

# Chapter 2

## Sodium and Potassium in Health and Disease

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**Abstract** Sodium and potassium are essential for human health. They are important ions in the body and are associated with many physiologic and pathophysiologic processes. The chapter summarizes the basic physiologic actions of sodium and potassium on membranes of the neurologic and muscular systems. It provides information regarding the kinetics, i.e., absorption, distribution, and excretion of these ions and their movement between the intracellular and extracellular compartments. It also explains the physiologic systems that can influence proper homeostasis between sodium and potassium. Concentrations of sodium in the blood that exceed or do not reach the normal value range are called hypernatremia or hyponatremia, respectively. Similarly, the clinicians recognize hyperkalemia and hypokalemia. Pathologies associated with these states are described and examples of some of the diseases are presented here.

**Keywords** homeostasis • hyperkalemia • hypernatremia • hypokalemia • hyponatremia • potassium • sodium

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## 1 Introduction

This chapter provides an overview of sodium and potassium and their importance in human physiology and pathology. Sodium and potassium are essential in maintaining cellular homeostasis. Most metabolic processes are dependent on or affected by these electrolytes. Among the functions of these electrolytes are maintenance of osmotic pressure and water distribution in various body fluid compartments, maintenance of proper pH, regulation of the proper function of the heart and other muscles, involvement in oxidation-reduction (electron transport) reactions, and participation in catalysis as cofactors for enzymes.

Dietary requirements for sodium and potassium vary widely, but generally, daily intake should be only in small amounts [1]. Normal plasma levels for sodium in adults range from 136 to 146 mEq/L, and this balance is normally maintained by an average dietary intake of 90 to 250 mEq per day. Sodium excretion tends to reflect sodium intake, and on an average diet, urine sodium excretion will range between 80 and 180 mEq per day.

Potassium is essential for the proper function of all cells, tissues, and organs in the human body. It is also crucial to heart function and plays a key role in skeletal and smooth muscle contraction, making it important for normal digestive and muscular function. Normal plasma levels for potassium in adults range from 3.5 to 5.0 mEq/L, and this balance is usually maintained in adults on an average dietary intake of 80 to 200 mEq per day. It is noted that the normal intake, minimal need, and maximum tolerance for potassium is almost the same as that for sodium.

Sodium ions are the major cations of extracellular fluid, whereas, potassium ions are the major cations of the intracellular fluid [2]. To maintain internal fluid and electrolyte balance, water, sodium, and potassium are in constant movement between the intracellular and extracellular body compartments. Potassium and sodium ions are particularly important in the renal regulation of acid-base balance because hydrogen ions are substituted for sodium and potassium ions in the renal tubule. Potassium plays a key role in that potassium bicarbonate is the primary intracellular inorganic buffer. Potassium enters the cell more readily than sodium and initiates the brief sodium-potassium exchange across the cell membranes.

In the nerve cells, this sodium-potassium flux generates the electrical potential that aids the conduction of nerve impulses. When potassium leaves the cell, it changes the membrane potential and allows the nerve impulse to progress. This electrical potential gradient, created by the “sodium-potassium pump”, helps generate muscle contractions and regulates the heartbeat. Discovery of the sodium-potassium pump in the 1950s by a Danish scientist, Jens Christian Skou, marked an important step forward in our understanding of how ions enter and leave cells. This physiologic function is of particular significance for excitable cells such as nerve cells, which depend on this pump for responding to stimuli and transmitting impulses [3]. Cellular uptake of potassium is regulated by the sodium-potassium pump, while movement of potassium out of the cell is governed by passive forces (cell membrane permeability and chemical and electrical gradients to the potassium ions). Another of the pump’s most important functions is preventing the swelling of cells. If sodium is not pumped out, water accumulates within the cell causing it to swell and ultimately burst.

Abnormal levels of these electrolytes may result in a variety of pathological disorders [2]. For example, too high a concentration of sodium, a condition called hypernatremia, leads to edema (swelling of tissues due to excess fluid retention) thirst, and lessened urine production. Hyponatremia is a low level of serum sodium and is usually characterized by headache, confusion, seizures, muscle spasms, nausea, and vomiting. Too much potassium, called hyperkalemia, characterized by irritability, nausea, decreased urine production, and cardiac arrest. Fatigue is the most common symptom of chronic potassium deficiency. Early symptoms include muscle weakness, slow reflexes, and dry skin or acne; these initial problems may progress to nervous disorders, insomnia, slow or irregular heartbeat, and loss of gastrointestinal tone. A sudden loss of potassium may lead to cardiac arrhythmia. Low potassium may impair glucose metabolism and lead to elevated blood sugar. In more severe potassium deficiency, there can be serious muscle weakness, bone fragility, central nervous system changes, decreased heart rate, and even death.

Potassium is very important in cellular biochemical reactions and energy metabolism; it participates in the synthesis of proteins from amino acids in the cell. Potassium also functions in carbohydrate metabolism; it is active in glycogen and glucose metabolism, converting glucose to glycogen that can be stored in the liver for future energy. Potassium is important for normal growth and for building muscle.

Though sodium is readily conserved by the body, there is no effective method for potassium conservation. Even when a potassium shortage exists, the kidneys continue to excrete it. Since the human body relies on potassium balance for a regularly contracting heart and a healthy nervous system, it is essential to strive for this electrolyte's balance.

The renin-angiotensin-aldosterone system and vasopressin levels play an important role in regulating the electrolyte levels in the body. Pathological states of the system can be accompanied by imbalances of potassium and sodium levels.

A complex interplay of physiological control systems maintains fluid, sodium, and potassium homeostasis. When this interplay of physiological systems is disrupted, or when homeostatic mechanisms can no longer maintain intracellular, extracellular or interstitial fluid, an imbalance of sodium and potassium will occur. The following discussion will address some of the complexities of the physiology and pathology involved with sodium and potassium interactions.

## **2 Physiology of Sodium and Potassium in Humans**

### ***2.1 Action of Sodium and Potassium on Membranes***

#### **2.1.1 Nervous System**

One of the major roles of potassium/sodium balance in the body is that of the nerve impulse. A differential in sodium and potassium concentration forms a polarity across the nerve membrane that when stimulated (electrical, chemical, mechanical, or thermal) leads to depolarization and propagation of the nerve impulse along the cell membrane [4]. In the nerve cell, active sodium-potassium pumps create this differential by pumping two  $K^+$  atoms into the cell for every three  $Na^+$  atoms pumped out of the cell. Active pumping, along with negatively charged ions of other molecules inside the cell, leads to a voltage potential across the cell membrane. The resulting voltage is approximately  $-70mV$  [5]. Following membrane stimulation the membrane becomes permeable to  $Na^+$  ions, allowing  $Na^+$  inside the cell, thus eliminating the electrical potential across the membrane (depolarization). Depolarization propagates in all directions from the initial point. For a very brief time, the membrane is unable to depolarize again and remains unresponsive.

It is the nature of this delicate balance of sodium and potassium across the neuronal membrane that leads to diseases and physiological imbalances which result in a number of different neurological problems. Chemicals such as the organochlorine DDT gain their physiological disrupting power by interfering with the sodium channel across the axonal membrane, thus leading to variety of toxic effects, including lethality [6].

### 2.1.2 Muscular System

Similar in function to the membrane of neurons is the membrane function of the muscle fiber [2]. The muscle fiber, when stimulated by acetylcholine, depolarizes, propagating the depolarization into the deeper muscle through the transverse tubules, leading to the release of calcium ion followed by a contraction of the myofibrils of the muscle and thus movement of the muscle.  $\text{Na}^+$  and  $\text{K}^+$  play a key role in the depolarization of the muscle cell membrane. Polarization, as with the neuron, requires an active ion pump and energy in the form of ATP to create an ion gradient across the cell's membrane. As with neurons, the muscle cell membrane becomes impervious to  $\text{Na}^+$  while  $\text{Na}^+$  ions are actively pumped out of the cell and  $\text{K}^+$  ions into the cell; however, some  $\text{K}^+$  diffuse back out at a slower rate than  $\text{Na}^+$  is pumped out. This ion gradient, along with anions of many organic compounds and proteins inside the cell, create a voltage across the cell membrane. When the membrane is stimulated (electrically or mechanically, but usually chemically with acetylcholine), the membrane becomes permeable to sodium and voltage suddenly drops, thereby depolarizing the membrane. The depolarization propagates in all directions, moving into the muscle through transverse tubes, leading to  $\text{Ca}^{2+}$  release and the subsequent contraction of muscle.

Diseases and xenobiotics can interfere with many steps along this complicated process of muscle cell depolarization and contraction. Interference can occur at the cell membrane, with  $\text{Na}^+/\text{K}^+$  balance, with  $\text{Ca}^{2+}$  influx, and with many other pathways. Many toxins and therapeutic agents work by inhibiting cell depolarization and repolarization.

## 2.2 Homeostasis of Sodium and Potassium

Homeostasis of  $\text{Na}^+$  and  $\text{K}^+$  is critical to life, especially extracellular  $\text{K}^+$  levels. A number of homeostatic mechanisms keep  $\text{Na}^+$  and  $\text{K}^+$  regulated. Normal extracellular and intracellular  $\text{Na}^+$  and  $\text{K}^+$  are [7]:

intracellular  $\text{K}^+$  140 mEq/L  
extracellular  $\text{K}^+$  5 mEq/L  
intracellular  $\text{Na}^+$  12 mEq/L  
extracellular  $\text{Na}^+$  140 mEq/L

Intracellular  $\text{K}^+$  levels can be affected by insulin, aldosterone,  $\beta$ -adrenergic stimulation, acid base abnormalities, cell lysis, and strenuous exercise [8]. While short-term regulation involves cellular redistribution, long-term regulation involves renal excretion and reabsorption.

### 2.2.1 Absorption and Distribution of Potassium

The recommended intake of potassium for adolescents and adults is 4700 mg/day [9]. Following ingestion,  $K^+$  is rapidly absorbed by active uptake in the mucosal lining of the intestine. This rapid uptake could lead to severe  $K^+$  imbalance if it was not for the rapid absorption of  $K^+$  into cells (see Section 4.2). Ninetyeight percent of gastrointestinally absorbed  $K^+$  is stored in cells, with 2% being found extracellularly [8]. Even though cellular storage allows for the rapid regulation of extracellular  $K^+$ , long-term regulation is carried out in the kidney.

### 2.2.2 Absorption and Distribution of Sodium

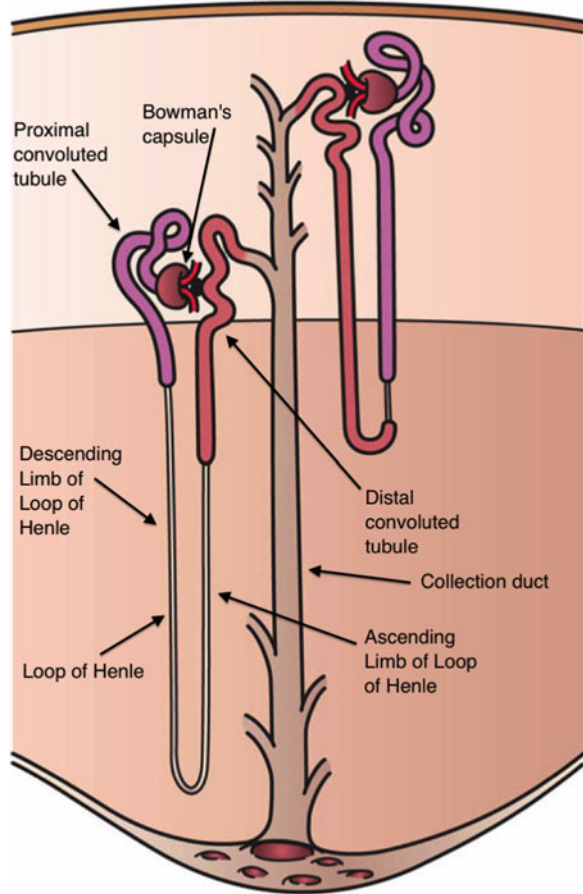
The average daily intake of sodium for males over 20 in the United States is 4,243 mg/day. For women it is 2,980 mg/day [10]. The Food and Drug Administration recommends that daily intake not exceed 2,300 mg/day for healthy individuals and no more than 1,500 mg/day for sensitive individuals (hypertensive, blacks, middle-aged, and older) [11].

Sodium is rapidly and actively taken up by the mucosal lining of the gastrointestinal (GI) tract [10]. Unlike  $K^+$ , however, it is not rapidly sequestered into the cells. Only around 10% of  $Na^+$  body burdens are found in the cells, 40% remains in extracellular fluid [4].  $Na^+$  is excreted through urine, feces, perspiration, and tears. It is also secreted back into the intestines at the rate of 25 grams per day. To remain in homeostasis, the intestines must absorb 25–35 of sodium every day [8]. This amount plus the amount of  $Na^+$  lost from other routes (urine and perspiration) needs to be reabsorbed every day for  $Na^+$  homeostasis to occur. It is easy to see why diseases such as diarrhea and intestinal influenza can easily upset the  $Na^+$  maintenance in the body and quickly lead to life threatening situations.

### 2.2.3 Potassium Excretion and Secretion in the Kidneys

A small percentage of excess  $K^+$  is excreted in the feces, while the bulk of  $K^+$  excretion occurs in the urine following filtration, reabsorption, and secretion in the kidneys (see Figure 1). The kidney filters around 800 mg of  $K^+$  per day of which approximately 65% and 27% is reabsorbed in the proximal tubule and loop of Henle, respectively [8]. These percentages remain fairly constant from day to day and do not significantly regulate daily variations from changes in diet and absorption. The work of regulating daily variations occurs mainly in the secretion of  $K^+$  in the distal tubules and cortical collecting tubules [11].

**Figure 1** Nephron.  
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of the Regents of the  
University of Michigan.  
[http://www.med.umich.edu/  
lrc/secondlook/](http://www.med.umich.edu/lrc/secondlook/).



Under normal potassium intake the amount of absorption exceeds what the body needs, and secretion into the distal tubules and cortical collecting tubules eliminates the excess through excretion in the urine. Under extreme  $K^+$  deficiencies reabsorption in the distal tubules can actually exceed secretion and thus conserve  $K^+$ .

#### 2.2.4 Sodium Excretion and Secretion in the Kidneys

Some sodium is lost in feces and sweat, but as was seen with potassium, the majority of sodium regulation in the body occurs in the kidney (see Figure 1). In the kidney, sodium ions (approximately 70%) are reabsorbed into the proximal tubules and loop of Henle after filtration through the glomerulus [4]. However, unlike  $K^+$ , the driving force of

$\text{Na}^+$  homeostasis is the glomerular filtration rate and tubule reabsorption. By the time the filtrate reaches the distal tubules almost all the  $\text{Na}^+$  has been reabsorbed.

As the filtrate formed at the glomerulus passes through the proximal tubules, loop of Henle, and distal tubules, the solution undergoes several transformations in tonicity that allows (along with active  $\text{Na}^+$  uptake throughout the loop) for reabsorption of water and  $\text{Na}^+$ . The ascending limb is impermeable to water yet still actively secretes  $\text{Na}^+$  causing the interstitial space around the ascending limb to become hypertonic. Since the interstitial space around the ascending limb is immediately adjacent to the descending limb, it creates an osmotic gradient between fluid inside the descending limb and the interstitial fluid. This gradient drives the removal of water from the descending limb, thereby increasing the fluid tonicity (forming a hypertonic solution). As the fluid makes its way out of the descending limb into the ascending limb the tubule becomes impermeable to water, yet  $\text{Na}^+$  continues to be actively pumped out. This results in a hypotonic fluid low in  $\text{Na}^+$  that leaves the ascending loop of Henle.

Following the reabsorption of  $\text{Na}^+$  in the ascending loop of Henle,  $\text{Na}^+$  reabsorption continues in the distal tubules. It is in this region of the kidney where water retention occurs. The pituitary gland, in response to decreased water concentration in the blood, releases stored antidiuretic hormone (ADH) into the circulatory system. ADH causes the epithelial cells of the distal convoluted tubules to become more permeable to water, thus concentrating urine and saving water during times of water stress.

$\text{Na}^+$  homeostasis is critical to life and thus requires the amount of sodium intake to equal the amount of  $\text{Na}^+$  excretion. There are numerous feedback loops and hormonal controls in play to regulate  $\text{Na}^+$  excretion such as blood pressure (pressure natriuresis and diuresis), blood volume, antidiuretic hormone, angiotensin II, arterial baroreceptor, low pressure stretch receptors reflexes, aldosterone, and natriuretic peptide. Regardless of the mechanism (complex or simple), all these feedbacks work by altering either glomerular filtration rates or by  $\text{Na}^+$  reabsorption. Xenobiotics, disease, or even fever can cause any of these mechanisms to alter  $\text{Na}^+$  balance. It is therefore necessary to have a complex system of redundancy and rapid response to maintain critical  $\text{Na}^+$  balance.

## ***2.3 Mechanism of Other Physiological Systems Influencing Sodium and Potassium Homeostasis***

### **2.3.1 Potassium**

*Aldosterone:* See the discussion of aldosterone's effects on  $\text{Na}^+$  below. Aldosterone increases the  $\text{Na}^+/\text{K}^+$  ATPase pump as  $\text{Na}^+$  is conserved,  $\text{K}^+$  is secreted into the urine.

*$\beta$ -adrenergic stimulation:* Activation of  $\beta_2$ -adrenergic receptors by stimulants such as epinephrine causes  $\text{K}^+$  to move into cells. Drugs that block  $\beta_2$  receptors can prevent the uptake of  $\text{K}^+$  into cells.

*Acid-base abnormalities:* The activity of the sodium-potassium ATPase pump is inhibited in the presence of increased hydrogen ion concentration. Therefore



disease or physiological states that affect acid-base balance can affect  $K^+$  homeostasis as well [8].

*Cell lysis:* Necrosis or major cell death can lead to the release of intracellular  $K^+$  causing a disruption in  $K^+$  homeostasis.

*Strenuous exercise:* Muscle cells release  $K^+$  during long-duration exercise. Usually this is not a problem except in individuals that may already be sensitive to  $K^+$  disturbances (diabetics, people taking beta blockers).

### 2.3.2 Sodium

*Pressure natriuresis and diuresis:* Blood pressure drives both urinary volume and the amount of  $Na^+$  filtered into the proximal tubule. While increases and decreases in natriuresis pressure can help regulate  $Na^+$  homeostasis when such pressure changes occur as a result of disease (e.g., hypertension) or other causes, the increase or decrease in pressure can cause imbalances in sodium.

*Blood volume:* Changes in blood volume quickly lead to changes in cardiac output and blood pressure. As discussed above, blood pressure changes can lead to changes in  $Na^+$  excretion.

*Antidiuretic hormone:* As previously discussed (see sodium excretion and secretion in the kidney), the pituitary gland, in response to decreased water concentration in the blood, releases stored antidiuretic hormone into the circulatory system. ADH causes the epithelial cells of the distal convoluted tubules to become more permeable to water, thus concentrating urine and saving water during times of water stress.

*Angiotensin II:* Decreased levels of angiotensin II result in decreased reabsorption of  $Na^+$  in the renal tubules. Thus decreases in angiotensin II are seen following increases in sodium intake. Angiotensin II works by modifying the natriuresis pressure mechanism, decreasing angiotensin II and increasing pressure when sodium needs to be excreted [12]. It also indirectly stimulates aldosterone secretion and constricts efferent arterioles. Angiotensin II is decreased by inhibiting renin, an angiotensin II precursor. In some individuals, this renin-angiotensin system (RAS) does not operate as efficiently, and greater increases in arteriole pressure are needed to excrete sodium. This may lead to hypertension in some individuals [8].

*Arterial baroreceptor and low pressure stretch receptors reflexes:* Sympathetic activity can constrict renal arterioles, increase tubular reabsorption, and stimulate renin release, all leading to increased retention of sodium. This type of reflex is likely to occur from decreased blood volume, as in following a large hemorrhage.

*Aldosterone:*  $Na^+$  absorption in the kidney (the ascending limb of the loop of Henle, the distal convoluted tubules, and collecting ducts) is greatly influenced by the amount of aldosterone excreted by the adrenal cortex [4]. When  $Na^+$  levels drop, the adrenal cortex secretes aldosterone, which results in an increase in the active reabsorption of  $Na^+$ .

### 3 Pathology Associated with Sodium Levels

#### 3.1 Hyponatremia

Hyponatremia represents a decrease in the serum sodium concentration below the lower end of the normal range (136 mEq/L) [13].

Clinical signs and symptoms associated with hyponatremia include hypotension, and decreased extracellular fluid osmolarity resulting in intracellular fluid increase [14]. Hyponatremia is the most common electrolyte disorder. In one study, the prevalence of hyponatremia was 28% in acute hospital care patients at the time of admission and 21% in ambulatory patients [15]. The risk factors for hyponatremia include use of diuretics, liver failure, heart failure, myocardial infarction, and endocrine changes which are mostly found in older patients. Hyponatremia is associated with various conditions that can be grouped into dilutional disorders (characterized by water intake in excess of output; the condition implies impaired water excretion) and depletional disorders (caused by sodium depletion in excess of water depletion or replacement of fluid losses with water alone). See Table 1 for pathologic states associated with hyponatremia.

**Table 1** Pathology associated with hyponatremia<sup>a</sup>.

Causes of hyponatremia	Associated diseases
Water intake higher than output; always impaired water excretion (dilutional disorders)	<i>Primary:</i> chronic renal failure, acute renal failure (recovery phase), SIADH <i>Neuroendocrine:</i> adrenal and pituitary insufficiency <i>With edema:</i> congestive heart failure, hepatic cirrhosis, toxemia in pregnancy <i>Osmotic:</i> severe hyperglycemia <i>Diuretics:</i> thiazides
Sodium depletion higher than water depletion or replacement of fluid losses with water alone (depletional disorders = extrarenal losses)	Severe diarrhea, vomiting, blood loss, excessive sweating

<sup>a</sup> All tables were modified from Chandrasoma and Taylor [14] and Merck [13].

Dilutional disorders include primary causes such as renal failure and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Other causes of dilutional disorders include neuroendocrine dysfunction (adrenal and pituitary insufficiency), diseases linked to sodium retention and edema (congestive heart failure, cirrhosis, nephrotic syndrome), osmotic hyponatremia (severe hyperglycemia in diabetes), and drug-induced disorders (mercurial diuretics, chlorothiazide diuretics). Hyponatremia with hypotonicity can also be induced by diets with high water and low salt intake or by excessive beer drinking.

SIADH is an example of a dilutional disorder. The syndrome was first described almost 50 years ago [16]. The diagnostic criteria include hyponatremia with

hypotonicity of plasma, high urine osmolarity relative to plasma, increased renal sodium excretion, absence of edema, and normal renal and adrenal function. SIADH explains about 60% of all types of chronic hyponatremia and is the most common type of hyponatremia in hospitalized patients [17]. SIADH is associated with 4 major etiologies: nonmalignant pulmonary diseases, neoplasms with ectopic hormone production, neurologic disorders, and use of several pharmaceuticals [18]. SIADH is linked to euvolemic hyponatremia described as an increase in total water with normal or near normal sodium levels. It is associated with inappropriate secretion of arginine vasopressin (AVP), the hormone that regulates excretion of water by kidneys. Excessive release of AVP unrelated to plasma osmolarity occurs in about 40% of patients with SIADH.

In the case of *impaired glomerular filtration rate* (renal failure) hyponatremia is caused by inadequate glomerular filtration of water (i.e., the body cannot get rid of water taken in). However, this usually happens when the filtration rate is substantially reduced to about 20–30% of the normal rate [14].

The common ground of diseases such as congestive heart failure, cirrhosis, and nephrotic syndrome is the *edematous state*. Hyponatremic patients with these diseases have abnormal renal retention of sodium resulting in extracellular fluid volume overload and edema. They also have retention of water causing hyponatremia with hypotonicity.

Drugs such as *thiazide diuretics* are an important cause of hyponatremia especially in elderly women. The mechanism of action is inhibition of  $\text{Na}^+\text{-Cl}^-$  symport (co-transporter) located in the cortical part of the ascending loop of Henle and the distal convoluted tubules of the kidneys resulting in the failure of these ions to reabsorb [19,20]. Thiazides also increase calcium reabsorption in the distal tubule. Complications of thiazide therapy are hyponatremia, hypokalemia, hypercalcemia, hyperglycemia, and hyperlipidemia.

Hyponatremia can also be induced by *loop diuretics* (e.g., furosemide, bumetanide). These diuretics block the  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport which facilitates ion movement from the tubular lumen into the tubular cells in the ascending part of the loop of Henle [20]. The mechanism of action of the loop diuretics lays in competing for the  $\text{Cl}^-$  binding sites of the symport. This may lead to natriuresis and hyponatremia, hypokalemia, hypomagnesemia, and dehydration.

Genetic mutation of the  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport encoding gene may lead to impaired function of the symport; the clinical presentation is severe volume depletion, hypokalemia, and metabolic alkalosis with increased prenatal mortality. The disease is called type I Bartter's syndrome [21].

A special case of hyponatremia is with hypertonicity. It was described in patients with uncontrolled *diabetes mellitus* with severe hyperglycemia [14]. The increased glucose concentration causes water to move from the intracellular to the extracellular compartment resulting in decreased sodium concentration (i.e., dilutional state).

Depletional disorders include severe diarrhea, vomiting, blood loss, and excessive sweating accompanied by large oral intake of water.

*Diarrhea* is an example of a condition linked to depletional hyponatremia. The most common causes of diarrhea are bacterial enterotoxins (e.g., *Vibrio cholerae*), bacterial invasion of gastric mucosa (e.g., some *Shigella*, *Salmonella*), and enteroviruses.

Diarrhea is also associated with hypokalemia and metabolic acidosis. The condition may become severe and lead to mortality, especially in susceptible populations such as the elderly, those debilitated by other diseases, and the very young. In a retrospective study in Nepal, 5 children died out of 57 who were admitted to the hospital with diarrhea [22]. Most patients (70%) were younger than 2 years. Electrolyte disturbance was reported in 46 (80%) patients, and acid-base disturbance was reported in all tested. Hyponatremia was present in 56% of patients and was either isolated (26%) or associated with hypokalemia (26%). Hypokalemia was found in 46% of patients and was isolated in 14%. In a two year prospective study in Nigeria, 191 children under 15 years of age were admitted to the hospital with diarrhea and protein energy malnutrition [23]. The most often observed disturbance was metabolic acidosis that was reported in 108 (56.3%) of patients. Hypokalemia was found in 45 (23.4%) and hyponatremia in 25 (13%) of patients. Clinical risk factors contributing to mortality in children hospitalized for diarrhea were studied in Turkey [24]. In a cohort of 400 children, 27 (6.75%) died. Significant factors contributing to fatalities included severe malnutrition, co-existent sepsis, hypoglycemia, hypoalbuminemia, *Shigella* infection, hyponatremia ( $p = 0.016$ ), hypokalemia ( $p = 0.00041$ ) and metabolic acidosis ( $p = 0.0069$ ).

### 3.2 Hypernatremia

Hypernatremia represents an elevation in the serum sodium concentration above the higher end of the normal range (145 mEq/L) [13].

Clinical signs and symptoms associated with hypernatremia include hypertension, increased extracellular fluid volume, and increased extracellular fluid osmolarity resulting in intracellular fluid loss [14]. See Table 2 for pathologic states associated with hypernatremia. Hypernatremia is not as common as hyponatremia. It is associated with abnormal renal excretion of water with inadequate water intake disorders such as in pituitary ADH deficiency (central diabetes insipidus) and nephrotic syndrome (nephrotic diabetes insipidus), in which kidneys are ADH unresponsive, or with osmotic diuresis such as severe glycosuria and manitol diuresis. Other diseases and states that may be accompanied by hypernatremia are chronic renal failure, recovery phase of acute renal failure, hypocalcemia, hypokalemia, and sickle cell anemia.

**Table 2** Pathology associated with hypernatremia.

Causes of hypernatremia	Associated diseases
Abnormal renal excretion of water with inadequate intake	Diabetes insipidus, renal failure, loop diuretics
Water depletion with normal renal water conservation	Excessive sweating; diarrhea (children)
Excessive intake of sodium with limited water intake	Poisoning

Another mechanism of hypernatremia is water depletion with normal renal conservation of water but inadequate intake of water; causes include excessive sweating and diarrhea (pronounced in children). For example, hypernatremia was reported in 6 children (3.1%) with severe diarrhea in a cohort of 191 (see Section 3.1.) [23]. However, hyponatremia was far more frequent. i.e., in 13% of the cohort.

## 4 Pathology Associated with Potassium Levels

### 4.1 Hypokalemia

Hypokalemia represents the low potassium levels. In adults, potassium blood levels drop below 3.5 mEq/L, which is the lower range of normal values.

Clinical signs and symptoms associated with hypokalemia include neuromuscular (weakness, paralysis, fasciculation and tetany), gastrointestinal (ileus, nausea, vomiting, abdominal distention), and renal effects (polyuria) [14]. Cardiac effects present themselves as dysrhythmias and conduction defects. ECG manifestations include decreased amplitude and broadening of the T waves, prominent U waves, ST segment depression, increased QRS duration, and increase in P wave amplitude and duration. The changes may lead to atrioventricular block and cardiac arrest [25–27]. With hypokalemia, cardiac arrest occurs during systole [28]. See Table 3 for pathologic states associated with hypokalemia.

**Table 3** Pathology associated with hypokalemia.

Causes of hypokalemia	Associated diseases
Increased extrarenal losses	Severe diarrhea, laxative abuse, vomiting, excessive sweating, villous adenoma
Increased renal losses	<i>With metabolic acidosis:</i> renal tubular acidosis, diabetic ketoacidosis <i>With metabolic alkalosis:</i> diuretics, post hypercapnea, mineralocorticoid excess syndrome, Bartter's syndrome <i>With no specific acid-base disorder:</i> acute renal failure (recovery phase), post obstructive diuresis, osmotic diuresis, saline intake
Potassium shifts into cells (redistribution)	Alkalemia, $\beta$ -adrenergic activity, familial hypokalemic periodic paralysis, theophylline toxicity

Potassium homeostasis depends on external balance (i.e., dietary intake and absorption *versus* excretion) and internal balance (i.e., the distribution of potassium between intracellular and extracellular fluids [14]).

External losses include those through the gastrointestinal tract (e.g., diarrhea, villous adenoma of recto-sigmoid colon, inadequate intake) or through the skin

(e.g., profuse sweating). Urine potassium is usually  $<20$  mEq/24 hours. In external losses through the kidneys, urine potassium is usually  $>20$  mEq/24 hours.

*Eating disorders and starvation:* Anorexia nervosa and bulimia are psychological eating disorders. Medical consequences of these eating disorders include heart damage, failure of the endocrine system, perforation of the stomach or esophagus, aspiration of vomit, erosions of teeth enamel, and depression [29]. Death by starvation has been reported in up to 24% of the patients with anorexia. Biochemical changes are also pronounced [30]. Hypokalemia is the most common electrolyte disturbance. It is often reflected by changes on the electrocardiograms. Metabolic alkalosis is found in patients who vomit or abuse diuretics, whereas acidosis is found in those abusing laxatives. In laxative abuse, potassium is lost directly from the intestines. In contrast, the loss of potassium in those who vomit is largely due to metabolic alkalosis, which is secondary to loss of hydrogen ions in the vomitus. This results in increased availability of bicarbonate from blood and increased renal excretion of potassium [31]. Hypokalemic nephropathy is also associated with laxative abuse. Severe chronic hypokalemia in these patients was found to result in a progressive decrease in renal function and histological changes suggestive of chronic glomerular damage. Chronic tubulo-interstitial nephropathy has been also reported [32,33].

Hypokalemia is also associated with starvation related to other causes. For example, hypokalemia was reported in malnourished children on poor protein-calorie diets all over the world. In these children, decrease in total body potassium was correlated with decreased muscle potassium established by analysis of biopsy samples [34–36]. This result correlated with loss of total muscle mass. In contrast, muscle water was increased. Wasting is one aspect of the muscle loss; however, a contributing factor may be a decreased muscle build-up. Several laboratory studies showed the importance of potassium in protein synthesis. A study in young chicken demonstrated that there was a significant decrease in the incorporation of injected L-leucine-1- $^{14}$ C into skeletal muscle of chicken fed a potassium-deficient diet [37]. Similarly, when rats were maintained on a potassium-deficient diet, the animals stopped growing within a few days and the incorporation of [ $^3$ H]leucine into skeletal muscle protein *in vivo* was reduced by 28–38% [38].

Related to the above topic is the *refeeding syndrome*. It illustrates the metabolic and clinical changes in the body that occur in the process of aggressive nutritional rehabilitation of starved patients. The most important manifestation is hypophosphatemia [39]. Hypokalemia, hypomagnesemia, hyperglycemia, fluid overload, and thiamine deficiency may also be present. During starvation, potassium is depleted in the cells. During refeeding, increased insulin secretion promotes cellular uptake of potassium, resulting in hypokalemia. The outcome is an imbalance of electrochemical potential on membranes leading to cardiac arrhythmias and arrest. Neuromuscular dysfunction is also observed. The refeeding syndrome was reported in up to 25% of adults with cancer.

Causes for potassium renal losses are complex [26,27]. Contributing clinical factors are increased mineralocorticoid-receptor stimulation (primary hyper-reninism distinguished by increased renin and aldosterone levels that cannot be suppressed

by saline); primary aldosteronism (e.g., Conn syndrome); a primary increase in the effectiveness and/or amount of non-aldosterone mineralocorticoid-receptor agonist (e.g., Cushing syndrome, congenital adrenal hyperplasia); and increased distal sodium delivery and/or non-reabsorbable ions in the distal nephron (e.g., magnesium deficit, Bartter syndrome) [27].

Clinical data indicate that renal losses of potassium are often related to adverse effects to therapy (e.g., penicillin, gentamicin, cisplatin, diuretics). For example, hypokalemia was reported in 10% to 40% of patients on thiazide diuretics [40]. The mechanism includes increased exchange of  $\text{Na}^+$  for  $\text{K}^+$  and increased production of aldosterone as a response to diuretic hypovolemia [19].

It is well established that acid-base imbalance and electrolyte disorders are associated with *diabetes*. Recent reports indicate that low potassium is a possible risk factor for developing type 2 diabetes [41].

Redistribution losses are the consequence of potassium shifts into cells from the extracellular fluids. By this mechanism, hypokalemia is present in respiratory alkalosis, increased  $\beta_2$ -adrenergic activity, theophylline toxicity, and in familial hypokalemic periodic paralysis.

Stimulation of  $\beta_2$ -adrenergic receptors redistributes potassium into cells by increasing the activity of sodium-potassium ATPase. States of increased sympathetic responsiveness can be observed in myocardial infarction, delirium tremens, or major head trauma. These states are also associated with shifts in potassium levels. Hypokalemia is common in *congestive heart failure* due to a defect in sodium-potassium ATPase activity and intracellular transfer of potassium caused by oxidative stress and neurohormonal activation [42]. Hypokalemia in the presence of congestive heart failure may lead to serious outcomes [43]. These include impaired diuresis because of decreased natriuresis and lack of suppression of renin secretion, reduced myocardial performance, and elevated risk for ventricular arrhythmia and sudden death. Recent studies indicated that heart failure itself may stimulate metabolic changes such as insulin resistance [44]. These in turn may worsen the primary condition. A study in hospitalized patients with heart failure and a depressed left ventricular ejection fraction reported 30-day and 1-year mortality as 7.1% and 25.5%, respectively [45]. Impaired renal function is a major factor that influences the prognosis of patients with heart failure [46].

## 4.2 *Hyperkalemia*

In adults, hyperkalemia refers to blood values of potassium  $>5$  mEq/L. Clinical manifestations of hyperkalemia include neuromuscular effects (weakness, ascending paralysis, and respiratory failure) and ECG changes (peaked T waves, flattened P waves, widened QRS complex) [14]. The changes in heart conductivity can lead to sinus arrest, ventricular tachycardia, and fibrillation at  $>10$  mEq/L [25]. With hyperkalemia, cardiac arrest occurs during diastole [28]. See Table 4 for pathologic states associated with hyperkalemia.

**Table 4** Pathology associated with hyperkalemia.

Causes of hyperkalemia	Associated diseases
Decreased excretion	Renal failure (acute and chronic), severe oliguria due to severe dehydration or shock
Endocrine dysfunction	Adrenocortical insufficiency, hyporeninemic-hypoaldosteronism
Potassium shifts out of cells (redistribution)	Acidosis, hypertonic states, massive release in burns, rhabdomyolysis or crush injury, or severe infection

Hyperkalemia is less common than hypokalemia. However, it still affects about 8% of patients in US hospitals [25]. There are two major mechanisms for hyperkalemia development. Redistribution hyperkalemia is caused by potassium shifting from the intracellular space into the extracellular space, thus raising serum potassium concentration. Potassium is forced out of cells in exchange for hydrogen ion in both metabolic and respiratory acidosis. Similarly, potassium leaks out of cells in hypertonic states, in burns and injuries, and in massive digitalis overdose.

Hyperkalemia secondary to impaired potassium excretion is the major cause of this electrolyte disorder. It may be due to aldosterone deficiency (e.g., primary adrenal failure, Addison's disease) or tubular unresponsiveness to aldosterone (e.g., chronic renal diseases, some pharmaceuticals). Hyperaldosteronism is a disease caused by an excess production of adrenal hormone aldosterone. This hormone is responsible for sodium and potassium balance, which then directly controls water balance to maintain appropriate blood pressure and blood volume. With adrenal insufficiency, there is inappropriate sodium excretion. When adrenal aldosterone production is increased (as in shock, heart failure, or cirrhosis) sodium excretion is decreased. People with a deficiency of aldosterone, especially found in association with cortisol deficiency in Addison's disease, have low blood volume and therefore low blood pressure, low sodium and high potassium. Just the opposite is seen in hyperaldosteronism.

There are several drugs that affect the renin-angiotensin-aldosterone system and thus may impact potassium levels. A review of studies that administered angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and direct renin inhibitors alone or in combination to patients with hypertension, heart failure, or chronic kidney disease revealed that the risk of hyperkalemia on monotherapy of hypertension is low ( $\leq 2\%$ ) but increases to about 5% in combination therapy [47]. Increased incidence was also observed in patients with heart failure or chronic kidney disease (5% to 10%).

The syndrome of hyporeninemic hypoaldosteronism (SHH) that also belongs to this category is associated with several renal diseases. SHH includes low plasma renin activity, low plasma aldosterone, and hyperkalemia. The syndrome is also common in patients with diabetes mellitus.

In a study of 210 outpatient diabetics, metabolic alkalosis was the most common acid-base imbalance [48]. The most common electrolyte disorders were hyponatremia in patients with serum creatinine  $< 1.2$  mg/dL, and hyponatremia and hyperkalemia in patients with higher creatinine levels ( $> 3.1$  mg/dL).



Renal diseases with changes in urine output are another obvious reason for potassium disbalance. Patients with *acute renal failure* present with anorexia, nausea, vomiting, lethargy, and increased blood pressure [28]. The onset of oliguria is sudden; proteinuria and hematuria are common. There is a progressive increase in serum urea nitrogen, creatinine, potassium, phosphate, and sulfate. In contrast, serum sodium, calcium, and bicarbonate are decreased. The etiology for inducing acute renal failure is numerous and the disease is classically divided into pre-renal, renal (intrinsic), and post-renal failure. Multiple animal models have been developed to induce acute renal failure by different mechanisms [49]. These laboratory studies contribute to a better understanding of the disease. In *chronic kidney disease*, the changes develop at a slower rate. Therefore, the organism has time to compensate for partial loss of function. For example, uremia and azotemia occur only when renal failure is advanced; usually when the creatinine clearance decreases to about 30–40% of normal [14]. The inability to concentrate urine, resulting in polyuria, is one of the early signs of chronic kidney failure. Metabolic acidosis is caused by the failure of hydrogen ion excretion. Hyperkalemia is one of the later signs of the disease; so is the development of secondary hyperparathyroidism and renal osteodystrophy. When pre-dialysis mortality was studied in a large cohort of men (N = 1,227), both hypo- and hyperkalemia were linked to mortality in white patients [50]. Black patients seemed to better tolerate hyperkalemia than whites. Hypokalemia was associated with faster chronic kidney disease progression in both races.

## 5 Conclusion

Sodium and potassium are essential to life. These ions are involved in many physiological processes, and their imbalance may impair proper function in various organs and/or entire systems in the body. It is beyond the scope of this chapter to describe in detail all the diseases. The interested reader is encouraged to find more information in the medical texts and scientific papers cited here.

## Abbreviations

ADH	antidiuretic hormone
ATP	adenosine 5'-triphosphate
AVP	arginine vasopressin
DDT	dichlorodiphenyltrichloroethane
ECG	electrocardiogram
GI	gastrointestinal
RAS	renin-angiotensin system
SHH	syndrome of hyporeninemic hypoaldosteronism
SIADH	syndrome of inappropriate antidiuretic hormone

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