EDUCATIONAL COMMENTARY – ELECTROLYTES: Na⁺, K⁺, Ca⁺, Mg⁺

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LEARNING OUTCOMES
On completion of this exercise, the participant should be able to

- discuss the role of sodium, potassium, calcium, and magnesium in the body;
- explain how sodium, potassium, calcium, and magnesium are regulated by the body;
- identify causes of sodium, potassium, calcium, and magnesium imbalances; and
- identify symptoms of sodium, potassium, calcium, and magnesium imbalances.

INTRODUCTION

The human body is a remarkable machine. Mechanisms within the body maintain fluid balance, electroneutrality, and pH within very tight ranges. Electrolytes, ions capable of carrying an electric charge, play an important role in this process as they regulate fluid volume, osmotic pressure, acid-base balance, myocardial cell contractibility, and neuromuscular cell excitability. Approximately 60% of body weight is water, and bodily fluid is typically divided into two major compartments, the intracellular fluid (ICF) and the extracellular fluid (ECF). The ICF, located within the cell membrane, accounts for roughly 66% of total body water and contains primarily potassium ions (K⁺) and phosphate ions (PO₄⁻).¹ The ECF, defined as the fluid found outside the cell membranes, can be further subdivided into the interstitial fluid (fluid between and around the cells) and the intravascular fluid (plasma). The ECF is composed primarily of sodium ions (Na⁺) and chloride ions (Cl⁻). Sodium, K⁺, calcium (Ca⁺²), and magnesium (Mg⁺²) are the primary cations, positively charged ions, in the body and exist in different concentrations in the various compartments of the body.

Sodium (Na⁺)

Role/Function
Sodium is the major cation of the ECF, accounting for approximately 90% of all the extracellular cations.² Owing to its abundance, Na⁺ plays a significant role in water distribution, plasma volume, and maintenance of osmotic pressure. Slight changes in plasma Na⁺ concentration will result in substantial changes in plasma volume. When Na⁺ is lost from the plasma, plasma volume is decreased as extracellular water shifts into the cells to restore normal plasma osmolality and Na⁺ concentration. In contrast, an increased concentration of Na⁺ in the ECF triggers an increase in plasma volume to reduce elevated plasma osmolality. In addition to its role in maintaining osmotic pressure, Na⁺ also functions in the maintenance of acid-base balance and excitation of nerve and muscle cells.
Regulation
Changes in plasma osmolality and volume resulting from variations in Na⁺ concentration initiate a series of regulatory effects on osmoreceptors and endocrine glands to alter intake and excretion of water. Hyperosmotic conditions or decreased blood volume as the result of increased Na⁺ concentration trigger osmoreceptors of the hypothalamus, producing the sensation of thirst. Increased fluid intake increases the water content of the ECF, thereby diluting elevated levels of Na⁺ and decreasing the plasma osmolality. In the presence of antidiuretic hormone (ADH) or vasopressin, aldosterone, and natriuretic peptides, the kidneys also play a key role in the regulation of Na⁺. Antidiuretic hormone, released from the posterior pituitary gland in response to increased plasma osmolality and/or decreased plasma volume, acts on the distal convoluted tubules (DCT) and collecting ducts of the nephron to increase renal water resorption, thereby increasing plasma volume and decreasing plasma osmolality. Pressure-sensing mechanisms of the juxtaglomerular apparatus in the afferent arteriole of the nephron also respond to changes in blood pressure due to variations in circulating blood volume. Decreased pressure to the juxtaglomerular apparatus due to decreased ECF volume causes the kidney to release renin and the eventual stimulation of the adrenal cortex to release aldosterone. Aldosterone in turn acts on the DCT to increase Na⁺ resorption and water retention. When the juxtaglomerular apparatus senses increased pressure, it inhibits secretion of renin and aldosterone. Natriuretic peptides promote renal excretion of water and Na⁺ by decreasing resorption in the proximal convoluted tubules.

Hyponatremia
Hyponatremia, the decreased concentration of plasma Na⁺, is due to increased loss of Na⁺ (depletional hyponatremia), or increased water retention or water imbalance related to Na⁺ loss (dilutional hyponatremia). Depletional hyponatremia can result from renal or nonrenal losses. Renal loss of Na⁺ is seen with the use of diuretics that inhibit resorption of Cl⁻ and Na⁺ in the ascending loop of Henle (e.g., thiazides), in patients with hypoaldosteronism (Addison disease) where Na⁺ is lost to the urine due to lack of Na⁺ resorption, with salt-wasting nephropathies such as chronic interstitial nephritis and polycystic kidney disease, and in metabolic alkalosis with prolonged vomiting where renal loss of Na⁺ accompanies renal bicarbonate (HCO₃⁻) excretion. Nonrenal loss of Na⁺ can occur via the gastrointestinal (GI) tract (eg, vomiting and diarrhea) or the skin (eg, severe burns and trauma).

Dilutional hyponatremia is the result of decreased plasma concentrations of Na⁺ due to increased plasma water volume. Causes of dilutional hyponatremia include excess water intake; syndrome of inappropriate ADH (SIADH), in which excess ADH secretion leads to increased renal water retention; generalized edema; acute and chronic renal failure; and hyperglycemia. Patients with generalized edema due to conditions such as congestive heart failure, cirrhosis, and nephrotic syndrome may experience dilutional hyponatremia resulting from decreased plasma volume. This decreased plasma volume stimulates the release of ADH and results in renal water retention. With hyperglycemia, high solute concentrations in
the ECF lead to an extracellular shift of water from the inside of cell to the ECF to restore osmotic equilibrium, thereby diluting the Na⁺ concentration.

**Hypernatremia**
Hypernatremia, an elevated concentration of Na⁺, is caused by decreased water intake, excess water loss relative to Na⁺ loss, and/or increased Na⁺ intake or retention. Those at greatest risk for hypernatremia are people who are unable to rehydrate themselves despite a normal thirst reflex, such as the elderly, people with altered mental status, and infants. Excess water loss relative to Na⁺ loss is seen with GI tract loss (eg, vomiting and diarrhea); excessive sweating without proper fluid replacement (eg, prolonged fever or exercise); and diabetes insipidus (lack of ADH or lack of response resulting in decreased water resorption and excessive water lost in the urine). Ingestion of large amounts of Na⁺ salts or infusion of large amounts of sodium chloride (NaCl) or sodium bicarbonate (NaHCO₃) may result in a net increase in Na⁺ concentration relative to water. Excess aldosterone as seen in hyperaldosteronism causes an increase in Na⁺ resorption in the kidneys and leads to hypernatremia as well.

**Symptoms of Sodium Imbalance**
Symptoms of Na⁺ imbalance result from changes in osmolality rather than as a direct consequence of the altered plasma Na⁺ concentration. Symptoms of hyponatremia are caused by swelling of the cells as water moves in to adjust the osmotic pressure of the ECF and ICF. Symptoms of hypernatremia are caused by dehydration of cells as water is lost to the ECF. Symptoms of hyponatremia and hypernatremia are similar and include both neurologic symptoms (eg, headache, lethargy, muscle weakness and loss of coordination, mental confusion, seizures, and coma) and GI tract symptoms (eg, nausea and vomiting).

**Potassium (K⁺)**
**Role/Function**
Potassium is the body’s major intracellular cation, with 98% of K⁺ located in the ICF.¹ The ratio of intracellular to extracellular K⁺ concentration results in a voltage difference across the cell membrane when the cell is at rest (resting membrane potential), making K⁺ a major determinant of resting membrane potential and essential for neuromuscular cell excitability. Alterations in resting membrane potential change the distance between the resting membrane potential and the threshold potential necessary to initiate an action potential and nerve impulse. Elevations in plasma K⁺ concentration decrease resting membrane potential, and result in less separation between the resting membrane potential and the threshold potential. Conversely, low plasma K⁺ concentrations increase resting membrane potential and move it farther from the threshold potential. The resulting overall difference between the cells’ resting membrane potential and threshold potential leads to alterations in cell excitability, causing muscle
weakness, paralysis, or arrhythmia. Potassium also participates in cellular metabolism in the regulation of protein and glycogen synthesis.

**Regulation**
Following consumption from food sources, $K^+$ is absorbed in the GI tract. A small amount is absorbed by muscle and liver cells, while most is excreted by the kidneys. Within the kidneys, $K^+$ filtered by the glomerulus is almost completely resorbed in the proximal convoluted tubules. Under the indirect control of aldosterone, $K^+$ is secreted in the urine in exchange for $Na^+$ in the DCT. To maintain the high intracellular concentrations of $K^+$ and high extracellular concentrations of $Na^+$, $K^+$ is constantly being transported into the cell and $Na^+$ out of the cell against the concentration gradient via the Na-K-ATPase pump in the cell membrane.

**Hypokalemia**
Defined as a decreased plasma $K^+$ concentration, hypokalemia can be due to renal loss, GI tract loss, or increased cellular uptake. The most common cause of hypokalemia due to renal loss is the use of diuretics that act on the proximal convoluted tubules to increase the flow of the filtrate through the tubules, thereby enhancing the excretion of $K^+$. In renal tubular acidosis, potassium excretion in the urine will increase to maintain electroneutrality as $H^+$ excretion is decreased. Increased renal $K^+$ excretion will also occur with increased $Na^+$ resorption in hyperaldosteronism. Hypomagnesemia will cause hypokalemia via the enhanced secretion of aldosterone and diminished activity of the Na-K-ATPase pump. Excess loss of $K^+$ from the GI tract and a resultant hypokalemia may result from vomiting, diarrhea, gastric suction, malabsorption, and laxative abuse. Alkalosis and insulin overdose both cause hypokalemia through a cellular shift of $K^+$. In alkalosis, a deficit of $H^+$ in the ECF causes more $H^+$ to move from the cell to the ECF and $K^+$ to move into the cell to maintain electrical neutrality. Insulin promotes the entry of $K^+$ into skeletal muscle and liver cells.

**Hyperkalemia**
Increased plasma $K^+$, or hyperkalemia, is seen in conditions with impaired renal excretion, altered cellular uptake, increased cell lysis, and/or increased intake. Renal excretion of $K^+$ is impaired in acute and chronic renal failure, by certain diuretics, and in hypoaldosteronism. Cellular potassium uptake is altered in the presence of diabetes mellitus with insulin deficiency as the hyperglycemia and resultant hyperosmolar plasma pulls water and $K^+$ from the cells. In metabolic acidosis, buffering of excess $H^+$ within the cells causes $K^+$ to exit the cells to maintain electro-neutrality. Digoxin toxicity is associated with a cellular shift in $K^+$ concentration and a resultant hyperkalemia as the Na-K-ATPase pump is inhibited. Increased cell lysis in muscle cells and white and red blood cells resulting from intravascular hemolysis, traumatic injury, or tumor lysis syndrome releases $K^+$ from the $K^+$-rich intracellular environment. The most common cause of hyperkalemia in hospitalized patients is increased intake via oral or intravenous $K^+$.
replacement therapy. Artifactual hyperkalemia or pseudohyperkalemia is commonly the result of sample hemolysis, prolonged tourniquet use, or excessive fist clenching, and release of K⁺ from red blood cells, white blood cells, and platelets during coagulation in vitro.

**Symptoms of Potassium Imbalance**

Symptoms of K⁺ imbalance are directly related to the changes produced in the cells’ resting membrane potential, which thereby alter neuromuscular conduction and produce cardiac-conduction defects. Hypokalemia causes an increase in the resting membrane potential, resulting in a decrease in cell excitability and causing muscle weakness, muscle cramps, paralysis, and tachycardia with the possibility of cardiac arrest. Although hyperkalemia initially causes an increase in cell excitability due to a decrease in the resting membrane potential, continued depolarization of the cell membranes causes inactivation of the Na⁺ channels in the cell membrane and an eventual decrease in cell excitability. Symptoms include muscle weakness, paralysis, conduction defects, respiratory muscle weakness, and bradycardia. Potassium levels greater than 10.0 mEq/L (10.0 mmol/L) are almost always associated with death due to vascular collapse of the heart.³

**Calcium (Ca²⁺)**

**Role/Function**

Calcium is the fifth most abundant element in the body. Calcium performs many important functions in the body, including bone mineralization, muscle contraction and excitability, blood hemostasis, and plasma membrane stability. Intracellularly, Ca²⁺ acts as an important second messenger in enzyme activation. Ninety-eight percent of the body’s Ca²⁺ is found as hydroxyapatite crystals in the skeleton and the remainder exists in 3 forms: ionized; bonded with anions bicarbonate, lactate, phosphate, or citrate; or bound to plasma proteins (predominantly albumin). Approximately 50% of the plasma Ca²⁺ exists in the ionized form which is the only physiologically active form. Another 10% of plasma Ca²⁺ is associated with anions and 40% is bound to proteins.⁴ Most laboratories offer both total Ca²⁺ and ionized Ca²⁺ measurements. Ionized Ca²⁺ is a more reliable indicator of Ca²⁺ disorders, as total Ca²⁺ measurements are often altered by changes in concentrations of anions and plasma proteins. As plasma concentrations of anions and proteins change due to serious illness or surgery, so does the concentration of bound Ca²⁺ and, therefore, the total Ca²⁺ measurement. Ionized Ca²⁺ levels, however, will remain unchanged.

**Regulation**

Calcium homeostasis is maintained by 3 regulators: parathyroid hormone (PTH), vitamin D, and calcitonin. Parathyroid hormone is released from the parathyroid gland in response to low plasma levels of ionized Ca²⁺. To restore ionized Ca²⁺ when plasma levels are low, PTH increases bone resorption by activating osteoclastic cells, which break down the hydroxyapatite crystals and release Ca²⁺ into the plasma. Parathyroid hormone also acts on the kidneys to enhance the resorption of Ca²⁺ in the renal
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tubules and stimulate the production of the active form of vitamin D, 1,25-(OH)₂D₃. This form of vitamin D acts to promote Ca⁺² absorption in the intestine and kidneys and stimulates bone resorption. Calcitomin, secreted by the parafollicular cells of the thyroid gland, is released in response to high Ca⁺² concentrations to counteract the effects of PTH and vitamin D by inhibiting osteoclastic activity of the bone and resorption of Ca⁺² in the kidneys.

**Hypocalcemia**

Hypocalcemia is often the result of chronic renal failure due to decreased synthesis of 1,25-(OH)₂D₃ and hyperphosphatemia as PO₄⁻ binds and lowers Ca⁺². Magnesium deficiency causes vitamin D resistance and inhibits the secretion and impairs the action of PTH, resulting in hypocalcemia. In primary hypoparathyroidism, decreased PTH excretion results in an increased excretion of Ca⁺² in the kidneys and abnormal vitamin D metabolism. Although rare, pseudohypoparathyroidism is a hereditary disorder that leads to Ca⁺² loss in the urine as a result of organ resistance to PTH in the presence of adequate PTH release. In addition, vitamin D deficiency and acute pancreatitis also cause decreased levels of Ca⁺². Hypoalbuminemia caused by chronic disease is the most common cause of decreased total Ca⁺² concentrations. While total calcium levels are decreased due to albumin deficiency, ionized Ca⁺² levels will be normal, illustrating the necessity for the use of ionized Ca⁺² levels in patients who are severely ill.

**Hypercalcemia**

The most common cause of hypercalcemia is primary hyperparathyroidism, with cancer running a close second. Hypercalcemia as a result of cancer is due to parathyroid hormone–related protein (PTHrP)–producing tumors associated with squamous cell cancers of the lung and other epithelial cell carcinomas. PTHrP binds to PTH receptors, causing the release of Ca⁺² from bone and inhibiting Ca⁺² excretion in the kidneys. Immobilization and bone metastases as seen with malignant melanoma, breast cancer, and lymphoma will increase plasma Ca⁺² by stimulating bone resorption. Additional causes of hypercalcemia include vitamin D intoxication, thiazide diuretics, renal failure, and hyperthyroidism (owing to the location of the parathyroid glands, embedded in the thyroid gland).

**Symptoms of Calcium Imbalance**

Owing to the role of Ca⁺² in neuromuscular activity, Ca⁺² imbalances often manifest as neuromuscular symptoms. Symptoms of hypocalcemia are the result of increased excitability of neuromuscular function and include tetany, muscle cramps, paresthesia, seizures, confusion, hallucinations, and cardiac arrhythmias. When Ca⁺² concentrations are elevated (hypercalcemia), decreased activity in nerve and muscle cells results in weakness, anorexia, lethargy, confusion, impaired concentration, and changes in cardiac function. Hypercalcemia is also associated with deposition of calcium in soft tissues of the kidney, joints, and cornea.
Magnesium (Mg^{2+})

**Role/Function**
Magnesium is the second-most abundant intracellular cation. Most of the total body Mg^{2+} is found in bone, with approximately 1% of the body’s total Mg^{2+} found in the plasma. Magnesium acts as a cofactor for more than 300 enzymes essential to normal body function. It plays an important role in neuromuscular transmission as well as in the synthesis of proteins, nucleic acids, carbohydrates, and lipids. It is required for ion transport and regulates intracellular K^+ movement.

**Regulation**
Although most of total body Mg^{2+} is found in the bone, bone stores do not readily transfer Mg^{2+} into the circulation. Regulation of Mg^{2+} occurs in the kidneys, where changes in intake are balanced by changes in urinary resorption under the influence of plasma Mg^{2+} concentrations, plasma Ca^{2+} concentrations, acid-base status, and several hormones. The renal threshold for Mg^{2+} is very close to the normal plasma concentration; therefore, increased excretion by the kidneys can be prompted with only slight elevations in plasma Mg^{2+}. In deficient states, Mg^{2+} is readily absorbed in the loop of Henle and DCT. Increased plasma Ca^{2+} concentrations, metabolic acidosis, and hypokalemia influence Mg^{2+} transport by inhibiting Mg^{2+} resorption in the loop of Henle. Although several hormones alter the resorption of Mg^{2+} in the kidneys, unlike with Na^+, K^+, and Ca^{2+}, no hormones are associated with Mg^{2+} homeostasis.

**Hypomagnesemia**
Hypomagnesemia is most often seen in hospitalized cases. The main sources of hypomagnesemia are reduced intake, GI tract loss, and renal loss. Intestinal loss may occur with severe diarrhea, malabsorption syndromes, nasogastric suctioning, pancreatitis, laxative abuse, and gastrointestinal bypass surgery. Increased renal excretion of Mg^{2+} is attributed to renal tubular disorders, metabolic acidosis, hypercalcemia, hyperaldosteronism, hyperparathyroidism, and drugs such as diuretics, cyclosporine, and aminoglycosides.

**Hypermagnesemia**
Although not as common as hypomagnesemia, hypermagnesemia is most commonly seen with renal failure and Mg^{2+} intoxication. Because the kidneys are the main regulators of Mg^{2+} homeostasis, plasma levels of Mg^{2+} will rise as kidney function is diminished and Mg^{2+} excretion is impaired. Those at greatest risk for hypermagnesemia are persons with renal failure who also take medications containing magnesium (eg, antacids, enemas, or laxatives). Decreased renal excretion of Mg^{2+} is also seen with hypoaldosteronism, hypothyroidism, and hypopituitarism. Hypermagnesemia may occur with therapeutic intravenous magnesium administration in preeclampsia or eclampsia where it is given to increase uterine blood flow and decrease uterine contractions.
Symptoms of Magnesium Imbalance
Symptoms of Mg\(^{2+}\) imbalance manifest as neuromuscular malfunction, cardiovascular malfunction, and abnormalities in Ca\(^{2+}\) metabolism. Neuromuscular malfunctions related to the role of Mg\(^{2+}\) in the regulation of acetylcholine at the neuromuscular junction are evidenced in hypomagnesemia with increased neuromuscular excitability, whereas hypermagnesemia depresses the neuromuscular system. Alteration of Mg\(^{2+}\) concentration also disrupts the balance of other essential electrolytes (ie, K\(^{+}\) and Ca\(^{2+}\)), leading to an alteration in Na-K-ATPase pump activity and a resultant change in resting membrane potential, causing cardiovascular malfunction and electrocardiogram changes. Because Ca\(^{2+}\) and Mg\(^{2+}\) regulation are closely associated, abnormalities in Ca\(^{2+}\) metabolism are associated with Mg\(^{2+}\) imbalances. Patients with decreased Mg\(^{2+}\) levels exhibit tetany, seizures, cramps, paralysis, agitation, and psychosis. Patients with increased Mg\(^{2+}\) concentrations exhibit respiratory center depression, hypotension, paralysis of involuntary muscles, lethargy, and bradycardia.

Summary
Electrolytes serve many crucial functions in the body. Homeostasis of Na\(^{+}\), K\(^{+}\), Ca\(^{2+}\), and Mg\(^{2+}\) is essential to fluid balance, nerve and muscle excitation, enzyme function, acid-base balance, and electroneutrality. Electrolyte imbalances are associated with alterations in their distribution and regulatory mechanisms. Imbalances in electrolyte concentrations affect the distribution of associated electrolytes throughout the body fluid compartments and manifest in similar ways, making it necessary to evaluate electrolytes as a group rather than individually.
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REFERENCES


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