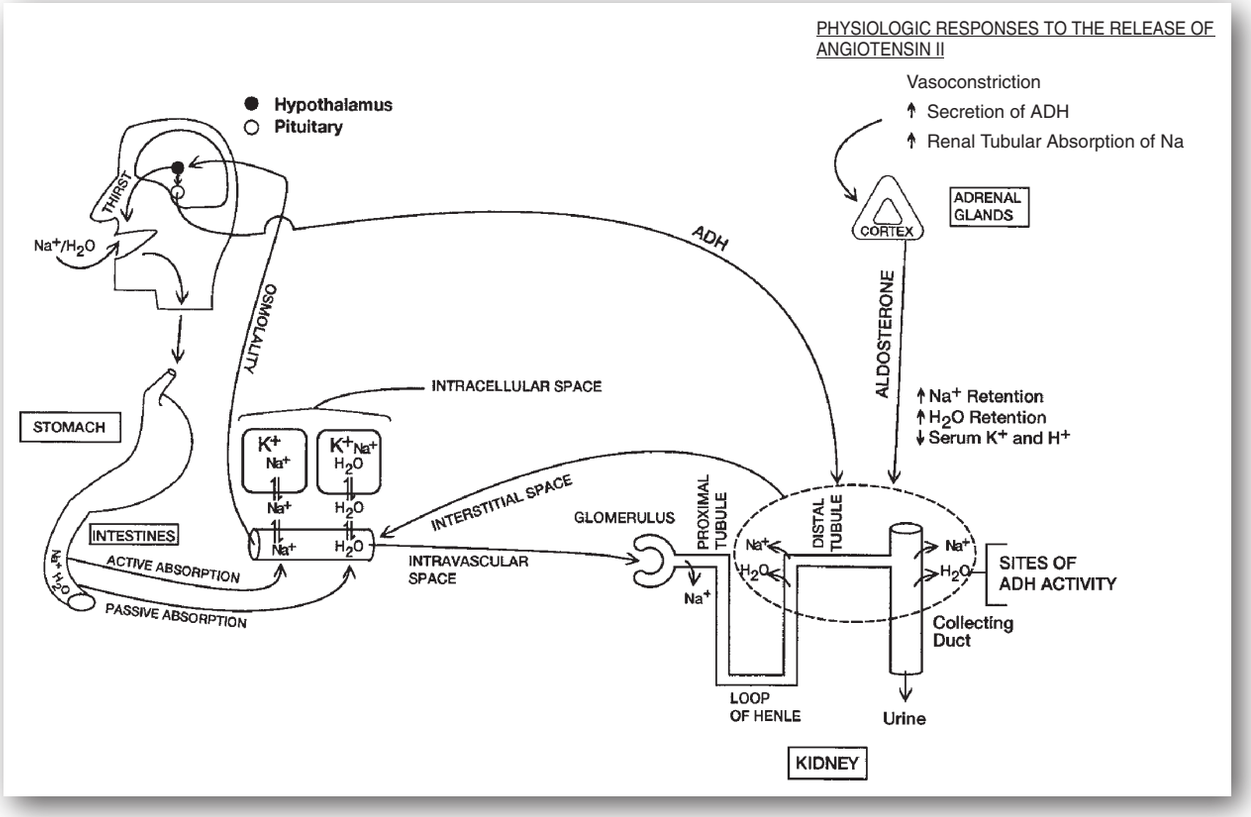

FIGURE 12-1. Homeostatic mechanisms involved in sodium, potassium, and water balance. Sodium is the principal cation in blood that contributes to serum osmolality and intravascular volume. When serum osmolality and intravascular volume are increased, baroreceptors in the carotid sinus, aortic arch, cardiac atria, hypothalamus, and juxtaglomerular apparatus in the kidney, promote urinary loss of sodium and water. The synthesis and release of ADH are increased which lead to increased water retention. In addition, elevated serum osmolality with increased serum sodium would suppress aldosterone release, which results in increased renal sodium excretion. In contrast, when serum osmolality is low due to excess intravascular water and decreased sodium, water will passively move from the blood stream to interstitial spaces (resulting in edema) and into cells (in brain cells, this can cause brain swelling). In addition, low serum osmolality detected by hypothalamic osmoreceptors, will suppress release of ADH resulting in decreased water reabsorption in the distal tubule, and stimulate the renin-angiotensin-aldosterone system (which enhances distal tubular reabsorption of sodium and potassium secretion). Serum osmolality also regulates the thirst response. When serum osmolality is high, hypothalamic osmoreceptors stimulate thirst so that the patient increases water intake. Together with increased ADH release the body will increase free water retention and eventually drive serum osmolality back within the normal range.

ADH release is stimulated by (1) hypovolemia (detected by baroreceptors); (2) thirst; (3) increased serum osmolality; and (4) angiotensin II. The plasma half-life of ADH is 10–20 minutes, and it is rapidly deactivated and eliminated by the liver, kidneys, and a plasma enzyme vasopressinase.

ADH regulates urinary water loss by augmenting the permeability of the collecting tubules to increase the net reabsorption of water. Circulating serum ADH binds to type 2 vasopressin (V2) receptors starting at the thick ascending loop, which contributes to the corticomedullary gradient and mechanism of water retention. More importantly, ADH also binds to the V2 receptors in the collecting tubule and promotes the formation of a water channel, known as *aquaporin-2*. Aquaporin-2 facilitates the reabsorption of water from the lumen back into the renal blood supply in the systemic circulation, causing a decrease in diuresis and net retention of water. However, if serum sodium is high but blood volume is normal (e.g., normovolemia with hyperosmolality), the effect from the baroreceptors overrides the further release of ADH, thus preventing volume overload (i.e., hypervolemia).[2]

In patients with the syndrome of inappropriate ADH (SIADH) secretion, an abnormally high quantity of ADH is present in the systemic circulation. This condition results in increased water reabsorption, which could cause a dilutional effect in serum sodium. In conjunction with increased free water intake, a low serum sodium concentration is commonly observed in these patients. Urine osmolality and urine electrolyte concentrations are often increased due to the decreased urinary excretion of free water associated with the increased effect of ADH. Conversely, in patients with central diabetes insipidus (DI), hypothalamic

ADH synthesis or release is decreased. Patients with DI commonly present with hypernatremia due to the increased renal wasting of free water. In some cases, the kidneys fail to respond to the circulating ADH in spite of appropriate synthesis and release of ADH from the hypothalamus. This condition is called *nephrogenic diabetes insipidus*. In either central or nephrogenic DI, patients usually produce a very large quantity of diluted urine, characterized by low specific gravity, low urine osmolality, and low urine sodium.[2] (Chapter 11 offers an in-depth discussion of the effects of other diseases on urine composition.)

Drugs may alter ADH release from the hypothalamus or the biological response to the hormone in the renal epithelial tissues. This may produce an imbalance of water and sodium in the body and exacerbate SIADH or DI.[4,5] SIADH is not uncommon with the chronic use of chlorpropamide, tolbutamide, cyclophosphamide, carbamazepine, oxcarbazepine, some opiate derivatives, oxytocin, vincristine, phenothiazines, some tricyclic antidepressants, and a number of serotonin reuptake inhibitors (**Table 12-3**). Because of their ability to increase renal reabsorption of free water, some of these drugs have an established role in the treatment of chronic hypernatremia or DI. For example, carbamazepine stimulates ADH release and enhances renal cell response to ADH. The dual effects result in a reported incidence of hyponatremia between 5% and 40% associated with its chronic use. But this antidiuretic effect also has established its role as an off-label pharmacotherapeutic option for DI. In contrast, demeclocycline and lithium alter the renal epithelial handling of sodium and water by decreasing the action of ADH, especially on the function and formation of aquaporin. They have been used in the treatment of SIADH. Other drugs that decrease the release and impair the renal response to ADH also may precipitate DI (**Table 12-4**). Based on published data, lithium, foscarnet, and clozapine are the most commonly reported causes of drug-induced DI. In addition, conivaptan, a mixed V1A/V2 antagonist, and tolvaptan, a selective V2 receptor antagonist, both modulate the renal handling of water by reducing renal water absorption and affect sodium homeostasis. These drugs are currently approved for the treatment of euvolemic and hypervolemic hyponatremia.

Renin-angiotensin-aldosterone system. Renin is a glycoprotein that catalyzes the conversion of angiotensinogen to angiotensin I, which is further converted to angiotensin II primarily in the lungs. However, angiotensin II also can be formed locally in the kidneys. Angiotensin II, a potent vasoconstrictor, is important in maintaining optimal perfusion pressure to end organs especially when plasma volume is decreased. In addition, it induces the release of aldosterone, ADH, and, to a lesser extent, cortisol.

Aldosterone is a hormone with potent mineralocorticoid activity. It affects the distal tubular reabsorption of sodium.[3] This hormone is released from the adrenal cortex. Besides angiotensin II, various dietary and neurohormonal factors including low serum sodium, high serum potassium, and low blood volume also can stimulate its release. Aldosterone acts on renal Na-K-ATPase to increase urinary excretion of potassium from the distal tubules in exchange for sodium reabsorption.

TABLE 12-3. Medications That Can Cause Hyponatremia Based on Published Data

Drugs That Alter *SODIUM and WATER* Homeostasis:
Amiloride
Indapamide
Loop diuretics
Thiazide diuretics
Trimethoprim
Drugs That Alter WATER Homeostasis:
Stimulator of central ADH production or release
Antidepressants:
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Tricyclic antidepressants (more common with amitriptyline, desipramine, protriptyline)
Antiepileptic drugs:
Carbamazepine
Oxcarbazepine
Valproic acid
Antipsychotic agents:
Phenothiazines (e.g., thioridazine, trifluoperazine)
Butyrophenones (e.g., haloperidol)
Antineoplastic agents:
Alkylating agents (cyclophosphamide, ifosphamide, melphalan)
Platinum (cisplatin, carboplatin)
Vinca alkaloids (more common with vinblastine and vincristine)
Others: levamisole, methotrexate
Cotrimoxazole (especially at high doses)
Opioid analgesics
3,4-methylenedioxymethylamphetamine (MDMA; aka Ecstasy)
Enhancers of ADH effect
Antiepileptic drugs (primarily carbamazepine and lamotrigine)
Antineoplastic agents (mostly cyclophosphamide)
Nonsteroidal anti-inflammatory drugs
Oral hypoglycemic agents:
Chlorpropamide
Tolbutamide
Drugs with unclear mechanisms
ACE inhibitors
Bromocriptine
Oxytocin
Venlafaxine

ACE = angiotensin-converting enzyme; ADH = antidiuretic hormone.

Because of its effect on renal Na/K exchange, aldosterone has a profound effect on serum potassium, while its effect on serum sodium is relatively modest. As serum sodium increases, so does water reabsorption, which follows the osmotic gradient.[3] Renal arteriolar blood pressure (BP) then increases, which helps maintain the glomerular filtration rate (GFR). Ultimately,

TABLE 12-4. Drugs That Can Cause Diabetes Insipidus by Decreasing Renal Response to ADH

Precipitant of Nephrogenic DI
Amphotericin B
Cidofovir
Cimetidine
Clozapine
Colchicine
Conivaptan
Cyclophosphamide
Demeclocycline
Epirubicin
Ethanol[a]
Fluvoxamine
Foscarnet
Gentamicin
Lithium
Methicillin[b]
Phenytoin[a] (uncommon at therapeutic doses)
Propoxyphene[b]
Tolvaptan
Verapamil
Vinblastine

ADH = antidiuretic hormone; DI = diabetes insipidus.
[a]Likely also involves central effect by inhibiting ADH release.
[b]Currently no longer available in the United States, although still available in some other countries.

more water and sodium pass through the distal tubules, overriding the initial effect of aldosterone.[2,3]

Natriuretic peptides. Atrial natriuretic factor (ANF), also known as *atrial natriuretic peptide*, is a vasodilatory hormone synthesized and primarily released by the right atrium. It is secreted in response to plasma volume expansion, as a result of increased atrial stretch. ANF inhibits the juxtaglomerular apparatus, zona glomerulosa cells of the adrenal gland, and the hypothalamus-posterior pituitary. As a result, a global down regulation of renin, aldosterone, and ADH, respectively, is achieved. ANF directly induces glomerular hyperfiltration and reduces sodium reabsorption in the collecting tubule. A net increase in sodium excretion is achieved. Therefore, ANF can decrease serum and total body sodium. Brain natriuretic peptide (BNP) is produced and secreted primarily by the ventricles in the brain, and to a much smaller extent, the atrium. Similar to ANP, BNP also regulates natriuretic, endocrine, and hemodynamic responses and may affect sodium homeostasis. An increase in blood volume or pressure, such as chronic heart failure and hypertension, enhances BNP secretion, which induces a significant increase in natriuresis and to a lesser extent, urinary flow (i.e., diuresis). Plasma BNP concentrations correlate with the magnitude of left ventricular heart failure and the clinical prognosis of patients with heart failure.

Hyponatremia

Hyponatremia is defined as a serum sodium concentration <135 mEq/L (<135 mmol/L). Although it can be the direct result of sodium deficit, hyponatremia may also occur when total body water content is low (i.e., dehydration), normal, or high (i.e., fluid overload). Therefore, natremic status must be evaluated in concert with volume status to determine the nature of an underlying disorder. Fluid status should be evaluated based on history of oral intake, vital signs; other supportive laboratory findings if available (e.g., serum blood urea nitrogen (BUN)–serum creatinine (SCr) ratio, hematocrit to hemoglobin (Hgb) concentration ratio, or urine electrolyte assessment); recent changes in body weight; recent medical, surgical, and nutrition history; and findings from the physical examination. More importantly, the patient's renal function, hydration status, and fluid intake and output must be thoroughly evaluated and closely monitored. The most common causes of hyponatremia can be broken down into two types: (1) sodium depletion in excess of total body water loss (e.g., severe dehydration with true depletion of total body sodium); or (2) dilutional hyponatremia (i.e., free water intake greater than water output with no change in sodium loss). Dilutional hyponatremia can be further categorized into five subtypes: (1) primary dilutional hyponatremia (e.g., SIADH and renal failure); (2) neuroendocrine (e.g., adrenal insufficiency and myxedema); (3) psychiatric disorder (e.g., psychogenic polydipsia); (4) osmotic hyponatremia (e.g., severe hyperglycemia); and (5) thiazide diuretic-induced.

Most patients with hyponatremia remain asymptomatic until serum sodium approaches 120 mEq/L. Infusion of hypertonic saline (e.g., 3% NaCl solution) is usually not necessary unless serum sodium concentration is <120 mEq/L, altered mental status is present, or if the patient is fluid restricted (e.g., heart failure, chronic renal failure). As with most electrolyte disorders, the chronicity of the imbalance is a major determinant of the severity of signs and symptoms. For example, hyponatremia in patients with congestive heart failure (CHF) secondary to chronic, progressive volume overload and decreased renal perfusion is less likely to be symptomatic than a patient who is hyponatremic due to rapid infusion of a hypotonic solution. The most commonly reported symptom associated with hyponatremia is altered mental status (**Table 12-5**). If serum sodium continues to fall, cerebral edema can worsen and intracranial pressure will continue to rise. More severe symptoms such as seizure, coma, and, subsequently, death may result.[2-6]

Hyponatremia associated with total body sodium depletion. Hyponatremia associated with low total body sodium reflects a reduction in total body water, with an even larger reduction in total body sodium. This condition is primarily caused by depletion of extracellular fluid, which stimulates ADH release to increase renal water reabsorption even at the expense of causing a transient hypo-osmotic state. Some common causes include vomiting; diarrhea; intravascular fluid losses due to burn injury and pancreatitis; Addison disease; and certain forms of renal failure (e.g., salt-wasting nephropathy).[2] This type of hyponatremia may also occur in patients treated too

TABLE 12-5. Signs and Symptoms of Hyponatremia

Agitation
Anorexia
Apathy
Depressed deep-tendon reflexes
Disorientation
Headache
Hypothermia
Lethargy
Muscle cramps
Nausea
Seizures
Vomiting

aggressively with diuretics who receive sodium-free solutions as replacement fluid.

Hyponatremia associated with normal total body sodium. Also called *euvolemic* or *dilutional hyponatremia*, this condition refers to impaired free water excretion without alteration in sodium excretion. Etiologies include any mechanism that enhances ADH secretion or potentiates its action at the renal collecting tubules. This condition can occur as a result of glucocorticoid deficiency, severe hypothyroidism, and administration of water to a patient with impaired water excretion capacity.[2,5] SIADH is associated with an excessive renal reabsorption of free water in the body due to continued ADH secretion despite low serum osmolality. This results in hyponatremia and increased urinary sodium loss. Patients with SIADH produce concentrated urine with high urine osmolality (usually >200 mOsm/kg H_2O) and urine sodium excretion (as reflected in a urine sodium concentration that is usually >20 mEq/L). They have normal renal, adrenal, and thyroid function and have no evidence of volume abnormalities.[25]

Impaired ADH response can be precipitated by many factors, including medications. SIADH has been reported in patients with certain tumors, such as lung cancer, pancreatic carcinoma, thymoma, and lymphoma. ADH release from the parvicellular and magnocellular neurons may be stimulated by cytokines such as interleukin (IL-2, IL-6, IL-1 β), and tumor necrosis factor (TNF-α). Likewise, head trauma, subarachnoid hemorrhage, hydrocephalus, Guillain-Barré syndrome, pulmonary aspergillosis, and occasionally tuberculosis may increase hypothalamic ADH production and release leading to SIADH (**Figure 12-2**).

In some cases, hyponatremia may not be associated with a sodium deficit. This scenario is associated with normal or even slightly elevated total body sodium, which is distributed in a much larger volume of total body water. It is frequently observed in hypervolemic states with compromised renal function such as CHF, cirrhosis, nephrotic syndrome, and chronic kidney disease (CKD). In these patients, renal handling of water and sodium is often impaired.[2,5]

The initial goal of therapy for most patients with hyponatremia is to raise the serum sodium concentration to 130 mEq/L over a few days. Mild, asymptomatic hyponatremia (>125 mEq/L) can usually be safely managed with a sodium-containing oral rehydration solution or an increase in oral sodium intake, provided that the oral route is viable (i.e., vomiting and diarrhea are controlled, evidence of functional intestine). Intravenous (IV) sodium therapy is preferred in more severe cases of hyponatremia. In most cases, sodium chloride 0.9% is used. If a hypertonic saline solution (e.g., NaCl 3% or higher) is used, it must be infused via a central venous catheter due to its high osmolarity.

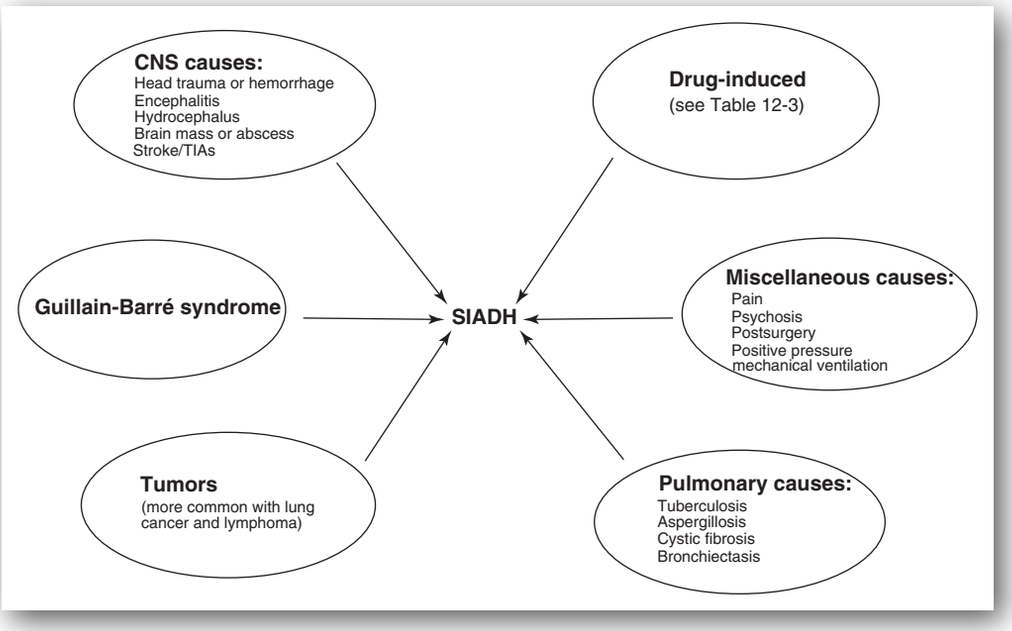

FIGURE 12-2. Etiologies of SIADH. TIAs = transient ischemic attacks.

The initial goal for treating hyponatremia is to increase serum sodium by 4–6 mEq/L within 24 hours of baseline in most cases. Neurological deficits would improve with this target rate of change in serum sodium concentration. The average rate of increase in serum sodium should not exceed 1–2 mEq/L/hr and 9 mEq/L in any given 24-hour period. There is no evidence that correction of serum sodium by >10 mEq/L in 24 hours or 18 mEq/L in 48 hours improves the outcomes in patients with acute or chronic hyponatremia. (**Minicase 1**.)

Tests for Assessing Fluid Status

Fractional Excretion of Sodium

Normal range: 1–2%

In most cases, natremic disorders cannot be effectively managed without first optimizing the overall fluid status of the patient. Therefore, when a serum sodium value is abnormal, the clinician should first evaluate whether vascular volume is optimal. In addition to physical examinations and history, the *fractional excretion of sodium* (FE_{Na}) may help validate these findings, especially in patients whose physical examination results may be limited by other confounders (e.g., the use of antihypertensive drugs, heart failure, or with acute renal failure). The FE_{Na} may be determined by the use of a random urine sample to determine renal handling of sodium. FE_{Na}, the measure of the percentage of filtered sodium excreted in the urine, can be calculated using the following equation:

$$FE_{Na} = 100 \times \frac{\text{sodium}_{\text{urinary}} \times \text{creatinine}_{\text{plasma}}}{\text{sodium}_{\text{plasma}} \times \text{creatinine}_{\text{urinary}}}$$

Values >2% usually suggest that the kidneys are excreting a higher than normal fraction of the filtered sodium, implying likely renal tubular damage. Conversely, FE_{Na} values <1% generally imply preservation of intravascular fluid through renal sodium retention, suggesting prerenal causes of renal dysfunction (e.g., hypovolemia and cardiac failure). Because acute diuretic therapy can increase the FE_{Na} to 20% or more, urine samples should be obtained at least 24 hours after diuretics have been discontinued.[2]

Blood Urea Nitrogen: Serum Creatinine Ratio

Normal range: <20:1

The *BUN: SCr ratio* can provide useful information to assess fluid status. When this ratio is higher than 20:1, dehydration is usually present. As extracellular fluid volume is diminished, the rate of increase in serum urea is much faster than that with SCr. Therefore, BUN increases by a larger magnitude

MINICASE 1

A Case of Hyponatremia

Jessica F., a 24-year-old woman, presents to the emergency department with lower abdominal pain, fatigue, headache, and dizziness. She had four episodes of vomiting and six episodes of diarrhea in the last 24 hours. She had salad at a salad bar for lunch the day before. About two hours after her lunch, she started to feel nauseated. The abdominal pain and vomiting started shortly after and the diarrhea started in the evening. She vomited her lunch, and her diarrhea was mostly watery without blood. She also experienced headache this morning. She has not been eating for the last 24 hours and can tolerate only small sips of water.

Upon presentation, she looks pale with sunken eyes. She is alert and oriented to time, person, and place. Neurological examination reviews no deficits. Her vital signs include BP 105/70 mm Hg at supine position (standing BP 90/65 mm Hg), HR 92 beats/min (standing 108 beats/min), and RR 20 breaths/min. She also has a fever at 100.6 °F. Blood work for serum electrolyte and complete blood count are ordered. Her electrolyte panel shows the following results: sodium 128 mEq/L, potassium 3.3 mEq/L, chloride 90 mEq/L, CO_2 content 21 mEq/L, BUN 28 mg/dL, creatinine 1 mg/dL, and glucose 77 mg/dL. She does not take any medication prior to this admission.

QUESTION: How would you interpret this patient's serum sodium concentration?

DISCUSSION: The patient's serum sodium concentration is lower than the normal range, suggesting hyponatremia. However, as mentioned above, sodium disorder cannot be fully assessed without evaluating a person's fluid status. Based on the history, she had excessive fluid loss due to repeated episodes of vomiting and diarrhea. Fever also will increase insensible fluid loss. Therefore, she is likely dehydrated (hypovolemic). Her vital signs (orthostatic hypotension with reflex tachycardia), and the findings from physical exam support dehydration. The laboratory results show an elevated BUN:SCr ratio of 28:1, which also is consistent with volume depletion. Increased loss of body fluids, especially from the GI tract, will lead to increased sodium loss. Her fluid intake has been very limited and likely inadequate to replenish the continued sodium loss, which results in hyponatremia. She is likely experiencing hyponatremia associated with total sodium deficiency due to uncontrolled vomiting, diarrhea, and insufficient oral intake.

The onset of the patient's hyponatremia is likely acute because there are no other established factors that would lead to chronic hyponatremia (e.g., use of diuretic drugs, selective serotonin reuptake inhibitors, etc.). Her symptoms of hyponatremia are mild as she shows no neurological deficit. Her headache is likely associated with her dehydration, mild hyponatremia, and possibly acid–base changes.

In summary, this patient has mild hyponatremia with hypovolemia. The cause seems to be from her acute illness—uncontrolled vomiting and diarrhea lead to increase sodium loss with insufficient sodium intake. She does not seem to experience major acute symptoms associated with hyponatremia at this point. The logical treatment approach for her will involve controlling her nausea, diarrhea, and vomiting, as well as treating hypovolemia with a sodium containing fluid (e.g., NaCl 0.9%) and managing other electrolyte disturbances.

than the SCr concentration in dehydrated individuals, leading to a rise in the BUN: SCr ratio. However, it should be noted that BUN will increase in the face of internal bleeding, CHF, renal failure, or significantly increased protein intake. If any of these conditions are present, additional signs and symptoms of dehydration should be assessed along with the increased BUN:SCr ratio.

Hypernatremia

Hypernatremia is defined as a serum sodium concentration >145 mEq/L (>145 mmol/L). High serum sodium concentrations are common in patients with either an impaired thirst expression (e.g., neurohypophyseal lesion, especially after suffering from a stroke) or an inability to replete water deficit through normal insensible losses (i.e., uncontrollable water loss through respiration or skin) or from renal or GI losses. All hypernatremic states increase serum osmolality. Similar to hyponatremia, hypernatremia may occur in the presence of high, normal, or low total body water content.[2,3,6]

The clinical manifestations of hypernatremia primarily involve the neurological system. These manifestations are the consequence of dehydration, particularly in the brain. In adults acute elevation in serum sodium above 160 mEq/L (>160 mmol/L) is associated with a 75% mortality rate. Unfortunately, neurological sequelae are common even in survivors. To assess the etiology of hypernatremia, it is important to determine (1) urine production; (2) sodium intake; and (3) renal solute concentrating ability, which reflects ADH activity.

Hypernatremia associated with low total body water occurs when the loss of water exceeds the loss of sodium.[3] The thirst mechanism generally increases water intake, but this adjustment is not always possible (e.g., institutionalized elderly patients). This condition also may be iatrogenic when hypotonic fluid losses (e.g., profuse sweating and diarrhea) are replaced with an excessive amount of salt-containing fluids. In these circumstances, fluid loss should be replaced with IV dextrose solutions or hypotonic saline solutions, which serve as a source of free water.[3,5] In hypernatremic patients presenting with high urine osmolality (>800 mOsm/L, roughly equivalent to a specific gravity of 1.023) and low urine sodium concentrations (<10 mEq/L), these laboratory results reflect an intact renal concentrating mechanism. Signs and symptoms of dehydration should be carefully examined. These include orthostatic hypotension, flat neck veins, tachycardia, poor skin turgor, and dry mucous membranes. In addition, the BUN: SCr ratio may be >20 secondary to dehydration.[2,5]

Hypernatremia may be associated with normal total body water, also known as *euvolemic hypernatremia*. This condition refers to an increased loss of free water without concurrent sodium loss.[2] Because of water redistribution between the intracellular and extracellular fluid, no plasma volume contraction is usually evident unless water loss is substantial. Etiologies include increased insensible water loss (e.g., fever, extensive burns) and central and nephrogenic DI. The clinician should be aware of drugs that may cause nephrogenic DI (Table 12-5).[2,5]

Free water supplementation by mouth or IV fluid administration with dextrose 5% is necessary for correcting hypernatremia and preventing hypovolemia. If the diagnosis of DI is subsequently established, vasopressin or desmopressin, a synthetic analog of vasopressin, will be a reasonable option for long-term maintenance therapy.

Hypernatremia also may be associated with high total body water. This form of hypernatremia is the least common because sodium homeostasis is maintained indirectly through the control of water, and defects in the system usually affect total body water more than total body sodium.[3] This form of hypernatremia usually results from exogenous administration of solutions containing large amounts of sodium:

- Resuscitative efforts using hypertonic sodium bicarbonate
- Inadvertent IV infusion of hypertonic saline solutions (i.e., solutions >0.9% sodium chloride)
- Inadvertent dialysis against high sodium-containing solutions
- Sea water, near drowning

Primary hyperaldosteronism and Cushing syndrome may also cause this form of hypernatremia. Large quantities of sodium can be found in the urine of these patients. Signs and symptoms include diminished skin turgor and elevated plasma proteins.[3,5] (**Minicase 2**.)

Potassium

Normal range: 3.8–5.0 mEq/L (3.8–5.0 mmol/L)

Potassium is the primary cation in the intracellular space, with an average intracellular fluid concentration of about 140 mEq/L (140 mmol/L). The major physiological role of potassium is in the regulation of muscle and nerve excitability. It may also play important roles in the control of intracellular volume (similar to the ability of sodium in controlling extracellular volume), protein synthesis, enzymatic reactions, and carbohydrate metabolism.[7,8]

Physiology

The most important aspect of potassium physiology is its effect on action potential, especially on muscle and nervous tissue excitability.[2] During periods of potassium imbalance, the cardiovascular system is of principal concern. Cardiac muscle cells depend on their ability to change their electrical potentials, with accompanying potassium flux when exposed to the proper stimulus, to result in muscle contraction and nerve conduction.[7,8] One important aspect of potassium homeostasis is its distribution equilibrium. In a 70-kg man, the total body potassium content is about 4000 mEq. Of that amount, only a small fraction (about 60 mEq) is distributed in the extracellular fluid; the remainder resides within cells. The average daily Western diet contains 50–100 mEq of potassium, which is completely and passively absorbed in the upper gastrointestinal (GI) tract. To enter cells, potassium must first pass through the extracellular compartment.

If the serum potassium concentration rises above 6 mEq/L (>6 mmol/L), symptomatic hyperkalemia is expected. Potassium homeostasis is altered by insulin, aldosterone, changes in acid–base balance, renal function, or GI and skin losses.

MINICASE 2

A Case of Hypernatremia After Resection of Pituitary Tumor

Theresa L., a 49-year-old woman with a recently diagnosed pituitary tumor, has been admitted to the hospital two days ago for tumor resection. On postoperative day 2, she complains that she feels thirsty and a little dizzy. The nurse reports that she has been asking for water throughout the morning. She also has used the bathroom four times this morning.

Current vital signs: SBP/DBP 108/80 mm Hg supine; 105/80 mm Hg lying down; HR 84–90 beats/min; RR 10–14 breaths/min; SpO_2 (saturation of peripheral oxygen via pulse oximetry) 99% on room air; breathing comfortably. Intake (last 24 hours): five 8-oz glasses of water, 200 mL juice from breakfast, and 2 cups of hot tea.

Output: 3130 mL of urine in the last 16 hours; weight: 63.7 kg today (64.2 kg yesterday; 64.7 kg preoperative).

Laboratory results: sodium 155 mEq/L, potassium 3.2 mEq/L, chloride 101 mEq/L, BUN 18 mg/dL, CO_2 content 24 mEq/L, creatinine 1 mg/dL, glucose 72 mg/dL. Urine osmolality 105 mOsm/kg H_2O; urine specific gravity 1.001.

QUESTION: How would you interpret this patient's serum sodium concentration?

DISCUSSION: The patient's serum sodium concentration is elevated, suggesting hypernatremia. The next step is to assess her fluid status and determine the cause(s) of the disorder(s). Based on the history, she has an unusually high urine output (over 3 L in 16 hours and frequent urination). Her urine osmolality and specific gravity show that she has diluted urine. This suggests that an excessive loss of free water likely has contributed to her hypernatremia. She is currently not dehydrated (based on her vital signs, BUN–SCr ratio) because she has been able to catch up with her urinary fluid loss with oral fluid Intake due to thirst. Her weight change suggests that she is trending toward a mild fluid deficit. Thus, she can be described as having normovolemic hypernatremia.

The onset of her hypernatremia is likely acute because it occurred within two days after her surgery. Her symptom of hypernatremia is limited to dizziness. Surgical procedures that could potentially affect pituitary gland functions are a major risk factor for sodium disorders because the release and regulation of ADH may be affected. In this patient's case, the supraopticohypophyseal tract was likely affected during removal of the tumor and this precipitated the symptoms and signs that are currently observed. The elevated urine output with persistent thirst suggests that an ADH-related disorder, DI, is likely present with a serious risk of altered sodium homeostasis. Her relatively normal vital signs were maintained by her ability to temporarily increase oral fluid intake. But if the DI defect is not corrected, she will develop hypovolemia very quickly. This is an acute medical problem, and the diagnosis should be established quickly with the help of several laboratory tests such as urine sodium, serum sodium, and urine osmolality.

In summary, this patient has hypernatremia, which appears to be manifested by altered renal water/salt regulation based on the urine electrolyte and osmolality. Although her volume status appears normal at this point, she can quickly develop hypovolemia if she is unable to keep up with the oral fluid intake. The cause of hypernatremia is likely related to the pituitary gland resection that caused DI. The logical treatment approach for her will involve free water provision to prevent free water deficit, as well as treating DI. If her oral water intake is unable to match the urinary water loss, she will require concurrent IV fluid therapy to prevent severe dehydration.

These conditions can be modulated by various pathological states as well as pharmacotherapy. Although potassium may affect different bodily functions, its effect on cardiac muscle is by far the most important clinical monitoring parameter. Life-threatening arrhythmias may result from either high or low serum potassium concentrations.[3,6-10]

Renal Homeostasis

When the serum potassium concentration is high, the body has two different mechanisms to restore potassium balance. One quick way is to shift the plasma potassium into cells, while the other slower mechanism is renal elimination.[10] The kidneys are the primary organs involved in the control and elimination of potassium. Potassium is freely filtered at the glomeruli and almost completely reabsorbed before the filtrate reaches the collecting tubules. However, an amount equal to about 10% of the filtered potassium is secreted into the urine at the distal and collecting tubules. Virtually all the potassium recovered in urine is, therefore, delivered via tubular secretion rather than glomerular filtration.[7]

In the distal tubule, potassium is secreted into the tubule, while sodium is reabsorbed. There are several mechanisms that can modulate this sodium–potassium exchange. Aldosterone plays an important role because it increases potassium secretion into the urine (**Figures 12-1** and **12-3**).[10] The hormone is secreted by the adrenal glands in response to high serum potassium concentrations. The delivery of large quantities of sodium and fluid to the distal tubules may also cause potassium secretion and its subsequent elimination, as seen in diuretic-induced hypokalemia.[11] As the delivery of sodium and fluid is decreased, potassium secretion declines.

The presence of other anions in the distal tubules can increase renal potassium loss because the negatively charged anions attract positively charged potassium ions. This mechanism is responsible for hypokalemia caused by renal tubular acidosis and the administration of high doses of drugs as sodium salts (e.g., sodium penicillin, disodium ticarcilin.[10] Potassium secretion also is influenced by the potassium concentration in distal tubular cells. When the intracellular potassium concentration is high, such as during dehydration,

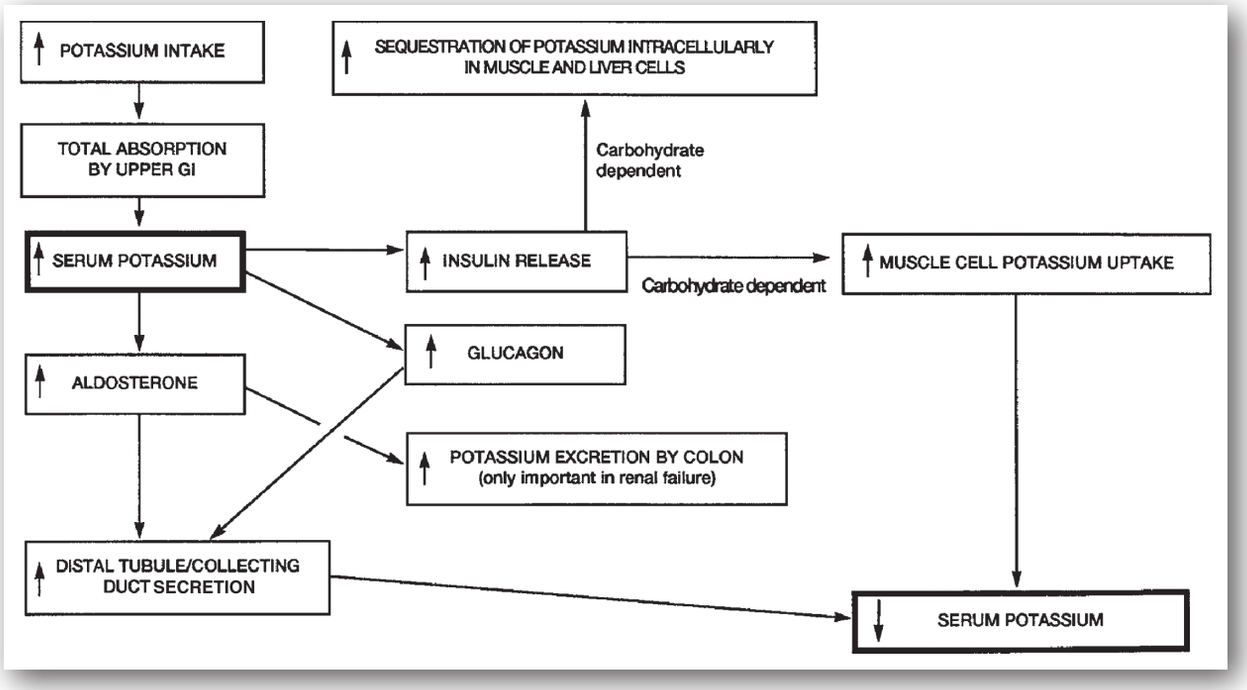

FIGURE 12-3. The acute homeostatic sequence of events in the body to maintain serum potassium within a narrow concentration range. An increased serum potassium will trigger an increase in aldosterone secretion, which increases distal tubular potassium secretion. In patients with hyperkalemia and renal failure, aldosterone will increase colonic potassium excretion. In patients with hyperkalemia and hyperglycemia, administration of insulin can shift potassium from the intravascular space into cells.

potassium secretion into the urine is increased. The modulation of renal potassium excretion by these mechanisms may take hours to correct a serum potassium concentration, even during drastic, acute changes. Extrarenal mechanisms, therefore, often play important roles in keeping the serum potassium concentration within the narrow acceptable range. Although the kidneys are the primary route of elimination, potassium secretion into the colon becomes important in patients with advanced renal failure.[10]

Acid–Base Homeostasis

Another potentially relevant factor influencing renal potassium secretion is serum pH. When arterial pH increases due to metabolic alkalosis, a compensatory efflux of hydrogen ions from the cells into the extracellular fluid (bloodstream) takes place with a concurrent influx of potassium ions into the cells to maintain an electropotential gradient.[7] During the early phase of metabolic alkalosis, the serum potassium concentration is transiently reduced due to a pH-dependent intracellular influx of serum potassium from the serum without altering the total body amount. Thus, although there is no immediate change in the amount of total body potassium, this movement of ions increases the cellular potassium content and results in hypokalemia. However, a shift in potassium and hydrogen ions also takes place in the renal distal tubular cells. In the presence of persistent alkalemia, renal potassium secretion into the urine is increased. Over time, the serum potassium concentration declines through increased renal loss, resulting in a reduced body store.

Metabolic acidosis has the opposite effect. Decreased pH results in an extracellular shift of potassium as a result of an intracellular shift of hydrogen ions, causing an elevated serum potassium concentration.[7] Because the intracellular potassium content of the distal tubular cell is decreased, secretion of potassium in the urine is diminished. Chronically, however, renal potassium loss gradually increases due to unknown mechanisms.

When a severe metabolic acid–base abnormality exists, adjustment of the measured serum potassium concentration may be necessary to more accurately assess body potassium status. For every 0.1 unit reduction in arterial pH from 7.4, roughly 0.6 mEq/L (range: 0.2–1.7 mEq/L) could be added to the serum potassium value:

$$K_{corr} = ([7.4 - pH]/0.1 \times 0.6\ mEq/L) + K_{uncorr}$$

where K_{corr} is the corrected serum potassium concentration and K_{uncorr} is the uncorrected or measured serum potassium concentration.[7] It is important to note that K_{corr} is a hypothetical value and only reflects what the serum potassium concentration would be if the serum pH is normalized and in the absence of other factors affecting potassium homeostasis. As long as the serum pH remains abnormal, the measured serum potassium concentration (K_{uncorr}) is the true reflection of actual serum potassium concentration. The K_{corr} value should always be assessed together with the actual serum potassium concentration and the patient's clinical presentation. The clinical value of calculating K_{corr} is mostly to avoid overcorrection of potassium based solely on K_{uncorr}, as well as to provide a more

complete picture that reflects total potassium stores in the body. Clinicians should remember that regardless of the value of K_{corr}, a patient with a significantly abnormal measured (uncorrected) serum potassium concentration is still at risk for developing cardiac arrhythmias.

Acute Homeostasis

Figure 12-3 summarizes the acute homeostatic mechanism involved in potassium distribution. During hyperkalemia, along with the release of aldosterone, increased glucagon and insulin release also contribute to reducing the serum potassium concentration. Glucagon stimulates potassium secretion into the distal tubules and collecting ducts, while insulin promotes intracellular potassium uptake. Although insulin is not a major controlling factor in potassium homeostasis, it is useful for the emergency treatment of hyperkalemia.[7,12]

Pharmacological stimulation of β-2 adrenergic receptors may also affect the transcellular equilibrium of potassium. It leads to the movement of potassium from extracellular fluid to the intracellular fluid compartment. Therefore, β-2 adrenergic agonists (e.g., albuterol) can be used short term to treat certain hyperkalemic patients.[7-9]

Hypokalemia

Hypokalemia is defined as a serum potassium concentration <3.8 mEq/L (<3.8 mmol/L).[10] To interpret the significance of low potassium values, clinicians should determine whether hypokalemia is due to intracellular shifting of potassium (apparent deficit) or increased loss from the body (true deficit) (**Table 12-6**). Intracellular shifting occurs as a result of metabolic alkalosis, after administration of insulin, or giving large doses of β-2 adrenergic agonists (e.g., continuous or hourly use of albuterol in ICU patients receiving mechanical ventilation).[9,13] Increased elimination of potassium can occur in the kidneys or GI tract. There may be decreased potassium reabsorption in the proximal tubules or increased secretion in the distal tubules and collecting ducts.[10]

Amphotericin B. Proximal tubular damage can occur with amphotericin B therapy, resulting in renal tubular acidosis. Amphotericin B directly impairs the reabsorption of potassium, magnesium, and bicarbonate and leads to hypokalemia, hypomagnesemia, and metabolic acidosis.[7,13] A concurrent deficiency in magnesium may affect the ability to restore potassium balance. Magnesium functions as a cofactor to maintain the sodium–potassium adenosine triphosphate (ATP) pump activity and facilitates renal preservation of potassium. A patient with concurrent hypokalemia and hypomagnesemia will not respond to potassium replacement therapy effectively unless magnesium balance is restored.[7,8,12] Lipid formulations of amphotericin B may still affect potassium homeostasis, although the magnitude may be less severe and the presentation is less acute.

Diuretics. Nonpotassium-sparing diuretic agents are drugs most commonly associated with renal potassium wasting. Although their mechanisms of natriuretic action differ, diuretic-induced hypokalemia is primarily caused by increased secretion of potassium at the distal sites in the nephron in response to an increased load of exchangeable sodium.

TABLE 12-6. Etiologies of Hypokalemia

Apparent deficit—intracellular shifting of potassium
Alkalemia
β-2 adrenergic stimulation
Insulin (more common with IV bolus or infusion)
True deficit
Decreased intake
Alcoholism
Potassium-free IV fluids
Anorexia nervosa
Bulimia
Increased output (extrarenal)
Vomiting
Diarrhea
Laxative abuse
Intestinal fistulas
Renal loss
Corticosteroids- especially fludrocortisone and hydrocortisone
Amphotericin B
Loop and thiazide diuretics
Hyperaldosteronism
Cushing syndrome
Licorice ingestion
Patiromer

IV = intravenous.

Diuretics increase the distal urinary flow by inhibiting sodium reabsorption. This increased delivery of fluid and sodium in the distal segment of the nephron results in an increase in sodium reabsorption at that site. To maintain a neutral electropotential gradient in the lumen, potassium is excreted as sodium is reabsorbed. Therefore, any inhibition of sodium absorption by diuretics proximal to or at the distal tubules can increase potassium loss. Renal potassium excretion is further enhanced when nonabsorbable anions are present in the urine.

Loop diuretics (e.g., furosemide) or thiazides (e.g., hydrochlorothiazide) are associated with hypokalemia and the effect is dose-dependent. Serum potassium concentrations should be monitored regularly, especially in patients receiving high doses of loop diuretics, to avoid the increased risk of cardiovascular events secondary to hypokalemia and other electrolyte imbalances. In addition, elderly patients with ischemic heart disease and patients receiving digoxin are more susceptible to the adverse consequences of hypokalemia.[15-17] Other drugs commonly used in managing hypertension and other cardiac diseases such as spironolactone, triamterene, amiloride, eplerenone, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor antagonists are not expected to cause potassium loss due to their mode of action. On the contrary, they cause retention of potassium due to their effects related to aldosterone-dependent exchange sites in the collecting tubules.[11,18]

Other causes. Conditions that cause hyperaldosteronism, either primary (e.g., adrenal tumor) or secondary (e.g., renovascular hypertension), can produce hypokalemia.[13] Cushing syndrome leads to increased circulation of mineralocorticoids such as aldosterone. Corticosteroids with strong mineralocorticoid activity (e.g., fludrocortisone and hydrocortisone) also can cause hypokalemia.[10]

GI loss of potassium can be important. Aldosterone influences both renal and intestinal potassium handling.[10] A decrease in extracellular volume increases aldosterone secretion, which promotes renal and colonic potassium wasting. The potassium concentration in the GI fluid varies depending on the location of the GI tract ranging from 5 mEq/L (bile, duodenum) to 30 mEq/L (colon). Therefore, profuse and uncontrolled diarrhea can result in potassium depletion. In contrast, upper GI secretion contains a much lower amount of potassium, and loss secondary to vomiting is unlikely to be significant. However, with severe vomiting, the resultant metabolic alkalosis may lead to hypokalemia due to intracellular shifting of potassium and enhanced urinary elimination. Finally, patients receiving potassium-free parenteral fluids can develop hypokalemia if not monitored properly.[7,10]

Clinical diagnosis. Signs and symptoms of hypokalemia involve many physiological systems. Abnormalities in the cardiovascular system may result in serious consequences (i.e., disturbances in cardiac rhythm). Hypokalemia-induced arrhythmias are of particular concern in patients receiving digoxin. Both digitalis glycosides and hypokalemia inhibit the sodium–potassium ATP pump in the cardiac cells. Together, they can deplete intracellular potassium, which may result in fatal arrhythmias. The signs and symptoms of hypokalemia are listed in **Table 12-7**. Skeletal muscle weakness is often seen; severe depletion may lead to decreased reflexes and paralysis. Death can occur from respiratory muscle paralysis.[7,9,19]

Hyperkalemia

Hyperkalemia is defined as a serum potassium concentration >5 mEq/L (>5 mmol/L). As with hypokalemia, hyperkalemia may indicate a true or apparent potassium imbalance, although the signs and symptoms are indistinguishable.[10] To interpret a high serum potassium value, the clinician should determine whether hyperkalemia is due to apparent excess caused by extracellular shifting of potassium or true potassium excess in the body caused by increased intake with diminished excretion (**Table 12-8**).[4,6,9,11]

Causes. Because renal excretion is the major route of potassium elimination, renal failure is the most common cause of hyperkalemia. However, potassium handling by the nephrons is relatively well-preserved until the GFR falls to <10% of normal. Therefore, many patients with renal impairment can maintain a near normal, serum potassium concentration. They are still prone to developing hyperkalemia if excessive potassium is consumed and when renal function deteriorates.[9,12]

Increased potassium intake rarely causes any problem in subjects in the absence of significant renal impairment. With normal renal function, increased potassium intake will lead

TABLE 12-7. Signs, Symptoms, and Effects of Hypokalemia on Various Organ Systems

Cardiovascular
Decrease in T-wave amplitude
Development of U waves
Hypotension
Increased risk of digoxin toxicity
PR prolongation (with severe hypokalemia)
Rhythm disturbances
ST segment depression
QRS widening (with severe hypokalemia)
Metabolic/endocrine (mostly serve as compensatory mechanisms)
Decreased aldosterone release
Decreased insulin release
Decreased renal responsiveness to antidiuretic hormone
Neuromuscular
Areflexia (with severe hypokalemia)
Cramps
Loss of smooth muscle function (ileus and urinary retention with severe hypokalemia)
Weakness
Renal
Inability to concentrate urine
Nephropathy

TABLE 12-8. Etiologies of Hyperkalemia

Extracellular shifting of potassium associated with acidemia
True excess
Increased release of Intracellular potassium into blood stream
Hemolysis
Rhabdomyolysis
Muscle crush injuries
Burns
Increased total body potassium
Increased potassium intake (e.g., salt substitute, diet)
Decreased output or increased retention
Chronic or acute renal failure
Drugs
Potassium-sparing diuretics
Angiotensin-converting enzyme inhibitors
Nonsteroidal anti-inflammatory agents
Angiotensin II receptor antagonists
Unfractionated heparin
Trimethoprim (including drugs such as co-trimoxazole)
Deficiency of adrenal steroids
Addison disease

to increased renal excretion and redistribution to the intracellular space through the action of aldosterone and insulin, respectively. Interference with either mechanism may result in hyperkalemia. Decreased aldosterone secretion can occur with Addison disease or other defects affecting the hormone's adrenal output.[7,12] Pathological changes affecting the proximal or distal renal tubules also can lead to hyperkalemia.[7,12]

Use of potassium-sparing diuretics (e.g., spironolactone) is a common cause of hyperkalemia, especially in patients with renal function impairment. Concurrent use of potassium supplements (including potassium-rich salt substitutes) also will increase the risk. Similar to hypokalemia, hyperkalemia can result from transcellular shifting of potassium. In the presence of severe acidemia, potassium shifts from the intracellular to the extracellular space, which may result in a clinically significant increase in the serum potassium concentration.[10]

Clinical diagnosis. The cardiovascular manifestations of hyperkalemia are of major concern. They include cardiac rhythm disturbances, bradycardia, hypotension, and, in severe cases, cardiac arrest. At times, muscle weakness may occur before these cardiac signs and symptoms. To appreciate the potent effect of potassium on the heart, one has to realize that potassium is the principal component of cardioplegic solutions commonly used to arrest the rhythm of the heart during cardiac surgeries.[7,9,12]

Causes of spurious laboratory results. Several conditions will result in fictitious hyperkalemia in which the high serum concentration reported is not expected to have any significant clinical sequelae. Erythrocytes, similar to other cells, have high potassium content. When there is substantial hemolysis in the specimen collection tube, the red cells will release potassium in quantities large enough to produce misleading results. Hemolysis may occur when a very small needle is used for blood draw, the tourniquet is too tight, or when the specimen stands too long or is mishandled. When a high serum potassium concentration is reported in a patient without pertinent signs and symptoms, the test needs to be repeated to rule out hemolysis.[6,7,10]

A similar phenomenon can occur when the specimen is allowed to clot (when nonheparinized tubes are used) because platelets and white cells are also rich in potassium. In patients with leukemia or thrombocytosis, the potassium concentration should be obtained from plasma rather than serum samples. The normal plasma potassium concentration is 0.3–0.4 mEq/L lower than the serum values.

Management of chronic hyperkalemia includes decreasing dietary intake of potassium, discontinuing medications that increase serum potassium. For rapid correction of acute, symptomatic hyperkalemia, measures include: correcting metabolic acidosis with IV sodium bicarbonate; administering IV glucose and insulin or inhaled β-adrenergic agonists to shift potassium from the intravascular to the intracellular space; using high doses of loop diuretics to enhance renal excretion of potassium; administering sodium polystyrene sulfonate to increase colonic elimination of potassium; or initiating dialysis in the most severe cases. (**Minicase 3**.)

Chloride

Normal range: 95–103 mEq/L (95–103 mmol/L)

Physiology

Chloride is the most abundant extracellular anion with a low intracellular concentration (about 4 mEq/L). Chloride is passively absorbed from the upper small intestine. In the distal ileum and large intestine, its absorption is coupled with bicarbonate ion secretion. Chloride is primarily regulated by the renal proximal tubules, where it is exchanged for bicarbonate ions. Throughout the rest of the nephron, chloride passively follows sodium and water. In addition, the luminal and interstitial Cl/HCO_3 exchangers in the collecting duct also contribute to the renal regulation of chloride.

Chloride is influenced by the extracellular fluid balance and acid–base balance.[19,20] Although homeostatic mechanisms do not directly regulate chloride, they indirectly regulate it through changes in sodium and bicarbonate. The physiological role of chloride is primarily passive. It balances out positive charges in the extracellular fluid and, by passively following sodium, helps to maintain extracellular osmolality.

Hypochloremia and Hyperchloremia

Serum chloride values are used as confirmatory tests to identify fluid balance and acid–base abnormalities.[21] Like sodium, a change in the serum chloride concentration does not necessarily reflect a change in total body content. Rather, it indicates an alteration in fluid status and acid–base balance. One of the most common causes of hyperchloremia in hospitalized patients results from saline infusion. Chloride has the added feature of being influenced by bicarbonate. Therefore, it would be expected to decrease to the same proportion as sodium when serum is diluted with fluid and to increase to the same proportion as sodium during dehydration. However, when a patient is on acid-suppressive therapy (e.g., high-dose H2-blockers or proton pump inhibitors), has been receiving continuous or frequent nasogastric suction, or has profuse vomiting, a greater loss of chloride than sodium can occur because gastric fluid contains 1.5–3 times more chloride than sodium. Gastric outlet obstruction, protracted vomiting and self-induced vomiting also can lead to hypochloremia.

Drug and parenteral nutrition causes. Even though drugs can influence serum chloride concentrations, they rarely do so directly. For example, although loop diuretics (e.g., furosemide) and thiazide diuretics (e.g., hydrochlorothiazide) inhibit chloride uptake at the loop of Henle and distal nephron, respectively, the hypochloremia that may result is due to the concurrent loss of sodium and contraction alkalosis.[18,21] Because chloride passively follows sodium, salt and water retention can transiently raise serum chloride concentrations. This effect occurs with corticosteroids, and nonsteroidal anti-inflammatory agents (NSAIDs) such as ibuprofen. Also, parenteral nutrition solutions with high chloride concentrations are associated with an increased risk of hyperchloremia. Acetate or phosphate salts used in place of chloride salts (e.g., potassium chloride) reduce this risk. Acetazolamide also can cause hyperchloremia.

MINICASE 3

A Case of Hyperkalemia

Gary O., a 68-year-old man, is admitted to the cardiology service for further workup of dyspnea and shortness of breath. His chief complaints include worsening of shortness of breath in the last two days, swelling of his legs, and the need for extra pillows before he can go to bed for the past week. He experiences worsening fatigue and dyspnea with ordinary activities.

He admits to skipping his furosemide doses for the past two to three days because he does not like going to the bathroom all the time. He has been told that he needs furosemide for worsening shortness of breath. Otherwise, he takes his other medications "religiously."

Past medical history includes congestive heart failure (ejection fraction of 31% checked 5½ months ago), chronic atrial fibrillation, and type 2 diabetes mellitus.

Home medications: carvedilol 12.5 mg q 12 hr, furosemide 60 mg PO every morning and 20 mg every evening, glargine insulin 30 units daily, lisinopril 40 mg twice daily, potassium chloride 20 mEq PO daily, spironolactone 12.5 mg daily, and warfarin 5 mg daily.

Vital signs on admission: BP 110/78 mm Hg, HR 69 beats/min (baseline BP 118/82 mm Hg, and HR 68 beats/min); and weight: 80 kg (four weeks ago, clinic record), 90 kg (on admission).

Laboratory results: BNP: 532 pg/mL, sodium 133 mEq/L, potassium 5.7 mEq/L, chloride 101 mEq/L, CO_2 content 22 mEq/L, BUN 37 mg/dL, creatinine 2.1 mg/dL, (baseline creatinine 1.5 mg/dL), and glucose 72 mg/dL.

Other tests: EKG, atrial fibrillation, unchanged from baseline; oxygen saturation 92% on room air.

QUESTION: How would you interpret this patient's serum potassium concentration?

DISCUSSION: His serum potassium concentration, at 5.7 mEq/L is elevated. It is possible that his baseline potassium concentration is mildly elevated because there are several factors that would contribute to hyperkalemia: (1) he is taking a potassium supplement; (2) he is taking two drugs that can increase serum potassium—spironolactone and lisinopril; and (3) he has been renal insufficiency at baseline (creatinine 1.5 mg/dL). It is likely that his potassium concentration has increased more significantly in the last two days. His current state of hyperkalemia is likely exacerbated by two recent events: (1) nonadherence with furosemide in the last three days, which results in decreased renal potassium loss; and (2) worsening of heart failure (as suggested by increased BNP, weight gain of 10 kg, and increased leg swelling), which in turn decreases renal blood flow and results in worsening of acute renal failure (as suggested by an increased serum creatinine from 1.5–2.1 mg/dL)

The primary goal for managing hyperkalemia is to prevent/reverse cardiac symptoms. With a serum potassium of 5.7 mEq/L, there is a definite risk for arrhythmias. Therefore, a 12-lead EKG should be performed. If EKG changes are present and consistent with hyperkalemia, interventions that will decrease serum potassium concentration, such as IV insulin and dextrose or IV sodium bicarbonate, should be initiated right away. IV calcium (calcium gluconate 1 g) also should be administered to reduce the risk of arrhythmias. Regardless of the cardiac symptoms, his potassium supplement should be withheld. Because his blood pressure is not elevated, it also is reasonable to withhold spironolactone for now until the potassium concentration starts to decline.

In summary, this patient has hyperkalemia, most likely exacerbated by acute renal failure and continued use of a potassium supplement. Assessment of symptoms and signs of hyperkalemia should be performed as soon as possible.

Acid–base status and other causes. Acid–base balance is partly regulated by renal production and excretion of bicarbonate ions. The proximal tubules are the primary regulators of bicarbonate. These cells exchange bicarbonate with chloride to maintain the intracellular electropotential gradient. Renal excretion of chloride increases during metabolic alkalosis, resulting in a reduced serum chloride concentration.

The opposite situation also may be true: metabolic or respiratory acidosis results in an elevated serum chloride concentration. Hyperchloremic metabolic acidosis is not common but may occur when the kidneys are unable to conserve bicarbonate, as in interstitial renal disease (e.g., obstruction, pyelonephritis, and analgesic nephropathy), GI bicarbonate loss (e.g., cholera and staphylococcal infections of the intestines), and acetazolamide-induced carbonic anhydrase inhibition. Falsely elevated chloride is rare but may occur with bromide toxicity due to an inability to distinguish between these two halogens by the laboratory's chemical analyzer. Because the signs and symptoms associated with hyperchloremia and hypochloremia are related to fluid status or the patient's acid–base status and its underlying causes, rather than to chloride itself, the reader is referred to discussions in Chapter 13.

OTHER MINERALS

Magnesium

Normal range: 1.7–2.4 mg/dL (0.7–0.99 mmol/L) or 1.4–2 mEq/L

Physiology

Magnesium has a widespread physiological role in maintaining neuromuscular functions and enzymatic functions. Magnesium acts as a cofactor for phosphorylation of ATPs from adenosine phosphates. Magnesium also is vital for binding macromolecules to organelles (e.g., messenger ribonucleic acid to ribosomes).

The average adult body contains 21–28 g (1750–2400 mEq) of magnesium with the following distribution:

- About 50% in bone (about 30% or less of this pool is slowly exchangeable with extracellular fluid)
- 20% in muscle
- Around 10% in nonmuscle soft tissues
- 1–2% in extracellular fluid (for plasma magnesium, about 50% is free; approximately 15% is complexed to anions; and 30% is bound to protein, primarily albumin)

Approximately 30–40% of the ingested magnesium is absorbed from the jejunum and ileum through transcellular and paracellular mechanisms. Both passive diffusion down an electrochemical gradient and active transport process are involved. The extent of magnesium absorption may be affected by dietary magnesium intake, calcium intake, vitamin D, and PTH. However, conflicting data are available and the extent of these parameters in affecting absorption is unresolved. Certain medications (e.g., cyclosporine, tacrolimus, cisplatin, amphotericin B) can significantly increase renal magnesium loss, predisposing the patient to hypomagnesemia.

Urinary magnesium accounts for one third of the total daily magnesium output, while the other two thirds are in the GI tract (e.g., stool). Unbound serum magnesium is freely filtered at the glomerulus. All but about 3–5% of filtered magnesium is normally reabsorbed (100 mg/day). In other words, 97% of the filtered magnesium is reabsorbed under normal physiology. Reabsorption is primarily through the ascending limb of the loop of Henle (50–60%). About 30% is reabsorbed in the proximal tubule and 7% from the distal tubule. This explains why loop diuretics have a profound effect on renal magnesium wasting. The drive of magnesium reabsorption is mediated by the charge difference generated by the sodium-potassium-chloride cotransport system in the lumen.

The regulation of magnesium is primarily driven by the plasma magnesium concentration. Changes in plasma magnesium concentrations have potent effects on renal reabsorption and stool losses. These effects are seen over three to five days and may persist for a long time. Hormonal regulation of magnesium seems to be much less critical for its homeostasis.

Factors affecting calcium homeostasis also affect magnesium homeostasis.[22] A decline in serum magnesium concentration stimulates the release of PTH, which increases serum magnesium by increasing its release from the bone store and renal reabsorption. Hyperaldosteronism causes increased magnesium renal excretion. Insulin by itself does not alter the serum magnesium concentration. But in a hyperglycemic state, insulin causes rapid intracellular uptake of glucose. This process causes an increase in the phosphorylation by sodium–potassium ATPase on the cell membrane. Because magnesium is utilized as a cofactor for sodium potassium ATPase, serum magnesium concentration declines, resulting in hypomagnesemia. Excretion of magnesium is influenced by serum calcium and phosphate concentrations. Magnesium movement generally follows that of phosphate (i.e., if phosphate declines, magnesium also declines) and is the opposite of calcium.[21,22]

Other factors that increase magnesium reabsorption include acute metabolic acidosis, hyperthyroidism, and chronic alcohol use. Magnesium also regulates neuromuscular function. Magnesium depletion results in neuromuscular weakness as the release of acetylcholine to motor endplates is enhanced by the presence of magnesium. Motor endplate sensitivity to acetylcholine also is affected. When serum magnesium decreases, acetylcholine release increases, resulting in increased muscle excitation and this may lead to increased reflexes. Common symptoms associated with hypomagnesemia include weakness, muscle fasciculation with tremor, tetany, and increased reflexes. In addition, vasodilation may occur by a direct effect on blood vessels and ganglionic blockade due to hypomagnesemia.

Hypomagnesemia

Hypomagnesemia is defined as a serum magnesium concentration <1.7 mg/dL (<0.7 mmol/L). The common causes of hypomagnesemia include renal wasting, chronic alcohol use, diabetes mellitus, protein-calorie malnutrition, refeeding syndrome, and postparathyroidectomy. Because serum magnesium deficiency can be offset by magnesium release from bone, muscle, and the heart, the serum value may not be a useful indicator of cellular depletion and complications (e.g., arrhythmias). However, low serum magnesium usually indicates low cellular magnesium as long as the patient has a normal extracellular fluid volume.[22,23]

Causes. Magnesium deficiency is more common than magnesium excess. Depletion usually results from excessive loss from the GI tract or kidneys (e.g., use of loop diuretics). Magnesium depletion is not commonly the result of decreased intake because the kidneys can cease magnesium elimination in four to seven days to conserve the ion. However, with chronic alcohol consumption, deficiency can occur from a combination of poor intake, poor GI absorption (e.g., vomiting or diarrhea), and increased renal elimination. Depletion also can occur from poor intestinal absorption (e.g., small-bowel resection). Diarrhea can be a source of magnesium loss because diarrhea stools may contain as much as 14 mEq/L (7 mmol/L) of magnesium. Chronic use of proton-pump inhibitors also has been linked to hypomagnesemia.

Urinary magnesium loss may result from diuresis or tubular defects, such as the diuretic phase of acute tubular necrosis. Some patients with hypoparathyroidism may exhibit low magnesium serum concentrations from renal loss and, possibly, decreased intestinal absorption. Other conditions associated with magnesium deficiency include hyperthyroidism, primary aldosteronism, diabetic ketoacidosis, and pancreatitis. Magnesium deficiency associated with these conditions may be particularly dangerous because often there are concurrent potassium and calcium deficiencies. Although loop diuretics lead to significant magnesium depletion, thiazide diuretics do not cause hypomagnesemia, especially at lower doses (<50 mg/day). Furthermore, potassium-sparing diuretics (e.g., spironolactone, triamterene, and amiloride), are also magnesium-sparing and have some limited clinical role in diuretic-induced hypokalemia and hypomagnesemia.[22,24]

Clinical diagnosis. Magnesium also affects the central nervous system (CNS). Magnesium depletion can cause personality changes, disorientation, convulsions, psychosis, stupor, and coma.[22,25] Severe hypomagnesemia may result in hypocalcemia due to intracellular cationic shifts. Many symptoms of magnesium deficiency result from concurrent hypocalcemia.

Perhaps the most important effects of magnesium imbalance are on the heart. Decreased magnesium in cardiac cells may manifest as a prolonged QT interval, which is associated with an increased risk of arrhythmias, especially torsades de pointes.[25] Moderately decreased concentrations can cause electrocardiogram (EKG) abnormalities similar to those observed with hypokalemia.

A 24-hour urine magnesium excretion test may be helpful in determining the magnitude of a total body magnesium deficiency. If the value is normal, the patient is not considered deficient as long as serum magnesium is also normal. The diagnosis of total body magnesium deficiency is established when the 24-hour urinary magnesium excretion is low even in the presence of normal serum magnesium concentration.

Hypermagnesemia

Hypermagnesemia is defined as a serum magnesium concentration >2.4 mg/dL (>0.99 mmol/L).

Causes. Besides magnesium overload (e.g., overreplacement of magnesium, treatment for preeclampsia, and antacid/laxative overuse), the most important risk factor for hypermagnesemia is renal dysfunction. Rapid infusions of IV solutions containing large amounts of magnesium, such as those given for myocardial infarction, preeclampsia, and status asthmaticus, may result in hypermagnesemia.

Clinical diagnosis. Plasma magnesium concentrations below 6 mg/dL (<2.5 mmol/L) rarely cause serious symptoms. Nonspecific symptoms, such as muscle weakness, decrease in deep tendon reflexes or fatigue, may be present. As magnesium concentration rises above 6 mg/dL, more notable symptoms such as lethargy, mental confusion, and hypotension may be observed (**Table 12-9**).[22,24,27] In severe hypermagnesemia (12 mg/dL), life-threatening symptoms, including coma, paralysis, or cardiac arrest, can be observed and urgent therapy is indicated.

Treatment for severe or symptomatic hypermagnesemia may include IV calcium gluconate 1–2 g over 30 minutes to reverse the neuromuscular and cardiovascular blockade of magnesium. Increased renal elimination of magnesium can be achieved by forced diuresis with IV saline hydration and a loop diuretic agent. Hemodialysis should be reserved as a last resort.

TABLE 12-9. Signs and Symptoms of Hypermagnesemia

6–8.5 mg/dL	5–7 mEq/L	Bradycardia, flushing, sweating, sensation of warmth, fatigue, drowsiness
8.5–12 mg/dL	7–10 mEq/L	Lower blood pressure, decreased deep-tendon reflexes, altered mental status possible
>12 mg/dL	>10 mEq/L	Flaccid paralysis and increased PR and QRS intervals, severe mental confusion, coma, respiratory distress and asystole

Calcium

Normal range: 9.2–11 mg/dL (2.3–2.8 mmol/L) for adults

Physiology

Calcium plays an important role in the propagation of neuromuscular activity; regulation of endocrine functions (e.g., pancreatic insulin release and gastric hydrogen secretion), blood coagulation including platelet aggregation, and bone and tooth metabolism.[2,28]

The serum calcium concentration is closely regulated by complex interactions among PTH, serum phosphate, vitamin D system, and the target organ (**Figure 12-4**). About one third of the ingested calcium is actively absorbed from the proximal area of the small intestine, facilitated by 1,25-dihydroxycholecalciferol (1,25-DHCC or calcitriol, the most active form of vitamin D). Passive intestinal absorption is negligible with intake of <2 g/day. The average daily calcium intake is 2–2.5 g/day.

The normal adult body contains about 1000 g of calcium, with only 0.5% found in the extracellular fluid; 99.5% is integrated into bones. Therefore, the tissue concentration of calcium is small. Because bone is constantly remodeled by osteoblasts and osteoclasts, a small quantity of bone calcium is in equilibrium with the extracellular fluid. Extracellular calcium exists in three forms:

1. Complexed to bicarbonate, citrates, and phosphates (6%)
2. Protein bound, mostly to albumin (40%)
3. Ionized or free fraction (54%)

Intracellular calcium. Imbalance of body calcium results in disturbances in muscle contraction and nerve action.[28] Within the cells, calcium maintains a low concentration. The calcium that is attracted into the negatively charged cell is either actively pumped out or sequestered by mitochondria or the endoplasmic reticulum. Such differences in concentrations allow calcium to be used for transmembrane signaling. In response to stimuli, calcium is allowed either to enter a cell or released from internal cellular stores where it interacts with specific intracellular proteins to regulate cellular functions or metabolic processes.[2,26,27] Calcium enters cells through one of the three types of calcium channels that have been identified: T (transient or fast), N (neuronal), and L (long lasting or slow). Subsets of these channels may exist. Calcium channel-blockers are likely to affect the L channels.[29]

In muscle, calcium is released from the intracellular sarcoplasmic reticulum. The released calcium binds to troponin and stops troponin from inhibiting the interaction of actin and myosin. This interaction results in muscle contraction. Muscle relaxation occurs when calcium is pumped back into the sarcoplasmic reticulum. In cardiac tissue, calcium becomes important during phase 2 of the action potential. During this phase, fast entry of sodium stops and calcium entry through the slow channels begins (**Figure 12-5**), resulting in contraction. During repolarization, calcium is actively pumped out of the cell.[2]

Calcium channel-blocking drugs (e.g., nifedipine, diltiazem, and verapamil) inhibit the movement of calcium into muscle cells, thus decreasing the strength of contraction. The areas

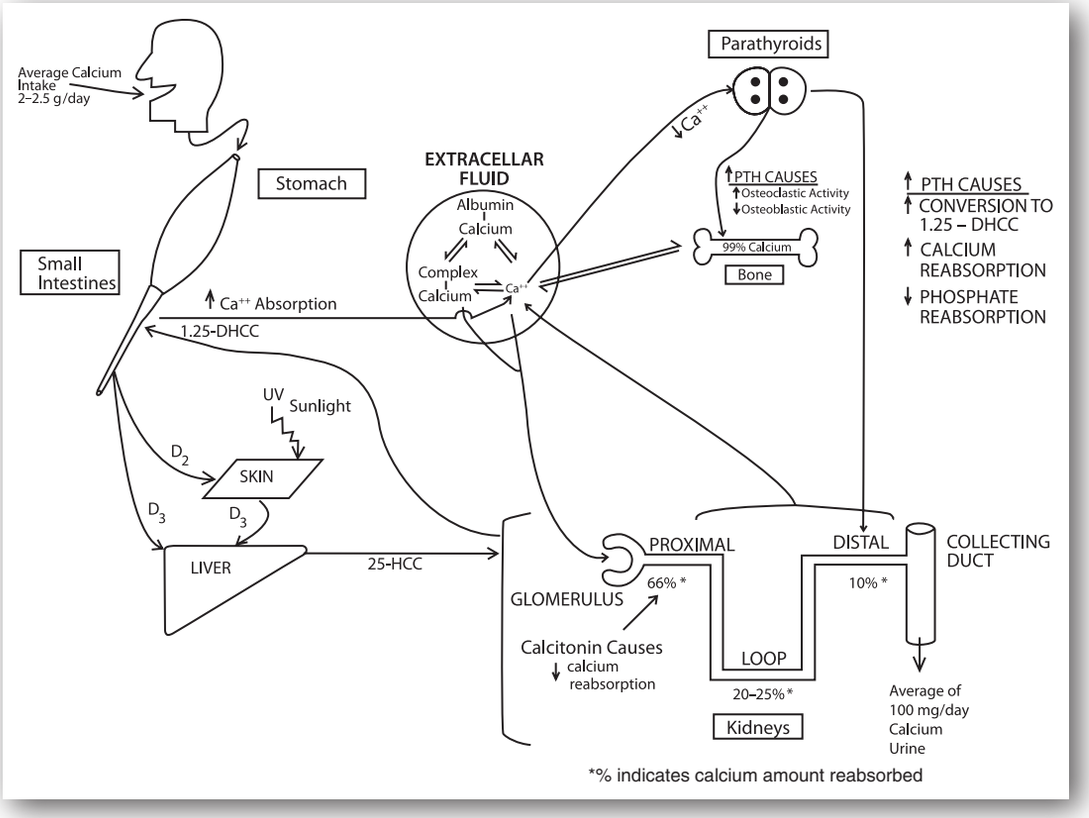

FIGURE 12-4. Calcium physiology: relationship with vitamin D, calcitonin, PTH, and albumin. The primary source of calcium is from diet. Absorption of calcium takes place in the small intestine. Vitamin D, more specifically, calcitriol or 1,25-DHCC, has the most potent effect on intestinal extraction of calcium. Once absorbed, calcium is transported in the extracellular fluid by albumin to various organs. Bones serve as an important reservoir for calcium. When serum calcium concentration decreases, PTH release is increased and it stimulates osteoclast activity, which releases calcium into the plasma to maintain normocalcemia. Calcium also is excreted renally. Only about 10% of dietary calcium is normally lost in the urine.

Although humans can synthesize a limited amount of vitamin D with optimal UVB exposure, the majority of vitamin D comes from the diet, which many include ergocalciferol (vitamin D_2, primarily from plants) and cholecalciferol (vitamin D_3, primarily from animal sources). The endogenous vitamin D formed by the body is cholecalciferol (D_3).

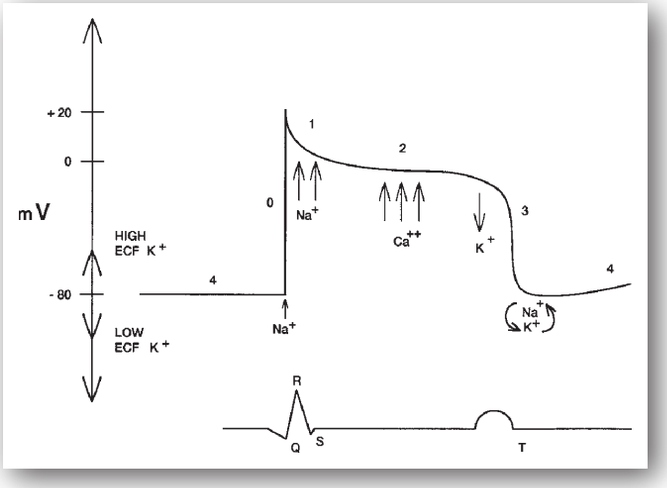

FIGURE 12-5. Cardiac intracellular potential and its relationship to the EKG.

that are most sensitive to these effects appear to be the sinoatrial and atrioventricular nodes and vascular smooth muscles, which explains the hypotensive effects of nifedipine.

Extracellular calcium. Complexed calcium usually accounts for <1 mg/dL (<0.25 mmol/L) of blood calcium. The complex usually is formed with bicarbonate, citrate, or phosphate. In patients with CKD, calcium also may be bound with sulfate because the anion is retained. Phosphate plays an important role in calcium homeostasis. Under normal physiological conditions, the product of calcium concentration and phosphate concentration (calcium–phosphate product) is relatively constant: an increase in one ion necessitates a corresponding decline in the other. In addition, many homeostatic mechanisms that control calcium also regulate phosphate. This relationship is particularly important in renal failure; the decreased phosphate excretion may ultimately lead, through a complex mechanism, to hypocalcemia, especially if the hyperphosphatemia is untreated.[30,31]

Protein-bound calcium is bound primarily to serum albumin (80%) and globulins (20%). Protein-bound calcium is in equilibrium with ionized calcium, which is affected by the serum anion concentration and blood pH. This equilibrium is important because ionized calcium is the physiologically active moiety. Alkalosis increases protein binding of calcium, resulting in a lower free fraction, whereas acidosis has the opposite effect. In patients with respiratory or metabolic alkalosis, the signs and symptoms of hypocalcemia may become more pronounced due to increased binding. Conversely, signs and symptoms of hypercalcemia become more apparent in patients with metabolic or respiratory acidosis. Therefore, total serum calcium concentration, which is commonly reported by clinical laboratories, is not as clinically significant as the quantity of available ionized calcium. In fact, it is the free calcium concentration that is closely regulated by the different homeostatic mechanisms.

Clinically, serum protein concentrations, especially albumin, have an important influence in regulating the amount of physiologically active calcium in the serum. The normal serum calcium range is 9.2–11 mg/dL (2.3–2.8 mmol/L) for a patient with a serum albumin of approximately 4 g/dL. In normal healthy adults, only 40–50% of the total serum calcium is free from protein-binding and thus considered as physiologically active. In patients with hypoalbuminemia (due to acute illnesses, severe malnutrition), the free concentration of calcium is elevated despite a "normal" total serum calcium concentration. Therefore, it is a common practice to either measure ionized calcium or to correct the total serum calcium concentration based on the measured albumin concentration. The following formula is commonly used in an attempt to "correct" total serum calcium concentration:

$$Ca_{corr} = ([4.0 - \text{albumin}] \times 0.8\ \text{mg/dL}) + Ca_{uncorr}$$

where Ca_{corr} is the corrected serum calcium concentration, and Ca_{uncorr} is the uncorrected (or measured total) serum calcium concentration. For example, a clinician may be asked to write parenteral nutrition orders for an emaciated cancer patient. The serum albumin is 1.9 g/dL (19 g/L), and the total serum calcium concentration is 7.7 mg/dL (1.9 mmol/L). At first glance, one might consider the calcium to be low. But with the reduced serum albumin concentration, more ionized calcium is available to cells.

$$Ca_{corr} = ([4.0 - 1.9] \times 0.8) + 7.7 = 9.4\ \text{mg/dL}\ (2.34\ \text{mmol/L})$$

The corrected serum calcium concentration is, thus, within the normal range. More importantly, the patient does not exhibit any signs and symptoms of hypocalcemia. Calcium supplementation is not indicated. In the presence of severe hypoalbuminemia, as in critically ill patients, an apparently low total serum calcium may in fact be sufficient or in some instances, excessive. Administration of IV albumin can lead to a significant decline in serum calcium concentration due to the resultant increased binding. The measured total calcium concentration will need to be corrected with the new albumin concentration.

Although this serum calcium correction method may be useful, the clinician must be aware of its limitations and potential for inaccuracy. The correction factor of 0.8 represents an average fraction of calcium bound to albumin under normal physiology. To have an accurate determination of the free concentration, a direct measurement of serum ionized calcium concentration should be available in most clinical laboratories (normal range: 4–4.8 mg/dL or 1–1.2 mmol/L). Ultimately, the patient's clinical presentation is the most important factor to determine if immediate treatment for a calcium disorder is indicated.

Although calcium absorption takes place throughout the entire small intestine, the proximal region of the small intestine (jejunum and proximal ileum) are the most active and regulated areas. Calcium absorption from the human GI tract is mediated by two processes: (1) transcellular active transport, a saturable, vitamin D–responsive process mediated by specific calcium binding proteins primarily in the upper GI tract, particularly in the distal duodenum and upper jejunum; and (2) paracellular processes, a nonsaturable linear transfer via diffusion that occurs throughout the entire length of the intestine. Under normal physiology, the total calcium absorptive capacity is the highest in the ileum because of the longer residence time. The rate of paracellular calcium absorption is fairly stable regardless of calcium intake. However, when dietary calcium intake is relatively limited, the efficiency of transcellular calcium transport becomes higher and accounts for a significant fraction of the absorbed calcium. Transcellular calcium transport is closely regulated by vitamin D, although other mechanisms also may be involved. Specifically, 1,25-DHCC induces the intestinal expressions of transcellular calcium transporters through its binding with the vitamin D receptors (VDR) in the intestinal epithelial cells.

Effect of vitamin D. A small amount of calcium is excreted daily into the GI tract through saliva, bile, and pancreatic and intestinal secretions. However, the primary route of elimination is filtration by the kidneys. Calcium is freely filtered at the glomeruli, where approximately 65% is reabsorbed at the proximal tubules under partial control by calcitonin and 1,25-DHCC. Roughly 25% is reabsorbed in the loop of Henle, and another 10% is reabsorbed at the distal tubules under the influence of PTH.

Despite being classified as a vitamin, the physiological functions of vitamin D more closely resemble a hormone. Vitamin D is important for the following:

- Intestinal absorption of calcium
- PTH-induced mobilization of calcium from bone
- Calcium reabsorption in the proximal renal tubules
- Vitamin D must undergo several conversion steps before the active form, calcitriol or 1,25-DHCC, is formed. It is absorbed by the intestines in two forms, 7-dehydrocholesterol and cholecalciferol. 7-dehydrocholesterol is converted into cholecalciferol in the skin by the sun's ultraviolet radiation. Hepatic and intestinal enzymes, including CYP27A1, CYP2J2 and CYP3A4, convert cholecalciferol to 25-hydroxycholecalciferol

(25-HCC or calcidiol or calcifediol), which is then further activated by CYP27B1 in the kidneys to form the active 1,25-DHCC or calcitriol. This last conversion step is regulated by PTH. When PTH is increased during hypocalcemia, renal production of calcitriol increases, which increases intestinal absorption of calcium.[30,32]

Influence of calcitonin. Calcitonin is a hormone secreted by specialized C cells of the thyroid gland in response to a high level of circulating ionized calcium. Calcitonin lowers serum calcium levels in part by inhibiting osteoclastic activity, thereby inhibiting bone resorption. Also, it decreases calcium reabsorption in the renal proximal tubules to result in increased renal calcium clearance.[28] Calcitonin is used for the treatment of acute hypercalcemia and several different forms of the hormone are available.

Influence of parathyroid hormone. PTH is the most important hormone involved in calcium homeostasis. It is secreted by the parathyroid glands, which are embedded in the thyroid, in direct response to low circulating ionized calcium. PTH closely regulates, and also is regulated by the vitamin D system to maintain the serum ionized calcium concentration within a narrow range. Generally, PTH increases the serum calcium concentration and stimulates the enzymatic activity of CYP27B1 to promote renal conversion of calcidiol to calcitriol, which enhances intestinal calcium absorption. Conversely, calcitriol is a potent suppressor of PTH synthesis via a direct mechanism that is independent of the serum calcium concentration.[28,31] The normal reference range for serum PTH concentrations is 10–65 pg/mL (10–65 ng/L).

Tubular reabsorption of calcium and phosphate at the distal nephron is controlled by PTH; it increases renal reabsorption of calcium and decreases the reabsorption of phosphate, resulting in lower serum phosphate and higher serum calcium concentrations. Perhaps the most important effect of PTH is on the bone. In the presence of PTH, osteoblastic activity is diminished and bone resorption processes of osteoclasts are increased. These effects increase serum ionized calcium, which feeds back to the parathyroid glands to decrease PTH output.[30]

The suppressive effect of calcitriol on PTH secretion is used clinically in patients with CKD who have excessively high serum PTH concentrations due to secondary hyperparathyroidism. PTH is a known uremic toxin, and its presence in supraphysiological concentrations has many adverse effects (e.g., suppression of bone marrow erythropoiesis and increased osteoclastic bone resorption with replacement by fibrous tissue).[33] **Figure 12-6** depicts the relationship between serum PTH and serum calcium concentrations.

Abnormalities. True abnormal serum concentrations of calcium may result from an abnormality in any of the previously mentioned mechanisms, including the following:

- Altered intestinal absorption[8,30,31,34]
- Altered number or activity of osteoclast and osteoblast cells in bone[8,30,31,34]
- Changes in renal reabsorption of calcium[8,30,31,34]
- Calcium or phosphate IV infusions

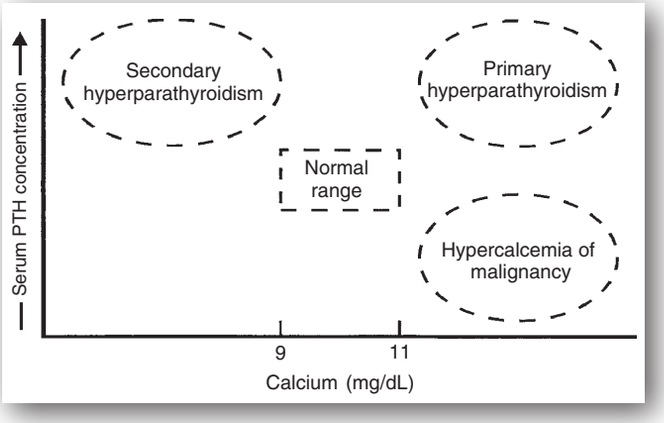

FIGURE 12-6. Interpretation of serum PTH concentrations with concomitant serum calcium concentrations.

Patients with CKD have increased serum phosphate and decreased serum calcium concentrations as a result of the following factors that interact via a complex mechanism: decreased phosphate clearance by the kidneys, decreased renal production of calcitriol, and skeletal resistance to the calcemic action of PTH. This interaction is further complicated by the metabolic acidosis of renal failure, which can increase bone resorption to result in decreased bone integrity.

Hypocalcemia

Hypocalcemia indicates a total serum calcium concentration of <9.2 mg/dL (<2.3 mmol/L). The most common cause of hypocalcemia is low serum proteins. As discussed previously, decreased serum protein leads to an increased free fraction of ionized calcium. If there is no other coexisting factor that could impair or alter calcium homeostasis, this should not be associated with a functional calcium deficit and clinical symptoms. Therefore, a serum protein concentration should always be taken into consideration when interpreting serum total calcium concentration. Even in the case of true, mild hypocalcemia, the patient may remain asymptomatic and often no treatment is required.

The most common causes of a true reduction in total serum calcium are disorders of vitamin D metabolism or impaired PTH production (**Table 12-10**). Osteomalacia (in adults) and

TABLE 12-10. Common Etiologies of Hypocalcemia

Diminished intake
Medications (see text)
Hyperphosphatemia
Hypoalbuminemia
Hypomagnesemia
Hypoparathyroidism (common)
Pancreatitis
Renal failure
Secondary hyperparathyroidism
Hypovitaminosis D (common)

rickets (in children) can result from severe deficiency in dietary calcium or vitamin D, diminished synthesis of vitamin D_3 from insufficient sunlight exposure, or resistance of the intestinal wall to the action of vitamin D. The reduction in serum calcium leads to secondary hyperparathyroidism, which increases bone resorption. Over a long period of time, bones lose their structural integrity and become more susceptible to fracture. The diminished serum calcium concentration, if significant, may result in tetany. Other notable findings may include EKG changes (QT prolongation) and arrhythmias.

Diminished intake. Although uncommon, diminished intake of calcium is an important cause of hypocalcemia, especially in patients receiving long-term total parental nutrition solutions.[37,38]

Medications. Excessive use of certain drugs to lower serum calcium by either increasing bone deposition or decreasing renal reabsorption of calcium may lead to hypocalcemia. These drugs include calcitonin, glucocorticoids, loop diuretics, etidronate, pamidronate, alendronate, cinacalcet, and denosumab.

IV bicarbonate administration and hyperventilation can lead to alkalemia, resulting in decreased ionized serum calcium. This decrease is usually important only in patients who already have low serum calcium concentrations. Other drugs that may cause hypocalcemia include phenytoin, phenobarbital, aluminum-containing antacids, and cisplatin.

Another cause is rapid IV administration of phosphate salts, especially at high doses. Phosphate can bind calcium and form an insoluble complex that can deposit into soft tissues and clog the microcirculation, causing metastatic calcification, hardening of normally pliable tissues, or blockage of capillary blood flow.[37,38] Soft-tissue deposition of the calcium–phosphate complex in lungs and blood vessels occurs when the serum solubility product of calcium times phosphate is high. The product of serum calcium and phosphate concentrations (both expressed in mg/dL) is often calculated, especially in patients with CKD, to minimize the risk for tissue calcification. An increased risk of deposition is likely in patients with a calcium–phosphate product that exceeds 50 or in patients with alkalosis. Other than the IV route, a large amount of phosphate may be absorbed from the GI tract with the use of certain enema and laxative preparations.[33]

Hypoparathyroidism. Hypoparathyroidism can reduce serum calcium concentrations. The most common cause of hypoparathyroidism is thyroidectomy, when the parathyroid glands are removed along with the thyroid glands. Because PTH is the major hormone regulating calcium balance, its absence significantly reduces serum calcium.[38]

Secondary hyperparathyroidism. Hypocalcemia is commonly seen in patients with secondary hyperparathyroidism resulting from CKD (Figure 12-6). The mechanism is complex and involves elevated serum phosphate concentrations and reduced activation of vitamin D. PTH acts on bone to increase calcium and phosphate resorption. Because renal phosphate elimination is reduced because of renal failure, the serum phosphate concentration is often high and depresses the serum calcium level. Because of the high phosphate concentrations in the intestinal lumen, dietary calcium is bound and absorption is impaired, while phosphate absorption continues.

Metabolic acidosis. Common in CKD, metabolic acidosis further enhances bone resorption. With prolonged severe hyperparathyroidism, excessive osteoclastic resorption of bones results in replacement of bone material with fibrous tissues. This condition is termed *osteitis fibrosa cystica.*[31,34,35] Such diminution of bone density may result in pathological fractures. Although the serum total calcium concentrations are low, patients may not show symptoms of hypocalcemia because the accompanying acidosis helps to maintain ionized serum calcium through the reduction in protein binding.

Magnesium. Similar to potassium, calcium balance is affected by magnesium homeostasis. Therefore, if a patient develops concurrent hypocalcemia and hypomagnesemia as a result of loop diuretic therapy, calcium replacement therapy may not be effective until magnesium balance is restored.

Clinical diagnosis. As with any electrolyte disorder, the severity of the clinical manifestations of hypocalcemia depends on the acuteness of onset. Hypocalcemia can at times be a medical emergency with symptoms primarily in the neuromuscular system.[37,38] They include fatigue, depression, memory loss, hallucinations, and, in severe cases, seizures, and tetany. The early signs of hypocalcemia are finger numbness, tingling and burning of extremities, and paresthesia. Mental instability and confusion may be seen in some patients as the primary manifestation.

Tetany is the hallmark of severe hypocalcemia. The mechanism of muscle fasciculation during tetany is the loss of the inhibitory effect of ionized calcium on muscle proteins. In extreme cases, this loss leads to increased neuromuscular excitability that can progress to laryngospasm and tonic-clonic seizures. Chvostek and Trousseau signs are hallmarks of hypocalcemia. The *Chvostek sign* is a unilateral spasm induced by a slight tap over the facial nerve. The *Trousseau sign* is a carpal spasm elicited when the upper arm is compressed by an inflated BP cuff.[31,38,40]

As hypocalcemia worsens, the cardiovascular system may be affected, as evidenced by myocardial failure, cardiac arrhythmias, and hypotension.[37,38] Special attention should be paid to serum calcium concentrations in patients receiving diuretics, corticosteroids, digoxin, antacids, lithium, and parenteral nutrition and in patients with renal disease.

Hypercalcemia

Hypercalcemia indicates a total serum calcium concentration >11 mg/dL (>2.8 mmol/L).

Causes. The most common causes of hypercalcemia are malignancy and primary hyperparathyroidism (Figure 12-6). Malignancies can increase serum calcium by several mechanisms. Osteolytic metastases can arise from breast, lung, thyroid, kidney, or bladder cancer. These tumor cells invade bone and produce substances that directly dissolve bone matrix and mineral content. Some malignancies, such as multiple myeloma, can produce factors that stimulate osteoclast

proliferation and activity. Another mechanism is the ectopic production of PTH or PTH-like substances by tumor cells, resulting in a pseudohyperparathyroid state.[39,41]

In primary hyperparathyroidism, inappropriate secretion of PTH from the parathyroid gland, usually due to an adenoma, increases serum calcium concentrations. The other major cause of hypercalcemia in hyperparathyroidism is the increased renal conversion of calcidiol to calcitriol. As the serum calcium concentration rises, the renal ability to reabsorb calcium may be exceeded, leading to an increased urinary calcium concentration and the subsequent formation of calcium–phosphate and calcium–oxalate renal stones. Typically, this condition results from parathyroid adenomas but also may be caused by primary parathyroid hyperplasia of chief cells or parathyroid carcinomas.[31,41]

Approximately 2% of patients treated with thiazide diuretics may develop hypercalcemia. Patients at risk are those with hyperparathyroidism. The mechanism appears to be multifactorial and includes enhanced renal reabsorption of calcium and decreased plasma volume.

The milk-alkali syndrome (Burnett syndrome), rarely observed today, is another drug-related cause of hypercalcemia.[33] This syndrome occurs from a chronic high intake of milk or calcium products combined with an absorbable antacid (e.g., calcium carbonate, sodium bicarbonate, or magnesium hydroxide). This syndrome was more common in the past when milk or cream was used to treat gastric ulcers and before the advent of nonabsorbable antacids. Renal failure can occur as a result of calcium deposition in soft tissues.[33,42]

Hypercalcemia also can result from the following[28,40,41,43]:

- Excessive administration of IV calcium salts
- Calcium supplements
- Chronic immobilization
- Paget disease
- Sarcoidosis
- Hyperthyroidism
- Acute adrenal insufficiency
- Lithium-induced renal calcium reabsorption
- Excessive vitamin D, vitamin A, or thyroid hormone, which increases intestinal absorption
- Drugs (e.g., tamoxifen, teriparatide, androgenic hormones)

Clinical diagnosis. Similar to hypocalcemia and other electrolyte disorders, the severity of the clinical manifestations of hypercalcemia depends on the acuteness of onset. Hypercalcemia can be a medical emergency, especially when serum concentrations rise above 14 mg/dL (>3.5 mmol/L). Symptoms associated with this condition often consist of vague GI complaints such as nausea, vomiting, abdominal pain, dyspepsia, and anorexia. More severe GI complications include peptic ulcer disease, possibly due to increased gastrin release, and acute pancreatitis.[43,44]

Severe hypercalcemic symptoms primarily involve the neuromuscular system (e.g., lethargy, obtundation, psychosis, cerebellar ataxia, and, in severe cases, coma and death). However, EKG changes and spontaneous ventricular arrhythmias also may be seen. Also, it may enhance the inotropic effects of digoxin, increasing the likelihood of cardiac arrhythmias.[35-38]

Renal function may be affected by hypercalcemia through the ability of calcium to inhibit the adenyl cyclase–cyclic adenosine monophosphate system that mediates the ADH effects on the collecting ducts. This inhibition results in diminished conservation of water by the kidneys. The renal effect is further compounded by diminished solute transport in the loop of Henle, leading to polyuria, nocturia, and polydipsia.[28] Other chronic renal manifestations include nephrolithiasis, nephrocalcinosis, chronic interstitial nephritis, and renal tubular acidosis.

In addition, hypercalcemia can cause vasoconstriction of the renal vasculature, resulting in a decrease in renal blood flow and GFR. If hypercalcemia is allowed to progress, oliguric acute renal failure may ensue.[28] In the presence of high calcium–phosphate product, soft-tissue calcification by the calcium–phosphate complex may occur. The signs and symptoms described above are mostly seen in patients with severe hypercalcemia. With serum concentrations <13 mg/dL (3.2 mmol/L), most patients should be asymptomatic.

Causes of spurious laboratory results. False hypercalcemia can occur if the tourniquet is left in place too long when the blood specimen is drawn. This results from increased plasma-protein pooling in the phlebotomized arm. Falsely elevated calcium should be suspected if serum albumin is >5 g/dL (>50 g/L). **Table 12-11** contains the normal range values for tests related to calcium metabolism.

Phosphate

Normal range: 2.3–4.7 mg/dL (0.74–1.52 mmol/L) for adults

Many of the factors that influence serum calcium concentrations also affect serum phosphate, either directly or indirectly. Laboratory values for calcium and phosphate should, therefore, be interpreted together. Because phosphate exists as several organic and inorganic moieties in the body, some clinical laboratories simply report the phosphate value as phosphorus.

Physiology

Phosphate is a major intracellular anion with several functions. It is important for intracellular metabolism of proteins, lipids, and carbohydrates, and it is a major component

TABLE 12-11. Normal Ranges for Tests Related to Calcium Metabolism in Adults

Calcium (free)	4.6–5.8 mg/dL
Calcium (total)	9.2–11.0 mg/dL
Phosphate	2.3–4.7 mg/dL
PTH	10–65 pg/mL
Urine calcium	<250 mg/day in men
	<200 mg/day in women
Urine phosphate	1 g/day (average)

PTH = parathyroid hormone.

in phospholipid membranes, ribonucleic acids, nicotinamide diphosphate (an enzyme cofactor), cyclic adenine and guanine nucleotides (second messengers), and phosphoproteins. Another important function of phosphate is in the formation of high-energy bonds for the production of ATP, which is a source of energy for many cellular reactions. Phosphate is a component of 2,3-diphosphoglycerate (2,3-DPG), which regulates the release of oxygen from Hgb to tissues. In addition, phosphate has a regulatory role in the glycolysis and hydroxylation of cholecalciferol. It is also an important acid–base buffer.[35,40]

A balanced diet for adults usually contains about 800–1500 mg/day of phosphate. About two thirds is actively absorbed from the small intestine. Some of the phosphate is absorbed passively with calcium and some is absorbed under the influence of calcitriol, which also increases the intestinal absorption of calcium. However, phosphate is the first of the two to be absorbed.[40]

Phosphate absorption is diminished when a large amount of calcium or aluminum is present in the intestine due to the formation of insoluble phosphate compounds. Such large amounts of calcium and aluminum may result from the consumption of antacids. In fact, for patients with CKD who have high serum phosphate concentrations, calcium- and aluminum-containing antacids may be given with meals as phosphate binders to reduce intestinal phosphate absorption.[45] It should be noted that due to concerns of detrimental accumulation of aluminum in the CNS as well as the ability to worsen anemia and bone disease, chronic use of aluminum-containing antacids should be avoided.

Phosphate is widely distributed in the body throughout the plasma, extracellular fluid, cell membrane structures, intracellular fluid, collagen, and bone. Bone contains 85% of the phosphate in the body. About 90% of plasma phosphate is filtered at the glomeruli, and the majority is actively reabsorbed at the proximal tubule. Some reabsorption also takes place in the loop of Henle, distal tubules, and possibly the collecting ducts.[31] The amount of renal phosphate excretion is, therefore, the amount filtered minus the amount reabsorbed. Increased urinary phosphate excretion can result from an increase in plasma volume and the action of PTH, which can block phosphate reabsorption throughout the nephron. In contrast, vitamin D_3 and its metabolites can directly stimulate proximal tubular phosphate reabsorption. In all, 90% of eliminated phosphate is excreted renally, while the remainder is secreted into the intestine.[31,35,46] Renal handling of phosphate, especially the proximal tubules, therefore, plays an important role in maintaining the homeostatic balance of phosphate. Renal phosphate transport is active, saturable, and dependent on pH and sodium ion. However, fluctuation in serum phosphate mostly results from changes in either the GFR or the rate of tubular reabsorption.[2,31,35]

Serum phosphate and calcium concentrations as well as PTH and vitamin D levels are intimately related with each other. Serum phosphate indirectly controls PTH secretion via a negative feedback mechanism. With a decrease in the serum phosphate concentration, the conversion of calcidiol to calcitriol increases (which increases serum concentrations of both phosphate and calcium). Both the intestinal absorption and renal reabsorption of phosphate are increased. The concomitant increase in serum calcium then directly decreases PTH secretion. This decrease in serum PTH concentration permits a further increase in renal phosphate reabsorption.[30,31]

A true phosphate imbalance may result from an abnormality in any of the previously discussed mechanisms and hormones for maintaining calcium and phosphate homeostasis. They may include altered intestinal absorption, altered number or activity of osteoclast and osteoblast cells in bone, changes in renal calcium and phosphate reabsorption, and IV infusions of calcium or phosphate salts.[35,40]

Hypophosphatemia

Hypophosphatemia indicates a serum phosphate concentration of <2.3 mg/dL (<0.74 mmol/L). The following three mechanisms commonly contribute to decreased serum phosphate concentrations:

- Increased renal excretion[40,47,48]
- Intracellular shifting
- Decreased phosphate or vitamin D intake[41,47,48]

To identify the etiology of hypophosphatemia, the serum and urine phosphate concentrations should be evaluated simultaneously. Low urine and serum phosphates indicate either a diminished phosphate intake or excessive use of phosphate-binders. An increased urine phosphate suggests either hyperparathyroidism or renal tubular dysfunction. If the increased urine phosphate is accompanied by elevated serum calcium, the presence of primary hyperparathyroidism or decreased vitamin D metabolism must be considered.

Common causes. Hypophosphatemia commonly results from decreased renal reabsorption or increased GFR, a shift of phosphate from extracellular to intracellular fluid, alcoholism, or malnutrition. Phosphate is added to total parenteral nutrition solutions for muscle growth and replenishment of hepatic glycogen storage in malnourished patients. The infusion of concentrated glucose solution increases insulin secretion from the pancreas, which facilitates glucose and phosphate cell entry. Phosphate is used to form phosphorylated hexose intermediates during cellular utilization of glucose. An inadequate phosphate content in these nutritional fluids can decrease anabolism, glycolysis, and ATP and 2,3-DPG production.[48]

Infusion of concentrated glucose solutions, especially when accompanied by insulin, can produce hypophosphatemia through intracellular phosphate shifting. This condition, known as *refeeding syndrome*, can occur when an inadequate amount of phosphate is given during total parenteral nutrition (i.e., when a large amount of phosphate is taken up by the newly produced cells during anabolism).

Hypophosphatemia also can occur during treatment of hyperkalemia with insulin and dextrose. In addition, aluminum- and calcium-containing antacids, as well as magnesium hydroxide, are potent binders of intestinal phosphate.[45]

Overuse of these agents can severely reduce serum phosphate concentrations in patients with normal renal function. Moreover, calcitonin, glucagon, and β-adrenergic stimulants can decrease serum phosphate concentrations. Thiazide and loop diuretics can increase renal phosphate excretion. However, this effect is often insignificant clinically in otherwise healthy individuals.

Other conditions known to cause hypophosphatemia include nutritional recovery after starvation, treatment of diabetic ketoacidosis, decreased absorption or increased intestinal loss, alcohol withdrawal, the diuretic phase of acute tubular necrosis, and prolonged respiratory alkalosis. To compensate for respiratory alkalosis, carbon dioxide shifts from intracellular to extracellular fluid. This shift increases the intracellular fluid pH, which activates glycolysis and intracellular phosphate trapping. Metabolic acidosis, in contrast, produces a minimal change in serum phosphate.

Uncommon causes. Burn patients often retain a great amount of sodium and water. During wound healing, diuresis often ensues, which results in a substantial loss of phosphate. Because anabolism also occurs during recovery, hypophosphatemia may be inevitable without proper replacement. A moderate reduction in serum phosphate can occur from prolonged nasogastric suctioning, gastrectomy, small bowel or pancreatic disease resulting in malabsorption, and impaired renal phosphate reabsorption in patients with multiple myeloma, Fanconi syndrome, heavy-metal poisoning, amyloidosis, and nephrotic syndrome.[47,48]

Severe hypophosphatemia. Severe phosphate depletion (<1 mg/dL or <0.32 mmol/L) can occur during diabetic ketoacidosis. The resultant acidosis mobilizes bone, promotes intracellular organic substrate metabolism, and releases phosphate into the extracellular fluid. The glycosuria and ketonuria caused by diabetic ketoacidosis results in an osmotic diuresis that increases urinary phosphate excretion. The combined effects of these events may produce a normal serum phosphate concentration with severe intracellular deficiency. When diabetic ketoacidosis is corrected with insulin, phosphate accompanies glucose to move intracellularly. Serum phosphate is usually reduced within 24 hours of treatment. As the acidosis is corrected, there is further intracellular shifting of phosphate to result in profound hypophosphatemia. The accompanying volume repletion may exacerbate the hypophosphatemia further.

Clinical diagnosis. Patients with a moderate reduction in serum phosphate (2–2.3 mg/dL or 0.64–0.74 mmol/L) are often asymptomatic. Neurological irritability may occur as the serum phosphate concentration drops below 2 mg/dL (<0.64 mmol/L). Severe hypophosphatemia is often associated with muscle weakness, rhabdomyolysis, paresthesia, hemolysis, platelet dysfunction, and cardiac and respiratory failure.

CNS effects include encephalopathy, confusion, obtundation, seizures, and ultimately, coma. The mechanism for these effects may involve decreased glucose utilization by the brain, decreased brain cell ATP, or cerebral hypoxia from increased oxygen-Hgb affinity, secondary to diminished erythrocyte 2,3-DPG content. This decreased content results in decreased glycolysis, which leads to decreased 2,3-DPG and ATP production. The decreased contents of 2,3-DPG and ATP result in an increased affinity of Hgb for oxygen, eventually leading to decreased tissue oxygenation. The ensuing cerebral hypoxia may explain the persistent coma often seen in patients with diabetic ketoacidosis. Hemolysis may occur, but it is rarely seen at serum phosphate concentrations >0.5 mg/dL (>0.16 mmol/L).

Hyperphosphatemia

Hyperphosphatemia indicates a serum phosphate concentration >4.7 mg/dL (>1.52 mmol/L). There are three basic causes for elevated serum phosphate concentrations:

- Decreased renal phosphate excretion
- Shift of phosphate from intracellular to extracellular fluid
- Increased intake of vitamin D or phosphate-containing products (orally, rectally, or intravenously)

Elevated phosphate concentrations also may result from reduced PTH secretion, increased body catabolism, and certain malignant conditions (e.g., leukemias and lymphomas).[4,47,48]

Causes. The most common cause of hyperphosphatemia is renal dysfunction, which commonly occurs as the GFR falls below 25 mL/min. CKD results in secondary hyperparathyroidism, which can further reduce renal phosphate elimination. The increase in serum phosphate concentration increases the risk for deposition of insoluble calcium–phosphate complex in soft tissues (i.e., metastatic calcification). This deposition may further reduce the serum concentration of ionized calcium and lead to increased PTH production and release. A sustained period of high PTH levels leads to excessive bone resorption, which will severely weaken its structural integrity.[36,40]

Hyperphosphatemia can be caused by a shift of phosphate from intracellular to extracellular fluid. This shift of phosphate can result from massive cell break down after administering chemotherapy for leukemia or lymphoma, and during rhabdomyolysis and septic shock. In addition, hyperthyroidism can elevate serum phosphate by directly increasing renal tubular phosphate reabsorption.

Clinical diagnosis. Signs and symptoms of hyperphosphatemia commonly result from the accompanying hypocalcemia and hyperparathyroidism (see Hypocalcemia section). Renal function may diminish if hyperphosphatemia is left untreated. In the presence of renal dysfunction, phosphate excretion is further reduced to cause an even greater increase of serum phosphate concentration and a further decline in serum calcium concentration.[36,40,45] (**Minicase 4**.)

Causes of spurious laboratory results. Hemolysis can occur during phlebotomy, which may lead to a falsely elevated serum phosphate concentration. If the serum is not separated soon after phlebotomy, phosphate may be falsely decreased as it is taken up by the cellular components of blood.

Similar to what may occur to specimens for potassium concentration determination, when the blood is allowed to clot

MINICASE 4

Calcium and Phosphate Disorders in a Patient with Chronic Renal Failure

Michael S., a 72-year-old man, had a 1-week history of nausea, vomiting, and general malaise. His appetite has severely decreased over the past two months. He has a longstanding history of uncontrolled hypertension and type 2 diabetes mellitus as well as diabetic nephropathy, retinopathy, and neuropathy.

His physical examination reveals a BP of 160/99 mm Hg, diabetic retinopathic changes with laser scars bilaterally, and diminished sensation bilaterally below the knees. His laboratory values include serum sodium 146 mEq/L, potassium 4.7 mEq/L, chloride 104 mEq/L, total carbon dioxide content 15 mEq/L, SCr 3.2 mg/dL (3.1 mg/dL from one month ago), BUN 92 mg/dL, and random blood glucose of 181 mg/dL. Because of his renal failure, additional laboratory tests were obtained: calcium 7.5 mg/dL, phosphate 9.1 mg/dL, albumin 3.3 g/dL.

Over the next several days, he complains of finger numbness, tingling, and burning of extremities. He also has experienced increasing confusion and fatigue. A neurological examination is positive for both Chvostek and Trousseau signs. Repeated laboratory tests show substantial changes in serum calcium (6.1 mg/dL) and phosphate (10.4 mg/dL). His intact serum PTH is 280 pg/mL (10–65 pg/mL).

QUESTION: Please characterize this patient's calcium and phosphorus disorders?

DISCUSSION: He has three laboratory abnormalities that are related specifically to calcium–phosphate metabolism: (1) hypocalcemia, (2) hyperphosphatemia, and (3) secondary hyperparathyroidism. He is exhibiting classic signs and symptoms of hypocalcemia, such as finger numbness, tingling, burning of extremities, confusion, fatigue, and positive Chvostek and Trousseau signs.

Chronic kidney disease, as seen in this patient, is commonly associated with hypocalcemia, hyperphosphatemia, secondary hyperparathyroidism, and vitamin D deficiency. These calcium–phosphate abnormalities are responsible for the development of renal osteodystrophy. During the early stages of renal failure, renal phosphate excretion begins to decrease. His serum phosphate concentration was increased, and the ionized calcium concentration became reduced, which stimulated the release of PTH and resulted in secondary hyperparathyroidism. The higher concentration of PTH reduced his renal tubular phosphate reabsorption, thereby increasing its excretion. The hyperparathyroidism helped to maintain his serum phosphate and calcium concentrations within normal ranges during the early stage of renal failure (Figure 12-3).

As renal function continues to deteriorate (eGFR <30 mL/min), renal tubules cease to respond adequately to the high serum PTH concentration, resulting in hyperphosphatemia. In response to the hypocalcemia that followed, calcium was mobilized from the bone through the action of PTH. However, such a compensatory response was not sufficient as hypocalcemia and hyperphosphatemia continued. The persistent hyperphosphatemia could inhibit the conversion of calcidiol to calcitriol and further reduce the intestinal calcium absorption capacity. Therefore, hypocalcemia was worsened by the presence of hypovitaminosis D, which subsequently stimulated PTH secretion increasing mobilization of calcium from bone. The metabolic acidosis that is common in renal failure also may have contributed to the negative calcium balance in the bone.

This patient was relatively asymptomatic up to this point, primarily because these laboratory abnormalities developed over a long period of time and allowed the body to compensate. In the presence of nausea and vomiting and the lack of appetite, his oral calcium intake was probably reduced substantially, which might have enhanced his malaise. Because calcium is commonly reported as total calcium and not as the free or ionized fraction, his total serum calcium concentration must be corrected for his low serum albumin value. For every 1 g/dL reduction in serum albumin below 4 g/dL, 0.8 mg/dL should be added to his serum calcium concentration. Therefore, with his serum albumin concentration of 3.3 g/dL, his initial serum calcium value of 7.5 mg/dL is equivalent to a total calcium concentration of about 8.1 mg/dL. He does have true hypocalcemia, although the deficit is mild. It is important to note that his calcium and phosphorus derangements are severe. This patient has demonstrated neurological signs of hypocalcemia. His EKG should be checked to determine if his cardiac rhythm is affected by hypocalcemia.

with the use of nonheparinized tubes, phosphate may leach out of platelets to result in a falsely elevated concentration. In patients with thrombocytosis, phosphate concentrations should, therefore, be obtained from plasma rather than serum samples.

Serum phosphate may vary by 1–2 mg/dL (0.32–0.64 mmol/L) after meals. Meals rich in carbohydrate can reduce serum phosphate; meals with high phosphate contents, such as dairy products, can increase serum phosphate. If accurate assessment of the phosphate concentration is necessary, the blood specimen should be obtained from the patient after fasting.

TRACE ELEMENTS

Copper

Normal range: 70–140 mcg/dL (11–22 μmol/L) (males); 80–155 mcg/dL (13–24 μmol/L) (females) for serum copper, 23–50 mg/dL for ceruloplasmin, 0.47 ± 0.06 mg/g for erythrocyte superoxide dismutase

Physiology

The relationship between copper homeostasis and human diseases was uncovered in 1912 shortly after Wilson disease was described. In the early 1930s, a link between copper deficiency

and anemia was suspected, although the hypothesis was not proven at that time. In the 1970s, the physiological functions of copper were better understood and its link to various disease states was better appreciated. An official dietary copper recommendation and adequate daily dietary intake was introduced for the first time in 1979.

Copper plays an integral part in the synthesis and functions of many circulating proteins and enzymes. In addition, copper is an essential factor for the formation of connective tissues, such as the cross-linking of collagen and elastin. Copper also regulates the cellular uptake and physiological functions with iron.[49] In the CNS, copper is required for the formation or maintenance of myelin and other phospholipids. Cuproenzymes (copper-dependent enzymes) are crucial in the metabolism of catecholamines. For example, the functions of dopamine hydroxylase and monoamine oxidase are impaired by copper deficiency. Copper also affects the function of tyrosinase in melanin synthesis, which is responsible for the pigmentation of skin, hair, and eyes. Deficiency of tyrosinase results in albinism. Other physiological functions of copper include thermal regulation, glucose metabolism, blood clotting (e.g., factor V function), and protection of cells against oxidative damage.[50,51]

The normal adult daily intake of copper, based on a typical American diet, is about 2–3 mg. Plant copper is in the inorganic (free ionic) form, while meat (animal) copper is in the form of cuproproteins (copper–protein complex). Inorganic copper is absorbed in the upper portion of the GI tract (stomach and proximal duodenum) under acidic conditions. Cuproprotein copper is absorbed in the jejunum and ileum. Absorption of copper from the GI tract is a saturable process. The oral bioavailability of copper ranges from 15–97% and shows a negative correlation with the amount of copper present in the diet.

Once absorbed, copper is bound to a mucosal copper-binding protein called *metallothionein* (a sulfur-rich, metal-binding protein present in intestinal mucosa). From this protein, copper is slowly released into the circulation, where it is taken up by the liver and other tissues.[50] Animal data suggest that the liver serves as the ultimate depot for copper storage. Copper absorption may be reduced by a high intake of zinc (>50 mg elemental zinc /day), ascorbic acid, and dietary fiber. Zinc may induce the synthesis of intestinal metallothionein and form a barrier to copper ion absorption.[50,51]

The normal adult body contains 75–150 mg of copper, which is significantly lower when compared with other trace elements such as zinc and iron. Approximately one third of the total body copper is found in the liver and brain at high tissue concentrations.[52] Another one third is located in the muscles at low tissue concentrations. The rest is found in the heart, spleen, kidneys, and blood (erythrocytes and neutrophils).[50,52]

In the plasma, copper is highly bound (95%) to ceruloplasmin (also known as ferroxidase I), a blue copper protein.[49] This protein contains six to seven copper atoms per molecule. The fraction of plasma copper associated with ceruloplasmin seems to be relatively constant for the same individual. However, a significant interindividual variation exists. The remainder of the plasma copper is bound to albumin and amino acids or is free.[50,52] Copper is eliminated mainly by biliary excretion (average 25 mcg/kg/day), with only 0.5–3% of the daily intake in the urine.[50]

Ceruloplasmin is considered the most reliable indicator of copper status because of its large and relatively stable binding capacity with plasma copper. Therefore, when evaluating copper status in the body, ceruloplasmin concentration should be assessed together with plasma copper concentration.

Hypocupremia

Although it was thought that copper deficiency is relatively uncommon in humans, more cases have been reported recently in patients after bariatric surgery.[51] *Hypocupremia* usually occurs in infants with chronic diarrhea or malabsorption syndrome, such as after bariatric surgery or intestinal resection, or in low-birth-weight infants fed with milk (rather than formulas).[49,51,53] Premature infants, who typically have low copper stores, are at a higher risk for developing copper deficiency under these circumstances.[50]

Copper deficiency may occur in patients receiving long-term parenteral nutrition. Chronic malabsorption syndromes (e.g., celiac disease and ulcerative colitis), protein-wasting enteropathies, short bowel syndrome, and the presence of significant bowel resection or bypass (e.g., malabsorptive bariatric surgical procedures such as long-limb Roux-en-Y, or jejunoileal bypass) are all potential risk factors resulting in copper deficiency.[49,53] Individuals on a vegetarian diet may be at risk because (1) meat is a major food source of copper, and (2) plant sources often have high-fiber content that may interfere with copper absorption.[49]

Prolonged hypocupremia leads to a syndrome of neutropenia and iron-deficiency anemia, which are correctable with copper.[53] The anemia is normocytic or microcytic and hypochromic. It results mainly from poor iron absorption and ineffective heme incorporation of iron.[45,52] Copper deficiency can affect any systems or organs whose enzymes require copper for proper functioning. As such, copper deficiency may lead to abnormal glucose tolerance, arrhythmias, hypercholesterolemia, atherosclerosis, depressed immune function, defective connective tissue formation, demineralization of bones, and pathological fractures.[51]

Two well-known genetic defects are associated with impaired copper metabolism in humans. Menkes syndrome (also called *kinky-hair syndrome/steely-hair syndrome*) is an X-linked disorder that occurs in 1 out of every 50,000 to 100,000 live births. These patients have defective copper absorption, and are commonly deceased by the age of three. They have reduced copper concentrations in the blood, liver, and brain.[49,51] Most of them are children suffering from slow growth and retardation, defective keratinization and pigmentation of hair, hypothermia, and degenerative changes in the aortic elastin and neurons. Progressive nerve degeneration in the brain results in intellectual deterioration, hypotonia, and seizures. However, anemia and neutropenia, hallmark

symptoms of nutritional copper deficiency, are not found in Menkes syndrome. Administration of parenteral copper increases serum copper and ceruloplasmin concentrations but does not have any apparent effect on slowing disease progression.

Wilson disease is an autosomal recessive disease of copper storage. Its frequency is uncertain, but it is believed to be not as common as Menkes syndrome. Wilson disease appears to be associated with altered copper catabolism and excretion of ceruloplasmin copper into the bile. It is associated with elevated urinary copper loss and low plasma ceruloplasmin and low plasma copper concentrations. However, copper deposition occurs in the liver, brain, and cornea. If untreated, significant copper accumulation in these organs will eventually lead to irreversible damage such as cirrhosis and neurological impairment. Interestingly, treatment with dietary adjustment of copper intake does not seem to be effective. Chelation therapy using D-penicillamine is much more effective in preventing copper deposition. Oral zinc supplementation also has been used to reduce copper accumulation.

Hypercupremia

Copper excess, or *hypercupremia*, is not common in humans and usually occurs with a deliberate attempt to ingest large quantities of copper. The exact amount of copper that results in toxicity is unknown. Acute or long-term ingestion of >15 mg of elemental copper may lead to symptomatic copper poisoning.[52] Also, it has been reported that drinking water with 2–3 mg/L of copper is associated with hepatotoxicity in infants. Similar to other metallic poisonings, acute copper poisoning leads to nausea, vomiting, intestinal cramps, and diarrhea.[52] A larger ingestion can result in shock, hepatic necrosis, intravascular hemolysis, renal impairment, coma, and death.[53] Elevated intrahepatic copper concentrations may be present in patients with primary biliary cirrhosis and biliary atresia.[49,50,53] Long-term parenteral nutrition use is also a risk factor for hepatic copper overload. The mechanism is not well-established. Chronic cholestasis secondary to parenteral nutrition-associated liver disease has been suggested as the primary cause. Because copper plays an important role in the neurological system, it has been suggested that copper-induced free radical-induced neurodegeneration may be a contributing factor for Alzheimer disease. At present, there is no known treatment for hypercupremia.

Zinc

Normal range: 50–150 mcg/dL (7.7–23 μmol/L)

Physiology

Next to iron, zinc is the most abundant trace element in the body. It is an essential nutrient that is a constituent of, or a cofactor to, many enzymes. These metalloenzymes participate in the metabolism of carbohydrates, proteins, lipids, and nucleic acids.[50] As such, zinc influences the following[50,53]:

- Tissue growth and repair
- Cell membrane stabilization
- Bone collagenase activity and collagen turnover
- Immune response, especially T-cell mediated response
- Sensory control of food intake
- Spermatogenesis and gonadal maturation
- Normal testicular function

The normal adult body contains 1.5–2.5 g of zinc.[51] Aside from supplementation with zinc capsules, dietary intake is the only source of zinc for humans. Food sources of zinc include meat products, oysters, and legumes.[50] Food-based zinc is largely bound to proteins and released by gastric acid and pancreatic enzymes. Ionic zinc found in zinc supplements is absorbed in the duodenum directly.[50] Foods rich in calcium, dietary fiber, or phytate may interfere with zinc absorption, as can folic acid supplements.[50]

After absorption, zinc is transported from the small intestine to the portal circulation where it binds to proteins such as albumin, transferrin, and other globulins.[50] Circulating zinc is bound mostly to serum proteins; two thirds are loosely bound to albumin and transthyretin, while one third is bound tightly to α-2 macroglobulin.[53] Only 2–3% (3 mg) of zinc is either in free ionic form or bound to amino acids.[50]

Zinc can be found in many organs. Tissues high in zinc include liver, pancreas, spleen, lungs, eyes (retina, iris, cornea, and lens), prostate, skeletal muscle, and bone. Because of their mass, skeletal muscle (60–62%) and bone (20–28%) have the highest zinc contents among the body tissues.[50] Only 2–4% of total body zinc is found in the liver. In blood, 85% is in erythrocytes, although each leukocyte contains 25 times the zinc content of an erythrocyte.[51]

Plasma zinc concentration is a poor indicator of total body zinc store. Because 98% of the total body zinc is present in tissues and end organs, the plasma zinc concentration tends to be maintained by continuous shifting from intracellular sources. Additionally, metabolic stress, such as infection, acute myocardial infarction, and critical illnesses increase intracellular shifting of zinc to the liver and lower serum zinc concentrations, even when total body zinc is normal. Conversely, serum zinc concentrations may be normal during starvation or wasting syndromes due to release of zinc from tissues and cells.[50] Therefore, the serum/plasma zinc concentration alone has little meaning clinically. It has been suggested that the rate of zinc turnover in the plasma provides better assessment of the body zinc status. This may be achieved by measuring 24-hour zinc loss in body fluids (e.g., urine and stool). However, this approach is rarely practical for critically ill patients as renal failure is often present. Alternatively, zinc turnover and mobilization may be determined by adjusting plasma zinc concentrations with serum α-2 macroglobulin and albumin concentrations.[56,57] To more accurately assess the body zinc status, others have suggested monitoring the functional indices of zinc, such as erythrocyte alkaline phosphatase, serum superoxide dismutase, and lymphocyte 5' nucleotidase. However, the clinical validity of these tests remains to be substantiated, especially in patients who are acutely ill.

Zinc undergoes substantial enteropancreatic recirculation and is excreted primarily in pancreatic and intestinal

secretions. Zinc is also lost dermally through sweat, hair and nail growth, and skin shedding. Except in certain disease states, only 2% of zinc is lost in the urine.[50]

Hypozincemia

In Western countries, zinc deficiency is rare from inadequate intake. Individuals with serum zinc concentrations below 50 mcg/dL (<7.6 μmol/L) are at an increased risk for developing symptomatic zinc deficiency. It also must be emphasized that serum zinc exhibits a negative acute phase response. The presence of proinflammatory cytokines causes an intracellular and intrahepatic influx of zinc from the serum, which would lead to transient *hypozincemia*. Therefore, serum or plasma zinc concentration alone should not be used to assess zinc status in patients with acute illnesses or any acute inflammatory response. Given the caveats of measuring serum zinc concentrations in certain disease states, response to zinc supplements may be the only way of diagnosing this deficiency. In the presence of chronic diseases, it is difficult to determine if zinc deficiency is clinical or subclinical because of the reduced protein binding.[53] Conditions leading to deficiency may be divided into five classes (**Table 12-12**)[50,53]:

- Low intake
- Decreased absorption
- Increased utilization
- Increased loss
- Unknown causes

The most likely candidates for zinc deficiency are infants; rapidly growing adolescents; menstruating, lactating, or pregnant women; individuals with low meat intake; chronically ill patients who have been institutionalized for extended periods; patients with chronic uncontrolled diarrhea or ostomy output, and those who have been receiving zinc-deficient parenteral nutrition solutions.[53] Acrodermatitis enteropathica is an autosomal, recessive disorder involving zinc malabsorption that occurs in infants of Italian, Armenian, and Iranian heritage. It is characterized by severe dermatitis, chronic diarrhea, emotional disturbances, and growth retardation.[50] Examples of malabsorption syndromes that may lead to zinc deficiency include Crohn disease, celiac disease, and short-bowel syndrome.

Excessive zinc may be lost in the urine (hyperzincuria), as occurs in alcoholism, β-thalassemia, diabetes mellitus, diuretic therapy, nephrotic syndrome, sickle cell anemia, and treatment with parenteral nutrition. Severe or prolonged diarrhea (e.g., inflammatory bowel diseases and graft versus host disease) may lead to significant zinc loss in the stool.[50,53] Patients with end-stage liver disease frequently have depleted zinc storage due to decreased functional hepatic cell mass.

Because zinc is involved in a diverse group of enzymes, its deficiency manifests in numerous organs and physiological systems (**Table 12-13**).[50] Dysgeusia (lack of taste) and hyposmia (diminished smell acuity) are common. Pica is a pathological craving for specific food or nonfood substances (e.g., geophagia). Chronic zinc deficiency, as occurs in acrodermatitis enteropathica, leads to growth retardation, anemia, hypogonadism, hepatosplenomegaly, and impaired wound healing. Additional signs and symptoms of acrodermatitis enteropathica include diarrhea; vomiting; alopecia; skin lesions in oral, anal, and genital areas; paronychia; nail deformity; emotional lability; photophobia; blepharitis; conjunctivitis; and corneal opacities.[50,53]

TABLE 12-12. Etiologies of Zinc Deficiency

Low intake
Anorexia
Nutritional deficiencies
Alcoholism
Chronic kidney disease
Premature infants
Certain vegetarian diets
Exclusion of trace elements in parenteral nutrition
Decreased absorption
Acrodermatitis enteropathica
Malabsorption syndromes
Bariatric surgery
Short bowel syndrome
Increased utilization
Adolescence
Lactation
Pregnancy
Increased loss
Alcoholism
β-thalassemia
Cirrhosis
Diabetes mellitus
Diarrhea
Diuretic therapy
Enterocutaneous fistula drainage
Exercise (long term, strenuous)
Glucagon
Impaired enteropancreatic recycling
Nephrotic syndrome
Protein-losing enteropathies
Sickle cell anemia
Unknown causes
Arthritis and other inflammatory diseases
Down syndrome

Hyperzincemia

Zinc is one of the least toxic trace elements.[53] Clinical manifestations of excess zinc, *hyperzincemia,* occur with chronic, high doses of a zinc supplement. However, patients with Wilson disease who commonly take high doses of zinc rarely show signs of toxicity. This may be explained by the stabilization

TABLE 12-13. Signs and Symptoms of Zinc Deficiency

Signs
Acrodermatitis enteropathica
Anemia
Anergy to skin test antigens
Complicated pregnancy
Excessive bleeding
Maternal infection
Premature or stillborn birth
Decreased basal metabolic rate
Decreased circulating T_4 concentration
Decreased lymphocyte count and function
Effect on fetus, infant, or child
Congenital defects of skeleton, lungs, and CNS
Fetal disturbances
Growth retardation
Hypogonadism
Impaired neutrophil function
Impairment and delaying of platelet aggregation
Increased susceptibility to dental caries
Increased susceptibility to infections
Mental disturbance
Pica
Poor wound healing
Short stature in children
Skeletal deformities
Symptoms
Acne and recurrent furunculosis
Ataxia
Decreased appetite
Defective night vision
Hypogeusia
Hyposmia
Erectile dysfunction
Mouth ulcers

CNS = central nervous system; T_4 = thyroxine.

of serum zinc concentrations during high-dose administration.[50] As much as 12 g of zinc sulfate (>2700 mg of elemental zinc) taken over two days has caused drowsiness, lethargy, and increased serum lipase and amylase concentrations. Nausea, vomiting, and diarrhea also may occur.[50]

Serum zinc concentrations must be measured using nonhemolyzed samples. Erythrocytes and leukocytes, like many other cells, are rich in zinc. When they undergo hemolysis in the tube (e.g., too small a needle is used to draw the sample, tourniquet is too tight, or specimen left standing for too long or is mishandled), these cells release zinc into the specimen in quantities large enough to produce misleading results. This phenomenon also can occur when the specimen is allowed to clot, with the use of nonheparinized tubes.[50]

Manganese

Normal range: Varies depending on assay method, sample (whole blood versus plasma), and age. Whole blood method is generally preferred to detect toxicity.

Physiology

Manganese is an essential trace element that serves as a cofactor for numerous diverse enzymes involved in carbohydrate, protein, and lipid metabolism; protection of cells from free radicals; steroid biosynthesis; and metabolism of biogenic amines.[54] Interestingly, manganese deficiency does not affect the functions of most of these enzymes, presumably because magnesium may substitute for manganese in most instances.[53] In animals, manganese is required for normal bone growth, lipid metabolism, reproduction, and CNS regulation.[51]

Manganese has an important role in the normal function of the brain, primarily through its effect on biogenic amine metabolism. This effect may be responsible for the relationship between brain concentrations of manganese and catecholamines.[54]

The manganese content of the adult body is 10–20 mg. Manganese homeostasis is regulated through control of its absorption and excretion.[54] Plants are the primary source of food manganese because animal tissues have low contents.[54] Manganese is absorbed from the small intestine by a mechanism similar to that of iron.[51] However, only 3% to 4% of the ingested manganese is absorbed. Dietary iron and phytate may affect manganese absorption.[49]

Human and animal tissues have low manganese content.[54] Tissues relatively high in manganese are the bone, liver, pancreas, and pituitary gland.[49,54] Most circulating manganese is loosely bound to the β-1 globulin transmanganin, a transport protein similar to transferrin.[51,53] With overexposure, excess manganese accumulates in the liver and brain, causing severe neuromuscular signs and symptoms.[49]

Manganese is excreted primarily in biliary and pancreatic secretions. In manganese overload, other GI routes of elimination also may be used. Little manganese is lost in urine.[53,54]

Manganese Deficiency

Because of its relative abundance in plant sources, manganese deficiency is rare among the general population.[49] Deficiency normally occurs after several months of deliberate manganese omission from the diet.[53,54] Little is known regarding serum manganese concentrations and the accompanying disease states in humans.[53]

Information from the signs and symptoms of manganese deficiency comes from experimental subjects who intentionally followed low manganese diets for many months. Their signs and symptoms included weight loss, slow hair and nail growth, color change in hair and beard, transient dermatitis, hypocholesterolemia, and hypotriglyceridemia.[54]

Adults and children with convulsive disorders have lower mean serum manganese concentrations than normal subjects, although a cause-and-effect relationship has not been established. However, serum manganese concentrations correlate with seizure frequency.[54] Animals deficient in manganese show defective growth, skeletal malformation, ataxia, reproductive abnormalities, and disturbances in lipid metabolism.[49,53]

Manganese Excess

Manganese is one of the least toxic trace elements.[53] Overexposure primarily occurs from inhalation of manganese compounds (e.g., manganese mines).[54] The excess amount accumulates in the liver and brain resulting in severe neuromuscular manifestations. Symptoms include encephalopathy and profound neurological disturbances mimicking Parkinson disease.[49,53,54] These manifestations are not surprising because metabolism of biogenic amines is altered in both manganese excess and Parkinson disease. Other signs and symptoms include anorexia, apathy, headache, erectile dysfunction, and speech disturbances.[53] Inhalation of manganese products may cause manganese pneumonitis.[54]

Chromium

Average range: serum chromium 0.3–0.9 ng/mL; sample contamination (e.g., use of regular blood collection tubes not designed for trace elements may result in ranges from 2–5 ng/mL)

Physiology

The main physiological role of chromium is as a cofactor for insulin.[55] In its organic form, chromium potentiates the action of endogenous and exogenous insulin, presumably by augmenting its adherence to cell membranes.[49] The organic form is in the dinicotinic acid–glutathione complex or glucose tolerance factor (GTF).[51] Chromium is the metal portion of GTF; with insulin, GTF affects the metabolism of glucose, cholesterol, and triglycerides.[53] Therefore, chromium is important for glucose tolerance, glycogen synthesis, amino acid transport, and protein synthesis. Chromium also is involved in the activation of several enzymes.[51]

The adult body contains an average of 5 mg of chromium.[53] Food sources of chromium include brewer's yeast, spices, vegetable oils, unrefined sugar, liver, kidneys, beer, meat, dairy products, and wheat germ.[50,51] Glucose tolerance factor is present in the diet and can be synthesized from inorganic trivalent chromium (Cr^{+3}) available in food and dietary supplements.[50] Chromium is absorbed via a common pathway with zinc; its degree of absorption is inversely related to dietary intake, varying from 0.5–2%.[49,50] Absorption of Cr^{+3} from GTF is 10–25%, but the absorption is only 1% for inorganic chromium.[51]

Chromium circulates as free Cr^{3+}, bound to transferrin and other proteins, and as the GTF complex.[50,53] Glucose tolerance factor is the biologically active moiety and is more important than total serum chromium concentration.[53] Trivalent chromium accumulates in the hair, kidneys, skeleton, liver, spleen, lungs, testes, and large intestine. Glucose tolerance factor concentrates in insulin-responsive tissues such as the liver.[50,51]

The metabolism of chromium is not well-understood for several reasons[51]:

- Low concentrations in tissues
- Difficulty in analyzing chromium in biological fluids and tissue samples
- Presence of different chromium forms in food

Homeostasis is controlled by release of chromium from GTF and by dietary absorption.[50] The kidneys are the main site of elimination where urinary excretion is constant despite variability in the fraction absorbed.[53] However, excretion increases after glucose or insulin administration.[50, 53] Insulin, or a stimulus for insulin release, can therefore mobilize chromium from its stores. The chromium that is released will then be excreted in the urine. The amount of insulin in the circulation can thus affect the elimination and daily requirement of chromium.[55]

Chromium Deficiency

It is important to stress that the body store of chromium cannot be reliably assessed.[50] Serum or plasma chromium may not be in equilibrium with other pools. As with other trace elements, the risk for developing deficiency may be increased in patients receiving prescribed nourishment low in chromium content (e.g., parenteral nutrition solutions).[55] Marginal deficiencies or defects in utilization of chromium may be present in the elderly, patients with diabetes, or patients with atherosclerotic coronary artery disease.[50] The hepatic store of chromium decreases 10-fold in the elderly, suggesting a predisposition to deficiency. Because chromium is involved in lipid and cholesterol metabolism, its deficiency is a suspected risk factor for the development of atherosclerosis.[50,55]

Hyperglycemia increases urinary losses of chromium. Coupled with marginal intake, a type II diabetic patient is predisposed to chromium deficiency, which can further impair glucose tolerance.[50,55] Finally, multiparous women are at a higher risk than nulliparous women for becoming chromium deficient because, over time. Chromium intake may not be adequate to meet fetal needs and to maintain the mother's body store.[55]

The manifestations of chromium deficiency may involve insulin resistance and impaired glucose metabolism. Such manifestations may present clinically in three stages as the deficiency progresses:

- Glucose intolerance is present but is masked by a compensatory increase in insulin release.
- Impaired glucose tolerance and lipid metabolism are clinically evident.
- Marked insulin resistance and symptoms associated with hyperglycemia are evident.[55]

Chromium supplementation has been shown in diabetic patients to increase insulin sensitivity, improve glucose control, and shorten the QTc interval, suggesting a potential favorable effect on cardiovascular risk. However, there is at present no conclusive support demonstrating the benefit of chromium supplementation in diabetic patients or in those with impaired glucose metabolism.

Chromium deficiency may lead to hypercholesterolemia and become a risk factor for developing atherosclerotic disease.[50] Low chromium tissue concentrations have been associated with increased risk for myocardial infarction and coronary artery disease in both healthy subjects and diabetic patients, although a cause-and-effect relationship has not been established.[55,58]

Chromium Excess

Chromium has very low toxicity. The clinical significance of a high body store of chromium is unknown. Serum chromium concentrations may be increased in asymptomatic patients with metal-on-metal prosthetics.

SUMMARY

Hyponatremia and hypernatremia may be associated with high, normal, or low total body sodium. Hyponatremia may result from abnormal water accumulation in the intravascular space (dilutional hyponatremia), a decline in both extracellular water and sodium, or a reduction in total body sodium with normal water balance. Hypernatremia is most common in patients with either an impaired thirst mechanism (e.g., neurohypophyseal lesion) or an inability to replace water depleted through normal insensible loss or from renal or GI loss. Neurological manifestations are signs and symptoms often associated with sodium and water imbalance. The most common symptom of hyponatremia is confusion. However, if sodium continues to fall, seizures, coma, and death may result. Thirst is a major symptom of hypernatremia; elevated urine specific gravity, indicating concentrated urine, is uniformly observed.

Hypokalemia and hyperkalemia may indicate either a true or an apparent (due to transcellular shifting) potassium imbalance. Hypokalemia can occur due to excessive loss from the kidneys (diuretics) or GI tract (vomiting). The most serious manifestation involves the cardiovascular system (i.e., cardiac arrhythmias). Renal impairment, usually in the presence of high intake, commonly causes hyperkalemia. Like hypokalemia, the most serious clinical manifestations of hyperkalemia involve the cardiovascular system.

Serum chloride concentration may be used as a confirmatory test to identify abnormalities in fluid and acid–base balance. Hypochloremia may be diuretic-induced and results from the concurrent loss of sodium and also contraction alkalosis. Hyperchloremia may develop with the use of parenteral nutrition solutions that have a chloride:sodium ratio >1. Signs and symptoms associated with these conditions are related to the abnormalities in fluid or acid–base balance and underlying causes rather than to chloride itself.

Hypomagnesemia usually results from excessive loss from the GI tract (e.g., nasogastric suction, biliary loss, or fecal fistula) or from the kidneys (e.g., diuresis). Magnesium depletion is usually associated with neuromuscular symptoms such as weakness, muscle fasciculation with tremor, tetany, and increased reflexes. Increased magnesium intake in the presence of renal dysfunction commonly causes hypermagnesemia. Neuromuscular signs and symptoms that are opposite to those caused by hypomagnesemia may be observed.

The most common causes of true hypocalcemia are disorders of vitamin D metabolism and PTH production. Severe hypocalcemia can be a medical emergency and lead to cardiac arrhythmias and tetany, with symptoms primarily involving the neuromuscular system.

The most common causes of hypercalcemia are malignancy and primary hyperparathyroidism. Symptoms often consist of vague GI complaints such as nausea, vomiting, abdominal pain, anorexia, constipation, and diarrhea. Severe hypercalcemia can cause cardiac arrhythmias, which can be a medical emergency.

The most common causes of hypophosphatemia are decreased intake and increased renal loss. Although mild hypophosphatemia is usually asymptomatic, severe depletion (<1 mg/dL or <0.32 mmol/L) is typically associated with muscle weakness, rhabdomyolysis, paresthesia, hemolysis, platelet dysfunction, and cardiac and respiratory failure. The most common cause of hyperphosphatemia is renal dysfunction, often with a GFR below 25 mL/min. Signs and symptoms, if present, primarily result from the ensuing hypocalcemia and hyperparathyroidism.

Hypocupremia is uncommon in adults but can occur in infants, especially those born prematurely. Also susceptible are infants who have chronic diarrhea, malabsorption syndrome, or those whose diet consists mostly of milk. Prolonged hypocupremia results in neutropenia and iron-deficiency anemia that is correctable with copper.

Copper excess is not common and may result from a deliberate attempt to ingest large quantities. Similar to other metallic poisonings, acute copper poisoning leads to nausea and vomiting, intestinal cramps, and diarrhea.

Likely candidates for zinc deficiency are infants; rapidly growing adolescents; menstruating, lactating, or pregnant women; persons with low meat intake; institutionalized patients; and patients receiving parenteral nutrition solutions. Because zinc is involved with a diverse group of enzymes, its deficiency manifests in different organs and physiological systems. Zinc excess develops from chronic, high-dose zinc supplementation. Signs and symptoms include nausea, vomiting, diarrhea, drowsiness, lethargy, and increases in serum lipase and amylase concentrations.

Manganese deficiency can occur after several months of deliberate omission from the diet. Signs and symptoms include weight loss, slow hair and nail growth, color change in hair and beard, transient dermatitis, hypocholesterolemia, and hypotriglyceridemia. Manganese excess primarily occurs through inhalation of manganese compounds (e.g., manganese mines). As a result of manganese accumulation, severe neuromuscular manifestations occur, including encephalopathy and profound neurological disturbances, which mimic Parkinson disease. Inhalation of manganese products may cause manganese pneumonitis.

Chromium deficiency may be found in patients receiving prescribed chronic nutrition regimens that are low in

chromium content (e.g., parenteral nutrition solutions). Insulin resistance and impaired glucose metabolism are the main manifestations.

LEARNING POINTS

1. ***What does an abnormal serum electrolyte concentration mean?***

   ANSWER: An isolated abnormal serum electrolyte concentration may not always necessitate immediate treatment because it can be the result of a poor sample (hemolyzed blood sample), wrong timing (immediately after hemodialysis), or other confounding factors. Careful assessment of the patient's existing risk factors, history of illness, and clinical symptoms should be made to correctly interpret a specific laboratory result. Patients with abnormal serum electrolyte concentrations who are also symptomatic, especially with potentially life-threatening clinical presentations such as EKG changes, should be treated promptly. The cause or precipitating factor of the electrolyte abnormality should be identified and corrected, if possible.

2. ***How should we approach a patient who has an abnormal serum sodium concentration?***

   ANSWER: Alteration of serum sodium concentration can be precipitated by sodium alone (either excess or deficiency), or abnormal water regulation. It is important to fully assess the patient's sodium and fluid status, symptoms, physical exam findings, and medical and surgical history for factors that may precipitate sodium disorders. Because the homeostasis of sodium and water is closely regulated by the kidney, it is useful to check urine electrolytes and osmolality to help establish the diagnosis and guide clinical management.

3. ***What are the most common risk factors that can lead to hyperkalemia?***

   ANSWER: The leading cause of hyperkalemia is renal function impairment, especially acute renal insufficiency. Another important cause is drug-induced hyperkalemia (e.g., ACE inhibitors, potassium-sparing diuretic), and high-dietary intake (especially with CKD).

4. ***What is the clinical significance of abnormal serum calcium and phosphorus concentrations?***

   ANSWER: Severe hypocalcemia and hypercalcemia can result in neuromuscular problems. In addition, significant hypercalcemia may cause EKG changes and arrhythmias. Although hyperphosphatemia is not expected to cause any acute problems, severe hypophosphatemia can result in neurologic and CNS manifestations.

   In the presence of chronic hyperphosphatemia, especially in patients with CKD, the risk is increased for phosphorus to bind with calcium to form insoluble complexes which will result in soft tissue and vascular calcification. There is an increasing amount of evidence to show that such vascular calcification can increase the mortality and morbidity of CKD patients. Concurrent hypercalcemia will further increase the serum calcium–phosphorus product and exacerbate the calcification process.

5. ***What is the most common clinical presentation of hypocupremia and what are the causes of copper deficiency?***

   ANSWER: The most common clinical symptoms associated with hypocupremia are neurological symptoms, which may present as ataxia, spasticity, muscle weakness, peripheral neuropathy, loss of vision, anemia, and leukopenia. The most common causes include malabsorption and decreased nutrient consumption.

REFERENCES

1. Sterns RH, Spital A, Clark EC. Disorders of water balance. In: Kokko JP, Tannen RL, eds. Fluids and electrolytes. 3rd ed. Philadelphia: WB Saunders; 1996:63-109.
2. Berl T, Schrier RW. Disorders of water metabolism. In: Schrier RW, ed. Renal and electrolyte disorders. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:1-63.
3. Sterns RH, Nigwekar SU, Hix JK. The treatment of hyponatremia. *Semin Nephrol.* 2009; 29:282-99.
4. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis*. 2008; 52:144-53.
5. Verbalis JG, Goldsmith SR, Greenberg A et al. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med.* 2007; 120(11 Suppl 1):S1-21.
6. Halperin ML, Goldstein MB, eds. Fluid, electrolyte, and acid–base physiology: a problem-based approach. 2nd ed. Philadelphia: WB Saunders; 1994.
7. Zull DN. Disorders of potassium metabolism. *Emerg Med Clin North Am*. 1989; 7:771-94.
8. Oh MS, Carroll HJ. Electrolyte and acid-base disorders. In: Chernow B, ed. The pharmacologic approach to the critically ill patient. 3rd ed. Baltimore: Williams & Wilkins; 1994:957-68.
9. Peterson LN, Levi M. Disorders of potassium metabolism. In: Schrier RW, ed. Renal and electrolyte disorders. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:171-215.
10. Tannen RL. Potassium disorders. In: Kokko JP, Tannen RL, eds. Fluids and electrolytes. 3rd ed. Philadelphia: WB Saunders; 1996:111-99.
11. Rose BD. Diuretics. *Kidney Int*. 1991; 39:336-52.
12. Williams ME. Endocrine crises: hyperkalemia. *Crit Care Clin*. 1991; 7:155-74.
13. Freedman BI, Burkart JM. Endocrine crises: hypokalemia. *Crit Care Clin*. 1991;7:143-53.
14. James PA, Oparil S, Carter BL et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014; 311: 507-20.
15. Moser M. Current hypertension management: separating fact from fiction. *Cleve Clin J Med*. 1993; 60:27-37.
16. Papademetriou V, Burris JF, Notargiacomo A et al. Thiazide therapy is not a cause of arrhythmia in patients with systemic hypertension. *Arch Intern Med*. 1988; 148:1272-6.
17. Ellison DH. Diuretic drugs and the treatment of edema: from clinic to bench and back again. *Am J Kidney Dis*. 1994; 23:623-43.

18. Shapiro JI, Kaehny WD. Pathogenesis and management of metabolic acidosis and alkalosis. In: Schrier RW, ed. Renal and electrolyte disorders. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:115-53.
19. Kaehny WD. Pathogenesis and management of respiratory and mixed acid-base disorders. In: Schrier RW, ed. Renal and electrolyte disorders. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:154-70.
20. Koch SM, Taylor RW. Chloride ion in intensive care medicine. *Crit Care Med*. 1992; 20:227-40.
21. Alfrey AC. Normal and abnormal magnesium metabolism. In: Schrier RW, ed. Renal and electrolyte disorders. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:278-302.
22. Salem M, Munoz R, Chernow B. Hypomagnesemia in critical illness: a common and clinically important problem. *Crit Care Clin*. 1991; 7:225-52.
23. Rude RK. Magnesium disorders. In: Kokko JP, Tannen RL, eds. Fluids and electrolytes. 3rd ed. Philadelphia: WB Saunders; 1996:421-45.
24. Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. *Am J Kidney Dis*. 1994; 24:737-52.
25. Berkelhammer C, Bear RA. A clinical approach to common electrolyte problems: hypomagnesemia. *Can Med Assoc J*. 1985; 132:360-8.
26. Van-Hook JW. Endocrine crises: hypermagnesemia. *Crit Care Clin*. 1991; 7:215-23.
27. Kumar R. Calcium disorders. In: Kokko JP, Tannen RL, eds. Fluids and electrolytes. 3rd ed. Philadelphia: WB Saunders; 1996:391-419.
28. Zelis R, Moore R. Recent insights into the calcium channels. *Circulation*. 1989; 80(suppl IV):14-6.
29. Brown AJ, Dusso AS, Slatopolsky E. Vitamin D analogues for secondary hyperparathyroidism. *Nephrol Dial Transplant*. 2002; 17 (suppl)10:10-9.
30. Hruska KA, Slatopolsky E. Disorders of phosphorus, calcium, and magnesium metabolism. In: Schrier RW, Gottschalk CW, eds. Diseases of the kidney. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:2607-60.
31. Slatopolsky E, Lopez-Hilker S, Delmez J et al. The parathyroid-calcitriol axis in health and chronic renal failure. *Kidney Int*. 1990; 29(suppl):S41-7.
32. Hudson JQ, Johnson CA. Chronic renal failure. In: Young LY, Koda-Kimble MA, eds. Applied therapeutics: the clinical use of drugs. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:30.1-30.38.
33. Malluche HH, Mawad H, Koszewski NJ. Update on vitamin D and its newer analogues: actions and rationale for treatment in chronic renal failure. *Kidney Int*. 2002; 62:367-74.
34. Zaloga GP, Chernow B. Divalent ions: calcium, magnesium, and phosphorus. In: Chernow B, ed. The pharmacologic approach to the critically ill patient. 3rd ed. Baltimore: Williams & Wilkins; 1994:777-804.
35. Ritz E, Matthias S, Seidel A et al. Disturbed calcium metabolism in renal failure—pathogenesis and therapeutic strategies. *Kidney Int*. 1992; 42(suppl 38):S37-42.
36. Zaloga GP. Hypocalcemic crisis. *Crit Care Clin*. 1991; 7:191-200.
37. Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med*. 1992; 20: 251-62.
38. Mundy GR. Hypercalcemia of malignancy. *Kidney Int*. 1987;31:142-55.
39. Popovtzer MM. Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone activity. In: Schrier RW, ed. Renal and electrolyte disorders. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2003:216-77.
40. Hall TG, Schaiff RA. Update on the medical treatment of hypercalcemia of malignancy. *Clin Pharm*. 1993; 12:117-25.
41. Randall RE, Straus MB, McNeely WF et al. The milk-alkali syndrome. *Arch Intern Med*. 1961; 107:63-81.
42. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med*. 1992; 326:1196-203.
43. Davis KD, Attie MF. Management of severe hypercalcemia. *Crit Care Clin*. 1991;7:175-90.
44. Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis*. 1992;19:303-17.
45. Dennis VW. Phosphate disorders. In: Kokko JP, Tannen RL, eds. Fluids and electrolytes. 3rd ed. Philadelphia: WB Saunders; 1996:359-90.
46. Peppers MP, Geheb M, Desai T. Endocrine crises: hypophosphatemia and hyperphosphatemia. *Crit Care Clin*. 1991; 7:201-14.
47. Halevy J, Bulvik S. Severe hypophosphatemia in hospitalized patients. *Arch Intern Med*. 1988; 148:153-55.
48. Williams SR, ed. Nutrition and diet therapy. St. Louis, MO: CV Mosby; 1993.
49. Flodin N, ed. Pharmacology of micronutrients. New York: Alan R Liss; 1988.
50. Robinson CH, Lawler MR, Chenoweth WL et al., eds. Normal and therapeutic nutrition. 7th ed. New York: Macmillan; 1990.
51. Grant JP, Ross LH. Parenteral nutrition. In: Chernow B, ed. The pharmacologic approach to the critically ill patient. 3rd ed. Baltimore: Williams & Wilkins; 1994:1009-33.
52. Lindeman RD. Minerals in medical practice. In: Halpern SL, ed. Quick reference to clinical nutrition. 2nd ed. Philadelphia: JB Lippincott; 1987:295-323.
53. Hurley LS. Clinical and experimental aspect of manganese in nutrition. In: Prasad AR, ed. Clinical, biochemical, and nutritional aspects of trace elements. New York: Alan R Liss; 1982:369-78.
54. Mertz W. Clinical and public health significance of chromium. In: Prasad AS, ed. Clinical, biochemical, and nutritional aspects of trace elements. New York: Alan R Liss; 1982:315-23.
55. De Haan KE, De Goeij JJ, Van Den Hamer CJ et al. Changes in zinc metabolism after burns: observations, explanations, clinical implications. *J Trace Elem Electrolytes Health Dis*. 1992; 6:195-201.
56. Foote JW, Delves HT. Albumin bound and alpha-2-macroglobumin bound zinc concentrations in the sera of healthy adults. *J Clin Pathol*. 1984; 37:1050-4.
57. Cefalu WT, Hu FB. Role of chromium in human health and in diabetes. *Diabetes Care*. 2004; 27:2741-51.
58. Guallar E, Jiménez FJ, van 't Veer P et al. Low toenail chromium concentration and increased risk of nonfatal myocardial infarction. *Am J Epidemiol*. 2005; 162:157-64.

QUICKVIEW | Sodium

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	135–145 mEq/L (135–145 mmol/L)	Useful for assessment of fluid status
Pediatrics: premature neonates	128–148 mEq/L (128–148 mmol/L)	
Pediatrics: older children	138–145 mEq/L (138–145 mmol/L)	
Critical value	>160 or <120 mEq/L (>160 or <120 mmol/L)	Acute changes more dangerous than chronic abnormalities
Natural substance?	Yes	Most abundant cation in extracellular fluid
Inherent activity?	Yes	Maintenance of transmembrane electric potential
Location		
Storage	Mostly in extracellular fluid	
Secretion/excretion	Filtered by kidneys, mostly reabsorbed; some secretion in distal nephron	Closely related to water homeostasis
Major causes of…		
High results	Multiple (discussed in text)	Can occur with low, normal, or high total body sodium
Associated signs and symptoms	Mostly neurological	List 6-2
Low results	Multiple (discussed in text)	Can occur with low, normal, or high total body sodium
Associated signs and symptoms	Mostly neurological	List 6-1
After insult, time to…		
Initial elevation or positive result	Hours to years, depending on chronicity	The faster the change, the more dangerous the consequences
Peak values	Hours to years, depending on chronicity	
Normalization	Days, if renal function is normal	Faster with appropriate treatment
Drugs often monitored with test	Diuretics, ACE inhibitors, aldosterone antagonists, angiotensin II antagonists, ADH analogs	Any drug that affects water homeostasis
Causes of spurious results	None	

ACE = angiotensin-converting enzyme; ADH = antidiuretic hormone.

QUICKVIEW | Potassium

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults and pediatrics	3.8–5 mEq/L (3.8–5 mmol/L)	Age: >10 days old
Critical value	>7 or <2.5 mEq/L (>7 or <2.5 mmol/L)	Acute changes more dangerous than chronic abnormalities
Natural substance?	Yes	Most abundant cation; 98% in intracellular fluid
Inherent activity?	Yes	Control of muscle and nervous tissue excitability, acid–base balance, intracellular fluid balance
Location		
Storage	98% in intracellular fluid	
Secretion/excretion	Mostly secreted by distal nephron	Some via GI tract secretion
Major causes of…		
High results	Renal failure (GFR <10 mL/min)	Especially with increased intake
Associated signs and symptoms	Mostly cardiac	EKG changes, bradycardia, hypotension, cardiac arrest
Low results	Decreased intake or increased loss	Usually combination of the two
Associated signs and symptoms	Affects primarily cardiac system	Table 12-7
After insult, time to…		
Initial elevation or positive result	Hours to years, depending on chronicity	Acute changes can be life-threatening
Peak values	Hours to years, depending on chronicity	
Normalization	Days, if renal function is normal	Faster with appropriate treatment
Drugs often monitored with test	Diuretics, ACE inhibitors, amphotericin B, angiotensin receptor antagonists, cisplatin, trimethoprim	Some drugs are administered as potassium salts Be aware of potassium-sparing medications
Causes of spurious results	Hemolyzed samples (falsely elevated)	High potassium content in erythrocytes

ACE = angiotensin-converting enzyme; EKG = electrocardiogram; GFR = glomerular filtration rate; GI = gastrointestinal.

QUICKVIEW | Chloride

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults and pediatrics	95–103 mEq/L (95–103 mmol/L)	
Critical value		Depends on underlying disorder
Natural substance?	Yes	
Inherent activity?	Yes	Primary anion in extracellular fluid and gastric juice, cardiac function, acid–base balance
Location		
Storage	Extracellular fluid	Most abundant extracellular anion
Secretion/excretion	Passively follows sodium and water	Also influenced by acid–base balance
Major causes of…		
High results	Dehydration	
	Acidemia	
Associated signs and symptoms	Associated with underlying disorder	
Low results	Nasogastric suction	
	Vomiting	
	Serum dilution	
	Alkalemia	
Associated signs and symptoms	Associated with underlying disorder	
After insult, time to…		
Initial elevation or positive result	Hours to years, depending on chronicity	The faster the change, the more dangerous the consequences
Peak values	Hours to years, depending on chronicity	
Normalization	Days, if renal function is normal	Faster with appropriate treatment of underlying disorder
Drugs often monitored with test	Loop diuretics, chloride-containing IV fluids (e.g., saline solution), parenteral nutrition, drugs that cause diarrhea	
Causes of spurious results	Bromides; iodides (falsely elevated)	

IV = intravenous.

QUICKVIEW | Magnesium

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults and pediatrics	1.7 –2.4 mEq/L (0.7 –0.99 mmol/L)	
	1.4–2 mEq/L	
Critical value	>5 or <1 mEq/L (>2.5 or <0.5 mmol/L)	Acute changes more dangerous than chronic abnormalities
Natural substance?	Yes	
Inherent activity?	Yes	Enzyme cofactor, thermoregulation, muscle contraction, nerve conduction, calcium and potassium homeostasis
Location		
Storage	50% bone, 45% intracellular fluid, 5% extracellular fluid	
Secretion/excretion	Filtration by kidneys	3–5% reabsorbed
Major causes of...		
High results	Renal failure	Usually in presence of increased intake
Associated signs and symptoms	Neuromuscular manifestations	Table 12-9
Low results	Excessive loss from GI tract or kidneys	Alcoholism and diuretics
	Decreased intake	
Associated signs and symptoms	Neuromuscular and cardiovascular manifestations including weakness, muscle fasciculation, tremor, tetany, increased reflexes, and EKG abnormalities	More severe with acute changes
After insult, time to...		
Initial elevation or positive result	Hours to years, depending on chronicity	The faster the change, the more dangerous the consequences
Peak values	Hours to years, depending on chronicity	
Normalization	Days, if renal function is normal	Faster with appropriate treatment
Drugs often monitored with test	Diuretics, proton pump inhibitors	
Causes of spurious results	Hemolyzed samples (falsely elevated)	

EKG = electrocardiogram; GI = gastrointestinal.

QUICKVIEW | Calcium

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	Total calcium: 9.2–11 mg/dL (2.3–2.8 mmol/L) Ionized calcium: 4.6–5.8 mg/dL (1.16–1.45 mmol/L)	Approximately half of calcium in the blood is bound to serum proteins; only ionized (free) calcium is physiologically active
Pediatrics	Total calcium: 8–10.5 mg/dL (2–2.6 mmol/L) Ionized calcium: 1.16–1.45 mmol/L	See Chapter 21 for detailed listing of normal ranges based on patient's age
Critical value	>14 or <7 mg/dL (>3.5 or <1.8 mmol/L)	Also depends on serum albumin and pH values
Natural substance?	Yes	
Inherent activity?	Yes	Preservation of cellular membranes, propagation of neuromuscular activity, regulation of endocrine functions, blood coagulation, bone metabolism, phosphate homeostasis
Location		
Storage	99.5% in bone and teeth	Very closely regulated
Secretion/excretion	Filtration by kidneys	Small amounts excreted into GI tract from saliva, bile, and pancreatic and intestinal secretions
Major causes of…		
High results	Malignancy	Also thiazide diuretics, lithium, vitamin D, teriparatide, and calcium supplements
	Hyperparathyroidism	More severe with acute onset
Associated signs and symptoms	Vague GI complaints neurological and cardiovascular symptoms, and renal dysfunction	
Low results	Vitamin D deficiency Chronic kidney disease Hypoparathyroidism Hyperphosphatemia Pancreatitis Loop diuretics Calcitonin Denosumab	Hypocalcemia due to hypoalbuminemia is asymptomatic (ionized calcium concentration unaffected)
Associated signs and symptoms	Primarily neuromuscular (e.g., fatigue, depression, memory loss, hallucinations, seizures, tetany)	More severe with acute onset
After insult, time to…		
Initial elevation or positive result	Hours to years, depending on chronicity	The faster the change, the more dangerous the consequences
Peak values	Hours to years, depending on chronicity	
Normalization	Days, if renal function is normal	Faster with appropriate treatment
Drugs often monitored with test	Loop diuretics, calcitonin, vitamin D, calcium supplements, phosphate binders	
Causes of spurious results	Hypoalbuminemia	Ionized calcium concentration usually unaffected

GI = gastrointestinal.

QUICKVIEW | Phosphate

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	2.3–4.7 mg/dL (0.74–1.52 mmol/L)	
Pediatrics	4–7.1 mg/dL (1.3–2.3 mmol/L)	See Chapter 21 for detailed listing of normal ranges based on patient's age
Critical value	>8 or <1 mg/dL (>2.6 or <0.3 mmol/L)	Acute changes more dangerous than chronic abnormalities
Natural substance?	Yes	Most abundant intracellular anion
Inherent activity?	Yes	Bone and tooth integrity, cellular membrane integrity, phospholipid synthesis, acid–base balance, calcium homeostasis, enzyme activation, formation of high-energy bonds
Location		
Storage	Extracellular fluid, cell membrane structure, intracellular fluid, collagen, bone	85% in bone
Secretion/excretion	Filtration by kidneys	Mostly reabsorbed
Major causes of…		
High results	Decreased renal excretion	Renal failure the most common cause
	Extracellular shifting	
	Increased intake of phosphate or vitamin D	
Associated signs and symptoms	Due primarily to hypocalcemia and hyperparathyroidism	See Quickview for calcium (hypocalcemia)
Low results	Increased renal excretion	Also can occur in renal failure
	Intracellular shifting	
	Decreased intake of phosphate or vitamin D	
Associated signs and symptoms	Bone pain, weakness, malaise, hypocalcemia, cardiac failure, respiratory failure	Usually due to diminished intracellular ATP and erythrocyte 2,3-DPG concentrations
After insult, time to…		
Initial elevation or positive result	Usually over months to years	
Peak values	Usually over months to years	
Normalization	Over days with renal transplantation	
Drugs often monitored with test	Vitamin D, phosphate binders	
Causes of spurious results	Hemolyzed samples (falsely elevated) and methotrexate (falsely elevated)	

ATP = adenosine triphosphate.

QUICKVIEW | Copper

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	70–140 mcg/dL (11–22 µmol/L) (males); 80–155 mcg/dL (13–24 µmol/L) (females)	
Pediatrics	20–70 mcg/dL (3.1–11 µmol/L)	0–6 mo
	90–190 mcg/dL (14.1–29.8 µmol/L)	6 yr
	80–160 mcg/dL (12.6–25.1 µmol/L)	12 yr
Critical value	Not applicable	
Natural substance?	Yes	
Inherent activity?	Yes	Companion to iron enzyme cofactor, hemoglobin synthesis, collagen and elastin synthesis, metabolism of many neurotransmitters, energy generation, regulation of plasma lipid levels, cell protection against oxidative damage
Location		
Storage	One third in liver and brain; one third in muscles; the rest in heart, spleen, kidneys, and blood (erythrocytes and neutrophils)	95% of circulating copper is protein bound as ceruloplasmin
Secretion/excretion	Mainly by biliary excretion; only 0.5–3% of daily intake found in urine	
Major causes of…		
High results	Deliberate ingestion of large amounts (>15 mg of elemental copper) Wilson disease	Uncommon in humans
Associated signs and symptoms	Nausea, vomiting, intestinal cramps, diarrhea	Larger ingestions lead to shock, hepatic necrosis, intravascular hemolysis, renal impairment, coma, and death
Low results	Infants with chronic diarrhea	
	Malabsorption syndromes	
	Decreased intake over months	
	Menkes syndrome	
Associated signs and symptoms	Neutropenia, iron-deficiency anemia, abnormal glucose tolerance, arrhythmias, hypercholesterolemia, atherosclerosis, depressed immune function, defective connective tissue formation, demineralization of bones	Can affect any system or organ whose enzymes require copper for proper functioning
Drugs often monitored with test	Copper supplements, possibly during chronic total parenteral nutrition	Serum copper concentrations not routinely monitored

QUICKVIEW | Zinc

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults and pediatrics	50–150 mcg/dL (7.7–23 µmol/L)	Increased risk for developing symptomatic zinc deficiency
Critical value	<50 mcg/dL (<7.7 µmol/L)	
Natural substance?	Yes	
Inherent activity?	Yes	Enzyme constituent and cofactor; carbohydrate, protein, lipid, and nucleic acid metabolism; tissue growth; tissue repair; cell membrane stabilization; bone collagenase activity and collagen turnover; immune response; food intake control; spermatogenesis and gonadal maturation; normal testicular function
Location		
Storage	Liver, pancreas, spleen, lungs, eyes (retina, iris, cornea, lens), prostate, skeletal muscle, bone, erythrocytes, neutrophils	60–62% in skeletal muscle, 20–28% in bone, 2–4% in liver
Secretion/excretion	Primarily in pancreatic and intestinal secretions; also lost dermally through sweat, hair and nail growth, and skin shedding	Except in certain disease states, only 2% lost in urine
Major causes of...		
High results	Large intake	Uncommon in humans
Associated signs and symptoms	Drowsiness, lethargy, nausea, vomiting, diarrhea, increases in serum lipase and amylase concentrations	
Low results	Low intake (infants)	Rare from inadequate dietary intake
	Decreased absorption (acrodermatitis enteropathica)	
	Increased utilization (rapidly growing adolescents and menstruating, lactating, or pregnant women)	
	Increased loss (hyperzincuria)	
Associated signs and symptoms	Manifests in numerous organs and physiological systems	Table 12-3
Drugs often monitored with test	Zinc supplements, possibly during chronic total parenteral nutrition	Serum zinc concentrations not routinely monitored
Causes of spurious results	Hemolyzed samples; 24-hr intrapatient variability	High zinc content in erythrocytes and neutrophils

QUICKVIEW | Manganese

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	Varies depending on array method, whether sample is blood or plasma, and patient age	
Pediatrics	2–3 mcg/L (36–55 nmol/L)	
	2.4–9.6 mcg/L (44–175 nmol/L)	Newborn
	0.8–2.1 mcg/L (15–38 nmol/L)	2–18 yr
Critical value	Not applicable	
Natural substance?	Yes	
Inherent activity?	Yes	Enzyme cofactor; carbohydrate, protein, and lipid metabolism; protection of cells from free radicals; steroid biosynthesis; metabolism of biogenic amines; normal brain function
		Magnesium may substitute for manganese in most instances
Location		
Storage	Bone, liver, pancreas, pituitary gland	Circulating manganese loosely bound to transmanganin
Secretion/excretion	Primarily in biliary and pancreatic secretions; limited excretion in urine	Other GI routes also may be used in manganese overload
Major causes of…		
High results	Primarily through inhalation of manganese compounds, such as in manganese mines	One of least toxic trace elements
Associated signs and symptoms	Encephalopathy and profound neurological disturbances mimicking Parkinson disease	Accumulates in liver and brain
Low results	After several months of deliberate omission from diet	Rare from inadequate dietary intake
Associated signs and symptoms	Weight loss, slow hair and nail growth, hair color change, transient dermatitis, hypocholesterolemia, hypotriglyceridemia	Seen mostly in experimental subjects
Drugs often monitored with test	Manganese supplements, possibly during chronic total parenteral nutrition	Serum manganese concentration not routinely monitored

GI = gastrointestinal.

QUICKVIEW | Chromium

PARAMETER	DESCRIPTION	COMMENTS
Common reference ranges		
Adults	0.3–0.9 ng/mL, serum 0.7–28 ng/mL, whole blood	Analysis of chromium in biological fluids and tissues is difficult
Pediatrics	Unknown	Analysis of chromium in biological fluids and tissues is difficult
Critical value	Unknown	
Natural substance?	Yes	
Inherent activity?	Yes	Cofactor for insulin and metabolism of glucose, cholesterol, and triglycerides
Location		
Storage	Hair, kidneys, skeleton, liver, spleen, lungs, testes, large intestines	Chromium circulates as free Cr3+, bound to transferrin and other proteins, and as an organic complex
Secretion/excretion	Excretion in urine	Circulating insulin may affect excretion
Major causes of...		
Low results	Decreased intake	
Associated signs and symptoms	Glucose intolerance; hyperinsulinemia; hypercholesterolemia; possibly, increased risk of cardiovascular disease	Mainly due to its role as insulin cofactor
Drugs often monitored with test	Chromium supplement, possibly during chronic total parenteral nutrition	Serum chromium concentration not routinely monitored