Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019

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Total-body potassium (K^+) content and appropriate distribution of K^+ across the cell membrane is vitally important for normal cellular function. Total-body K^+ content is determined by changes in excretion of K^+ by the kidneys in response to intake levels. Under normal conditions, insulin and β-adrenergic tone also make important contributions in maintaining internal distribution of K^+. However, despite these homeostatic pathways, disorders of altered K^+ homeostasis are common. Appreciating the pathophysiology and regulatory influences that determine the internal distribution and external balance of K^+ is critical in designing effective treatments to restore K^+ homeostasis. We provide an up-to-date review of the regulatory aspects of normal K^+ physiology as a preface to highlighting common disorders in K^+ homeostasis and their treatment. This review of K^+ homeostasis is designed as a resource for clinicians and a tool for educators who are teaching trainees to understand the pivotal factors involved in K^+ balance.

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Introduction

Normal potassium (K^+) homeostasis maintains plasma K^+ concentration within a narrow range and is achieved by matching K^+ intake with excretion and ensuring proper distribution between extra- and intracellular fluid compartments. The latter is essential because ~2% of total-body K^+ is found in extracellular fluid, whereas 98% of exchangeable K^+ is in the intracellular compartment. This difference determines cellular voltage at rest, with the interior oriented negatively relative to the exterior, and is the reason that disorders in plasma K^+ homeostasis lead to clinical manifestations in excitable tissues. This review first discusses normal K^+ homeostasis and then describes an approach to patients with disturbances in plasma K^+ concentrations.

Normal K^+ Homeostasis

Internal Distribution of K^+

Case 1. *A 38-year-old woman with end-stage kidney disease due to diabetes mellitus is taken to the operating room for incision and drainage of a perirectal abscess. Current medications include metoprolol, 50 mg, twice daily and insulin. Preoperative laboratory tests show the following serum values: sodium (Na^+), 138 mEq/L; K^+, 4.9 mEq/L; chloride (Cl^-), 103 mEq/L; bicarbonate (HCO_3^-), 21 mEq/L; creatinine, 9.4 mg/dL; and urea nitrogen, 65 mg/dL. She was last dialyzed 1 day before admission. Intraoperatively she became hypotensive and intravenous phenylephrine was used to stabilize the blood pressure. In the recovery room, profound weakness is noted, preventing extubation and notably, plasma K^+ concentration is 6.4 mEq/L.*

Question 1: Which one of the following is the best explanation for the development of acute hyperkalemia?

a) Hypoaldosteronism
b) Metabolic acidosis
c) β-Adrenergic stimulation
d) α-Adrenergic stimulation
e) Pseudohyperkalemia

For the answer to the question, see the following text.

The kidney has the primary responsibility for maintaining total-body K^+ content, which averages 3,000 to 4,000 mEq in a 70-kg person. Of the total-body stores, only 60 to 80 mEq is found in extracellular fluid, maintained at a concentration normally ranging from 3.5 to 5.3 mEq/L. Large deviations outside this range are not compatible with life. To minimize transient increases in plasma K^+ concentrations that could adversely affect cell voltage, the body has developed a number of physiologic mechanisms to shift K^+ into cells pending adjustments in excretion, which occur over several hours.

Insulin release following a meal not only regulates glucose concentration but also plays an important role in shifting dietary K^+ into cells before excretion by the kidney. After binding to specific cell-surface receptors, insulin causes the insertion of GLUT4 (glucose

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

transporter type 4), facilitating glucose uptake in insulin-responsive tissues and stimulating K^+ uptake by increasing the activity of the adenosine triphosphatase sodium/potassium pump (Na^+/K^+-ATPase). In metabolic syndrome or chronic kidney disease (CKD), insulin-mediated glucose uptake is compromised but cellular K^+ uptake occurs normally, indicating differential regulation of insulin-mediated glucose and K^+ uptake.

Catecholamines play an important physiologic role in regulating K^+ distribution. Increases in interstitial K^+ concentration cause vasodilation, allowing blood flow to increase in exercising muscle. Catecholamines acting through β_2 receptors increase activity of the Na^+/K^+-ATPase and limit the increase in extracellular K^+ concentration that would otherwise occur. In states of total-body K^+ depletion, K^+ accumulation into the interstitial space is blunted, thus impairing skeletal muscle blood flow and contributing to the association of hypokalemia with rhabdomyolysis.

Changes in plasma tonicity and acid-base disorders affect internal K^+ balance as well. Accumulation of effective osmoles (such as glucose, mannitol, and sucrose) in the extracellular space create an osmotic gradient favoring water movement from the intracellular to the extracellular compartment. The decrease in cell volume concentrates intracellular K^+, favoring efflux through K^+-permeable channels. To a much greater extent than organic acidosis (high anion gap metabolic acidosis), mineral acidosis (hyperchloremic normal gap metabolic acidosis) causes a cell shift in K^+. Acidemia causes loss of K^+ from cells not because of a direct K^+/hydrogen ion (H^+) exchange, but instead seems to occur through a coupling triggered by the effects of acidosis on transporters that regulate cell pH in skeletal muscle (Fig 1). Changes in K^+ distribution in response to respiratory acid-base disorders tend to be small in magnitude.

Returning to case 1, the correct answer is α-adrenergic stimulation (d). The sympathetic nervous system plays an important role in the control of plasma K^+ concentrations. Increased K^+ intake leads to increased catecholamine secretion and through β_2-adrenergic receptors, stimulates enhanced K^+ uptake into skeletal muscle. Blockade of β-adrenergic receptors impairs the ability to dispose of a K^+ load. α-Adrenergic receptor stimulation shifts K^+ into the extracellular space, but this effect is negligible under basal conditions. In this patient, an endogenous K^+ load resulting from tissue injury during surgery led to hyperkalemia due to pharmacologic stimulation of α-adrenergic receptors (phenylephrine) in the setting of β-adrenergic receptor blockade (metoprolol).

Kidney K^+ Handling

K^+ is freely filtered by the glomerulus and nearly completely reabsorbed in the proximal tubule (through the paracellular pathway in approximate proportion to Na^+ and water) and ascending limb of Henle (where transcellular K^+ transport is mediated by the apical membrane

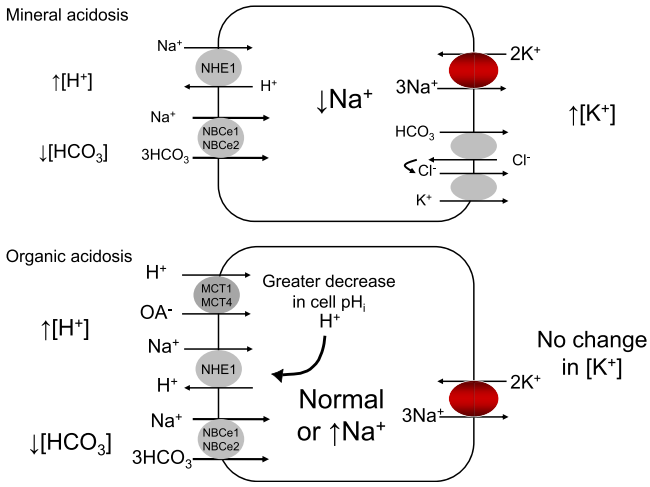

Figure 1. Transcellular K^+ distribution in skeletal muscle in response to organic versus mineral acidosis. The decrease in extracellular pH with mineral acidosis (hyperchloremic normal anion gap acidosis) will lower the rate of Na^+/H^+ exchange by the Na^+/H^+ exchanger (NHE1) and the inward rate of cotransport of Na^+ and HCO_3^- by electrogenic sodium bicarbonate cotransporter (NBCe) 1 and 2. As a result, the intracellular Na^+ concentration will decline, lessening Na^+/K^+-adenosine triphosphatase (Na^+/K^+-ATPase) activity and leading to a net loss of cellular K^+. At the same time, a lower extracellular HCO_3^- concentration will increase inward movement of Cl^- by Cl^-/HCO_3^- exchange, contributing to additional K^+ efflux by K^+/Cl^- cotransport. Organic acidosis (H^+-anion other than Cl^-) is characterized by a robust movement inward of the organic anion and H^+ through the monocarboxylate transporter (MCT1 and 4). This causes a decrease in intracellular pH, triggering inward Na^+ movement through Na^+/H^+ exchange and cotransport of Na^+ and HCO_3^-. The intracellular accumulation of Na^+ preserves Na^+-K^+ ATPase activity, so there is little change in extracellular K^+ concentration. Adapted from Palmer & Clegg (*Adv Physiol Educ.* 2016;40:480-490).

sodium/potassium/chloride [$Na^+/K^+/2Cl^-$] cotransporter). The reabsorptive component of kidney K^+ handling is largely independent of K^+ intake.

Maintenance of urinary K^+ excretion results primarily from secretion along the aldosterone-sensitive distal nephron (ASDN), which comprises the last portion of the distal convoluted tubule (DCT2), connecting tubule, and collecting duct. Tubule K^+ secretion is mediated by 2 types of apical K^+ channels and is driven by a transepithelial voltage that is oriented in the lumen-negative direction. The voltage is generated largely by Na^+ reabsorption through the epithelial Na^+ channels (ENaC) localized on the apical membrane. Aldosterone stimulates ENaC activity through mineralocorticoid receptors, which increase both channel number and the proportion of time that the channel is in the open state. K^+ secretion traverses inwardly rectifying K^+ channels (ROMK, also called Kir1.1) in principal cells and BK channels in principal and intercalated cells. The latter are activated primarily by increases in fluid flow rate, accounting for the flow dependence of K^+

excretion (Fig 2). The secretory component of K^+ handling is adjusted in line with physiologic needs.

Major determinants of K^+ excretion correspond to factors that regulate K^+ secretion along the ASDN and include luminal Na^+ delivery and flow rate, plasma K^+ concentration, circulating aldosterone and arginine vasopressin levels, and acid-base status. The increase in kidney K^+ excretion following high K^+ intake can be traced to increased Na^+ delivery and flow to the ASDN. Recent data suggest that this effect begins in the initial portion of the DCT (DCT1), where salt transport is driven exclusively by the thiazide-sensitive Na^+/Cl^- cotransporter (NCC). Increased plasma K^+ concentration sensed by Kir4.1/5.1 channels located on the basolateral surface of the DCT1 leads to alterations in activity of the WNK family of kinases and their regulatory proteins SPAK and OxSR1 in such a way that NCC activity is decreased (Fig 2). As a consequence, there is greater Na^+ delivery and flow to the aldosterone-sensitive K^+ secretory segments located in the later portions of the DCT (DCT2) and collecting duct, resulting in more K^+ secretion. With long-term high K^+ intake, the effect of plasma K^+ concentration on cells of the DCT1 is amplified by decreased Na^+ reabsorption in the thick ascending limb and proximal tubule due to medullary recycling and accumulation of K^+ in the interstitium. In contrast to high K^+ intake, decreased intake and decreased plasma K^+ concentrations lead to increased activity of the NCC in the DCT1. This change limits K^+ secretion by reducing Na^+ delivery and flow to the ASDN.

The effect of a K^+-deficient diet, reducing K^+ secretion while increasing Na^+ retention, has been linked to the pathogenesis of salt-sensitive hypertension. Conservation of K^+ and Na^+ by the kidney when there is K^+ deficiency may have evolved because simultaneous deficiency of dietary K^+ and Na^+ was probably faced by early humans. However, this effect may be deleterious in our current environment, in which typically dietary Na^+ intake is high and K^+ intake is low. By the same token, decreased NCC activity and natriuresis may explain the blood pressure–lowering effect of high K^+ intake. This effect is more pronounced in individuals with high salt intake and in trials in which black individuals predominated.

The ability of the normal kidney to maintain K^+ homeostasis when there is high dietary intake may have evolved to handle the nearly 4-fold greater intake of dietary K^+ of Paleolithic humans. Contributing to this robust response is the presence of a splanchnic sensing mechanism that can initiate the kaliuretic response as early as K^+ entry into the gastrointestinal tract. Gastric delivery of K^+ leads to dephosphorylation and decreased activity of the NCC in the DCT1. Splanchnic sensing of K^+ can trigger the renal excretory response independent of alteration in plasma K^+ concentration or mineralocorticoid activity (Fig 3). There are health benefits associated with eating diets high in K^+, and a preeminent hypothesis is that there is a mismatch between what the body can metabolize versus what modern humans consume, which may play

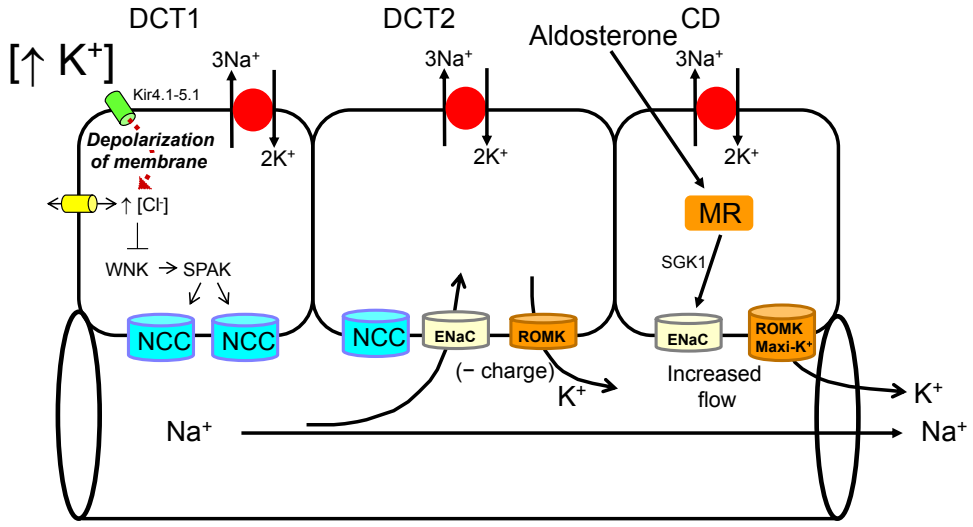

Figure 2. Mechanisms of K^+ secretion by the distal nephron. Increased plasma K^+ concentration depolarizes cells in the proximal portion of the distal convoluted tubule (DCT1) through effects dependent on the K^+ channel Kir4.1/5.1. The decrease in intracellular electronegativity leads to an increased intracellular Cl^- concentration that alters the WNK family of kinases and their regulatory proteins in such a way that Na^+/Cl^- cotransporter (NCC) activity is decreased. Increased Na^+ delivery and flow to the downstream distal portion of the DCT where aldosterone sensitivity begins (DCT2, connecting tubule, and collecting duct) along with increased aldosterone levels drive K^+ secretion. A reduction in plasma K^+ concentration activates NCC activity. This effect causes salt retention and reduces Na^+ delivery and flow to downstream segments resulting in decreased K^+ secretion. Abbreviations: CD, collecting duct; ENaC, epithelial sodium channel; MR, mineralocorticoid receptor; ROMK, renal outer medullary potassium channel; SPAK, Ste20-related proline/alanine-rich kinase.

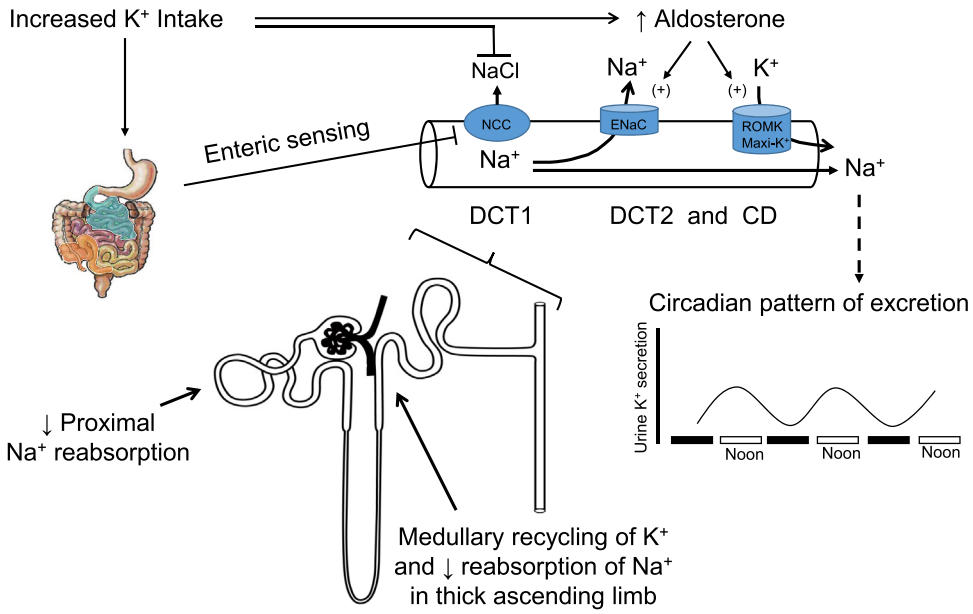

Figure 3. Mechanisms underlying the prodigious capacity of the normal kidney to excrete K^+. The distal convoluted tubule (DCT) has the capability to augment K^+ secretion in response to small changes in plasma K^+ concentration (Fig 2). This effect is magnified during long-term high K^+ intake in which K^+ accumulation in the renal interstitium exerts an inhibitory effect on Na^+ reabsorption in the thick ascending limb and proximal tubule, resulting in more delivery of Na^+ and flow to the aldosterone-sensitive distal nephron (ASDN). K^+ secretion can be triggered when K^+ enters into the gastrointestinal tract because there is an enteric K^+-sensing mechanism that results in inhibition of Na^+/Cl^- cotransporter (NCC) activity without a change in plasma K^+ concentration. Urinary K^+ secretion and expression of K^+ transporters exhibit a circadian pattern. Levels of renal outer medullary potassium channel (ROMK) gene expression are higher in daylight and during periods of activity (when renal K^+ excretion is greater), whereas H^+/K^+-adenosine triphosphatase (H^+/K^+-ATPase) expression follows the opposite pattern. Adapted from Palmer & Clegg (*Adv Physiol Educ*. 2016;40:480-490). Abbreviations: CD, collecting duct; DCT1, proximal portion of the distal convoluted tubule; DCT2, distal portion of the distal convoluted tubule where aldosterone sensitivity begins; ENaC, epithelial sodium channel.

a contributory role in the pathophysiology of chronic diseases such as obesity, hypertension, diabetes, kidney stones, and bone disease.

Aldosterone can signal the kidney to stimulate salt retention without K^+ secretion (in the setting of volume depletion) and to stimulate K^+ secretion without salt retention (in hyperkalemia), a pattern dubbed the "aldosterone paradox." The reciprocal relationship between urinary flow rates and distal Na^+ delivery with circulating aldosterone levels (discussed further next) may at least partially account for this paradox. In addition, unlike hyperkalemia, volume depletion leads to increases in both angiotensin II and aldosterone levels (Fig 4). Angiotensin II stimulates proximal Na^+ reabsorption and has a stimulatory effect on the NCC in the DCT1. In addition, angiotensin II exerts an inhibitory effect on ROMK in the ASDN. These effects in both the proximal and distal nephron allows for simultaneous Na^+ conservation without K^+ wasting. In addition, aldosterone has the capability to activate transport by intercalated cells along the connecting tubule and collecting duct to modulate K^+ secretion. Mineralocorticoid receptors in intercalated cells are phosphorylated within their ligand-binding domain, rendering them less active; thus, aldosterone primarily stimulates principal cells, resulting in electrogenic Na^+ reabsorption and K^+ secretion. In the setting of volume depletion, angiotensin II dephosphorylates mineralocorticoid receptors in intercalated cells, permitting aldosterone to activate the apical proton pumps (H^+-ATPase and H^+/K^+-ATPases) and the Cl^-/HCO_3^- exchanger (pendrin) in intercalated cells. This provides a pathway for electroneutral NaCl absorption while preventing excess K^+ secretion.

Nuances of K^+ Homeostasis

Circadian Rhythm of K^+ Secretion

K^+ handling by the kidney exhibits a circadian rhythm characterized by lower excretion at night and in the early morning hours and then increasing in the afternoon, in part to coincide with the timing of consumption of K^+-containing foods. This excretory pattern coincides with a circadian rhythm in the transcripts coding for kidney proteins related to K^+ secretion. Additionally, there is a circadian rhythm of glucocorticoid synthesis and secretion that also appears to coincide with the sleep/wake cycle and changes in plasma aldosterone levels.

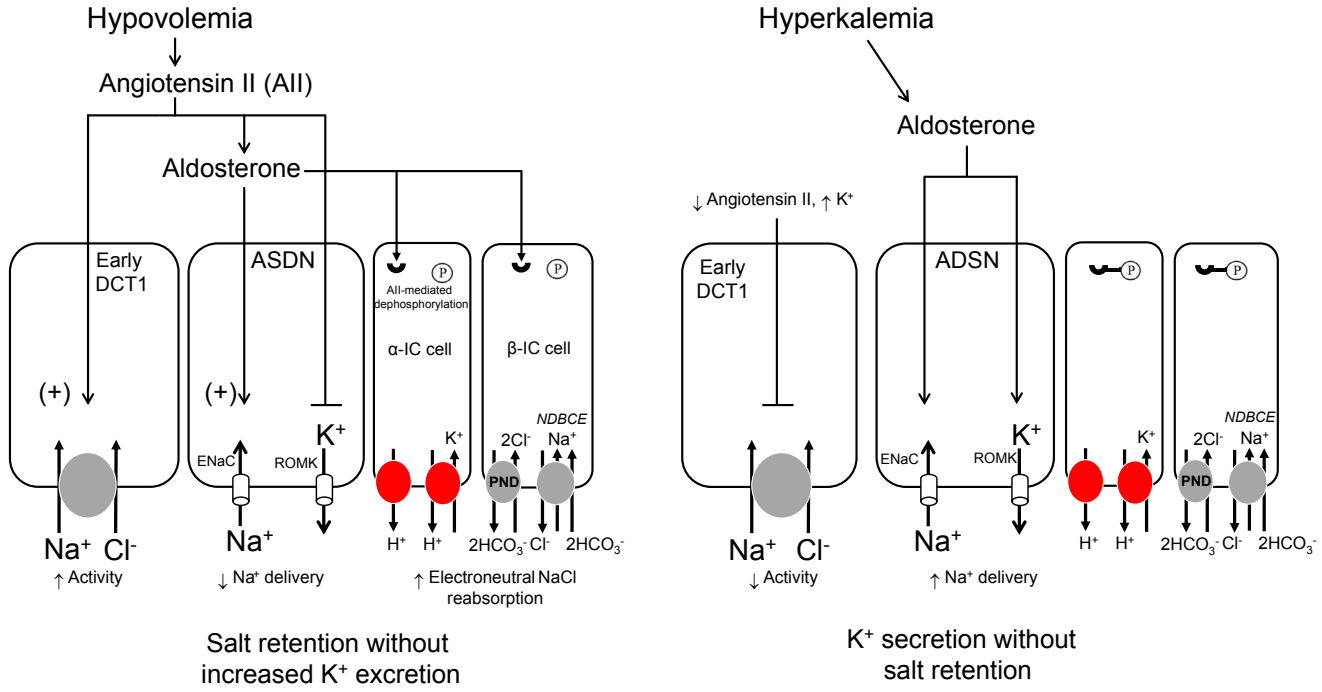

Figure 4. Mechanism to explain the aldosterone paradox. Under conditions of volume depletion (left side), increased circulating angiotensin II (AII) has a number of effects that provide a way to maximally conserve salt and minimize K^+ secretion. AII stimulates the Na^+-Cl^- cotransporter in the early distal convoluted tubule (DCT1), thereby reducing Na^+ delivery to downstream segments. In the aldosterone sensitive distal nephron (ASDN), AII exerts an inhibitory effect on renal outer medullary potassium channel (ROMK) and along with aldosterone stimulates epithelial Na^+ channel (ENaC) activity. Additionally, AII leads to dephosphorylation of the mineralocorticoid receptor in intercalated cells, which permits aldosterone stimulation of electroneutral NaCl transport. When hyperkalemia or increased dietary K^+ intake occur with normovolemia (right side), direct effects of K^+ along with low circulating AII levels lead to inhibition of Na^+-Cl^- cotransport activity and increased ROMK activity. Increased Na^+ delivery to the ENaC drives electrogenic secretion of K^+ through ROMK. Phosphorylated mineralocorticoid receptors prevent aldosterone-mediated electroneutral NaCl transport in intercalated cells.

Sexual Dimorphism in K^+ Homeostasis

The requirement for salt retention in females during unique physiologic states such as pregnancy and lactation has given rise to investigation of sex differences in characteristics of transport along the nephron. In females, more NCC proteins are present in the distal nephron due to effects of estrogen and prolactin. Studies examining the relative abundance of transporters throughout the nephron suggest that this increase in activity is a compensatory response to decreased salt reabsorption in more proximal portions of the nephron. Increased activity of the cotransporter would serve to limit Na^+ delivery to the ASDN and prevent K^+ loss. Studies suggest that female rats exhibit a lower plasma K^+ concentration set point than males in that administration of a high-K^+ meal leads to a marked increase in urinary Na^+ and K^+ excretion associated with decreased phosphorylation of the cotransporter. These sex differences in K^+ handling may serve to prevent hyperkalemia during pregnancy, when food intake markedly increases to provide nutrient support for the developing fetus.

Additional Readings

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Hypokalemia

Question 2: For cases 2-1 to 2-4, select the clinical description that best fits the laboratory values.

	Plasma					Urine			
Case	Na^+	K^+	Cl^-	HCO_3^-	Cr	Na^+	K^+	Cl^-	pH
2-1	136	2.5	110	16	1.0	45	35	40	7.0
2-2	135	2.2	88	35	0.8	25	30	<10	7.4
2-3	145	2.9	98	32	1.3	42	40	60	5.6
2-4	135	2.2	105	16	1.4	<10	15	65	6.8

Clinical Descriptions

a) A 28-year-old woman who works as a fashion model and appears emaciated
b) A 35-year-old woman with arthralgias and nephrocalcinosis
c) A 28-year-old man with human immunodeficiency virus (HIV) infection and chronic diarrhea
d) A 46-year man with blood pressure of 150/105 mm Hg taking no medications

For the answer to the question, see the following text.

All values expressed in mEq/L except for creatinine (Cr; mg/dL) and pH.

Hypokalemia is common clinically and is generally defined as K^+ concentration < 3.5 mEq/L (<3.5 mmol/L). Transient hypokalemia is usually due to cell shift, whereas sustained hypokalemia occurs because of inadequate intake or, more commonly, excessive K^+ loss. The cause can be determined in most cases with knowledge of the clinical setting, volume status, presence or absence of acid-base disorders, and urine electrolyte levels.

Assessment of urinary K^+ excretion is useful in distinguishing whether the kidney is responsible for hypokalemia or is responding appropriately to some other cause. A 24-hour urine collection is the most accurate way to assess kidney K^+ handling. A value less than 25 to 30 mEq/d is a normal response to K^+ depletion, whereas higher values suggest a component of kidney K^+ wasting. A more immediate assessment can be made by obtaining a spot urine K^+ concentration: 5 to 15 mEq/L is consistent with an extrarenal cause of hypokalemia, while >40 mEq/L implicates the kidney as the cause. However, a spot measurement is limited by variation in urinary concentration. A urine K^+ concentration of 40 mEq/L could reflect an appropriate response in a hypokalemic patient with highly concentrated urine from decreased water intake. If it occurred in the setting of decreased effective volume, although decreased volume stimulates aldosterone production, the absolute amount of K^+ in urine would stay relatively low on account of decreased Na^+ and water delivery to the distal nephron. As another example, a spot urine sample with K^+ concentration < 15 mEq/L may represent K^+ wasting by the kidneys if it occurs in the setting of a water diuresis. The response to therapy can also hint at the cause of hypokalemia. In general, a nonkidney disorder will be more easily corrected following K^+ administration (provided the underlying disturbance has abated), while continuing losses in urine complicate correction of hypokalemia.

The transtubular K^+ gradient (TTKG) is designed to avoid the limitations of a spot urine K^+ concentration when evaluating a dyskalemic patient. This formula provides an estimate of the ratio of K^+ in the lumen of the cortical collecting duct to that in the peritubular capillaries at a point at which tubular fluid is isotonic with plasma. In a hypokalemic patient, a ratio < 3 suggests an appropriate kidney response to the disorder, whereas a ratio > 7 implies kidney K^+ wasting. This calculation requires the urine Na^+ concentration to be at least 25 mEq/L and urine osmolality at least equal to plasma osmolality. Although clinical use of the TTKG has fallen out of favor in recent years, it is a useful construct for considering tubular K^+ handling.

Because urea and Na^+ are reabsorbed in the downstream medulla, some have questioned the utility of this calculation given that negligible absorption of osmoles distal to the collecting duct is assumed. Instead, urinary K^+-creatinine ratio can be used to assess K^+ handling by the kidneys. Because of the near-constant rate of creatinine secretion in urine, this ratio corrects for variation in urine concentration. A K^+-creatinine ratio < 13 mEq/g (another threshold reported in the urine is <2.5 mEq/mmol) suggests an appropriate response to gastrointestinal K^+ loss, remote use of diuretics, decreased dietary intake, and K^+ shift into cells. Higher ratios imply an inappropriate response by the kidney (Fig 5).

Decreased K^+ intake

The normal kidney can excrete urine virtually free of Na^+ in the setting of dietary Na^+ restriction. By contrast, ~15 mEq/d of K^+ continues to be excreted in response to a K^+-free diet. For this reason, dietary restriction of K^+ alone can potentially lead to hypokalemia over time. More commonly, dietary K^+ restriction simply exacerbates hypokalemia from other causes. During extreme K^+-deficient diets (eg, in anorexia nervosa, crash diets, alcoholism, and intestinal malabsorption), renal K^+ excretion is made worse by the frequent coexistence of magnesium (Mg^{2+}) deficiency. Under normal circumstances, intracellular Mg^{2+} inhibits K^+ secretion through the ROMK channel in the distal nephron, an effect that is overcome by cell depolarization caused by aldosterone-stimulated Na^+ reabsorption through the ENaC. Low intracellular Mg^{2+} concentration leads to persistent increases in renal K^+ excretion such that hypokalemia is refractory to treatment until the Mg^{2+} deficit is repaired. This kaliuretic effect intensifies when there is increased distal Na^+ delivery and increased aldosterone level, as discussed later.

Cellular Distribution

As indicated, there are important physiologic regulators of internal K^+ distribution, such as postprandial release of insulin that shifts dietary K^+ into cells and release of catecholamines to limit increases in extracellular K^+

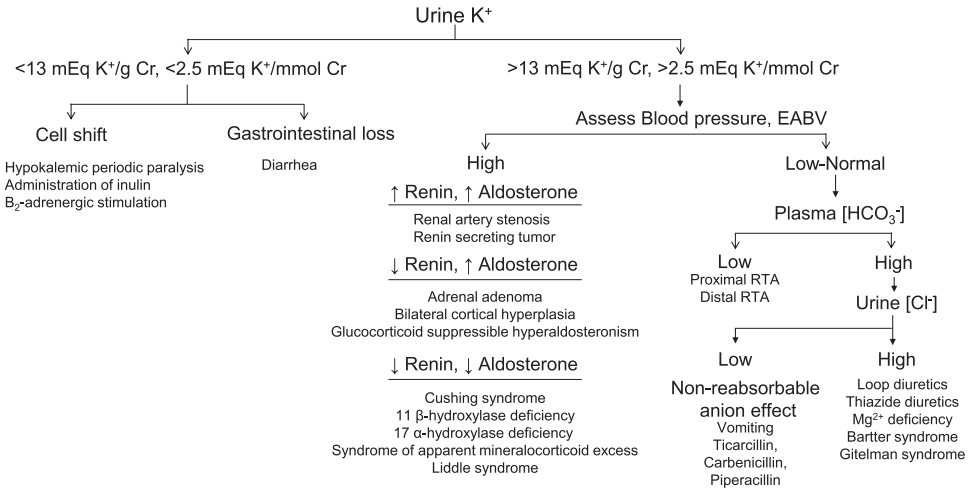

Figure 5. Flow diagram shows the approach to a patient with hypokalemia based on urinary potassium-creatinine ratio. The numeric values are two different thresholds reported in the literature that can be used to assess kidney potassium handling in a hypokalemic patient. Abbreviations: EABV, effective arterial blood volume; RTA, renal tubule acidosis. Adapted from Palmer & Clegg (*Adv Physiol Educ.* 2016;40:480-490 and *Clin J Am Soc Nephrol.* 2019;14:306-316).

concentration caused by contracting muscle during exercise. Exaggeration of these normal physiologic effects can lead to symptomatic hypokalemia. For instance, hypokalemia may occur as a complication of exogenous β-adrenergic agonist administration and the hyperadrenergic state that is frequently associated with alcohol withdrawal syndromes or myocardial infarction. Alkalemia from either respiratory or metabolic causes promotes K^+ entry into cells, although the effect is small (<0.4-mEq/L decrease for each 0.1-unit increase in pH). Box 1 lists several causes of hypokalemia through cell shift.

Hypokalemic periodic paralysis refers to muscle weakness or paralysis due to a sudden influx of K^+ into cells. The episodes are triggered by rest after exercise, stress, high-carbohydrate meals, and circumstances in which high levels of catecholamines or insulin are released. The acquired form of the disease occurs in association with hyperthyroidism and is more common in men of Asian or Mexican descent. These episodes resolve when the hyperthyroidism is successfully treated. The familial form is inherited as an autosomal dominant disorder due to mutations in the muscle calcium channel α-1 subunit gene (*CACNA1S*). The clinical features are similar to the acquired form, though there is a younger age at presentation (usually <20 years), an equal male-female distribution, and a predominance in whites. In both forms, the finding of reduced urinary K^+ excretion during attacks is useful in excluding severe weakness or paralysis resulting from hypokalemia due to kidney K^+-wasting disorders.

Decreased Total-Body K^+

Extrarenal Loss

Decreased total-body K^+ stores can be the result of K^+ loss from sites other than the kidney. Hypokalemia due to loss of K^+ in sweat is uncommon but can occur when large volumes of sweat are generated during intense exercise in a hot/humid environment. Secretory diarrhea is generally due to inhibition of intestinal NaCl or $NaHCO_3$ transport or active Cl^- secretion accompanied by the passive movement of Na^+, creating a fluid high in Na^+ and low in K^+. Despite the low K^+ content of stool, hypokalemia can develop when volume loss is high. The development of a hyperchloremic normal gap metabolic acidosis in this setting can prevent maximal lowering of urine K^+ concentration because acidemia exerts an inhibitory effect on proximal Na^+ reabsorption. Kidney K^+ excretion is increased in this setting due to increased distal Na^+ delivery. In addition, the degree of total-body K^+ depletion

Box 1. Factors That Cause Hypokalemia and Hyperkalemia Due to Cell Shift

Hypokalemia
- Alkalosis (effect is trivial)
- Insulin administration
- β_2-adrenergic stimulation
- Anabolism (treatment of pernicious anemia)
- Hypokalemic periodic paralysis
- Drugs/toxins/herbs (barium and chloroquine intoxication, cesium salts)

Hyperkalemia
- Metabolic acidosis (mineral and less so with organic acidosis)
- α-Adrenergic stimulation
- Hypertonicity (hyperglycemia, mannitol, sucrose)
- Tissue injury (rhabdomyolysis, hemolysis, tumor lysis)
- Hyperkalemic periodic paralysis
- Drugs/toxins/herbs (digoxin overdose, epsilon-aminocaproic acid, succinylcholine)

Adapted from Palmer & Clegg (*Adv Physiol Educ.* 2016;40:480-490).

may be underestimated due to the effect of acidosis to redistribute K^+ into the extracellular space. Chronic intestinal pseudo-obstruction (Ogilvie syndrome) can cause hypokalemia due to a secretory diarrhea driven by active K^+ secretion. In this setting, fecal electrolyte concentration is high in K^+ and low in Na^+.

Kidney K^+ Wasting

As mentioned, usually there is a balanced reciprocal relationship between distal Na^+ delivery and circulating aldosterone. This relationship contributes to the maintenance of normal K^+ balance despite wide variability in dietary salt intake. Kidney K^+ wasting occurs in pathophysiologic states that lead to coupling of high distal Na^+ delivery and increased aldosterone activity (Fig 6). This coupling can result from a primary increase in mineralocorticoid activity or a primary increase in distal Na^+ delivery.

A primary increase in mineralocorticoid activity can be the result of nonsuppressible renin secretion, aldosterone or nonaldosterone mineralocorticoid secretion, or a persistent mineralocorticoid-like effect. Kidney salt retention and expansion of extracellular fluid volume suppress proximal Na^+ reabsorption, resulting in a secondary increase in distal Na^+ delivery. Clinically these patients present with hypertension, hypokalemia, and metabolic alkalosis and can best be approached by measuring plasma renin activity and aldosterone concentration (Fig 5).

A primary increase in distal Na^+ delivery characterizes conditions in which there is a secondary increase in mineralocorticoid activity due to contraction of extracellular fluid volume. The increase in distal Na^+ delivery is considered primary because it is from causes other than volume expansion. These patients generally present with hypokalemia and normal or low blood pressure and can best be approached according to the presence of metabolic acidosis or metabolic alkalosis (Fig 5).

Falling under the category of metabolic acidosis are disorders that cause renal tubular acidosis (RTA). Distal (type 1) RTA arises from defects in H^+ secretion in the distal nephron causing interference with HCO_3^- regeneration and resulting in persistently alkaline urine. The inhibitory effect of acidosis on proximal Na^+ handling accounts for the primary increase in Na^+ delivery. Hypokalemia and K^+ depletion normally upregulate activity of the H^+/K^+-ATPase pump in α-intercalated cells in the collecting duct. Failure to increase pump activity would further increase K^+ wasting. The RTA associated with amphotericin B administration is due to increased luminal membrane permeability. This defect results in back leak of secreted H^+ and leakage of K^+ into the tubular lumen.

Proximal (type 2) RTA is the result of impaired HCO_3^- reclamation in the proximal tubule owing to a reduction in the tubular maximum for reabsorption. When plasma HCO_3^- concentration is greater than the tubular maximum, increased distal delivery of $NaHCO_3$ causes K^+ wasting. Urine pH is alkaline and urine Na^+ and K^+ concentrations are increased while urine Cl^- concentration is low. When plasma HCO_3^- concentration declines to the reduced tubular maximum, urine acidifies and the degree of K^+ wasting decreases. Increasing the plasma HCO_3^- concentration with alkali therapy worsens the hypokalemia because distal delivery of $NaHCO_3$ is again increased.

A primary increase in distal Na^+ delivery can be the result of a nonreabsorbable anion. The anion's identity can be determined using urine pH, urinary electrolyte concentrations, and clinical context. A high urine Na^+ and low Cl^- concentration in the setting of alkaline urine (pH 7-8)

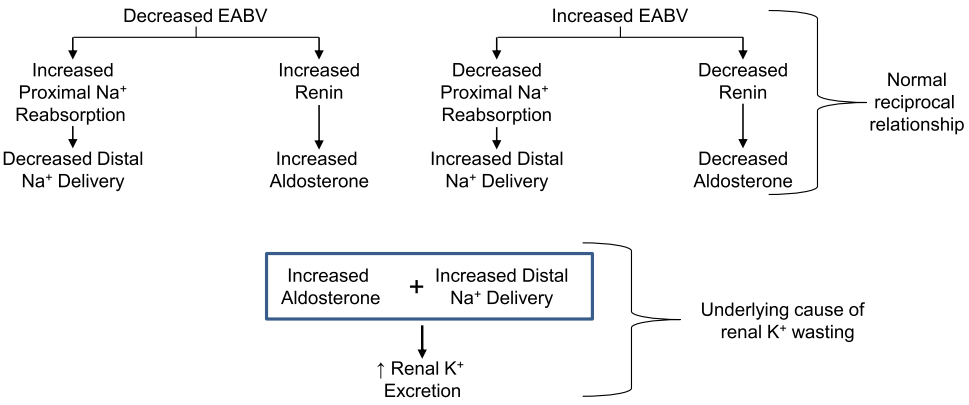

Figure 6. Under normal circumstances, the relationship between Na^+ delivery to the distal nephron and circulating aldosterone is balanced and reciprocal; this preserves K^+ balance during normal volume regulation. Kidney K^+ wasting occurs when increased Na^+ delivery is coupled to increased mineralocorticoid activity. For example, in uncontrolled diabetes, the osmotic diuretic effect of glucose and excretion of Na^+-ketoacid salts causes a primary increase in distal Na^+ delivery to the distal nephron. Meanwhile, mineralocorticoid activity is increased as a result of volume depletion. Use of thiazide or loop diuretics is also a cause of renal K^+ wasting through this coupling effect. In addition, high flow rates lower luminal K^+ concentration, establishing a gradient that favors K^+ diffusion into the luminal fluid. High flow also activates K^+ secretion through the Ca^{2+} activated maxi K^+ (BK) channel. Adapted from Palmer & Clegg (*Adv Physiol Educ.* 2016;40:480-490).

signifies substantial bicarbonaturia, as can occur with nasogastric suction or active emesis. The extrarenal generation of metabolic alkalosis results in urinary HCO_3^- excretion, necessitating some filtered Na^+ to accompany the base; meanwhile, urine Cl^- concentration stays low on account of neurohumoral activation because of volume contraction. However, urine pH < 6 implicates another nonreabsorbable anion, such as ketoanions or drugs such as ticarcillin disodium-clavulanate, piperacillin-tazobactam, or carbenicillin disodium. In patients with low effective volume, these antibiotics couple enhanced delivery of Na^+ to higher aldosterone levels in the distal nephron, resulting in metabolic alkalosis of a renal origin and causing low urine pH.

Loop and thiazide diuretics and their genetic equivalents (Bartter and Gitelman syndromes, respectively) should be considered in patients with hypokalemia and metabolic alkalosis when urine Na^+ and Cl^- concentrations are both increased. Increased distal Na^+ delivery coupled to increased mineralocorticoid levels not only increases K^+ secretion but also increases the rate of H^+ secretion, causing the development of metabolic alkalosis of a renal origin.

Considering question 2, the laboratory set of patient 2-1 indicates hypokalemic normal gap metabolic acidosis. This would be consistent with answer (b), the 35-year-old woman with arthralgias and nephrocalcinosis whose presentation suggests a distal (type 1) RTA as with Sjögren syndrome. The alkaline urine and positive urine anion gap further support the diagnosis of RTA.

For patient 2-2, laboratory values indicate hypokalemic metabolic alkalosis with a low urine Cl^- concentration. This would be consistent with answer (a) because evaluation of hypokalemia in a fashion model who is emaciated should include consideration of surreptitious vomiting. As discussed, the extrarenal generation of metabolic alkalosis results in urinary HCO_3^- excretion, along with some Na^+ to accompany the base, while urine Cl^- concentration remains low. HCO_3^- acts as a nonreabsorbable anion, causing increased distal Na^+ delivery and development of K^+ wasting. Urine pH of 7 or 8 indicates substantial bicarbonaturia.

The laboratory set for patient 2-3 best matches answer (d). A primary increase in mineralocorticoid levels (Conn syndrome) or effect (Liddle syndrome) leads to a Cl^--resistant form of metabolic alkalosis accompanied by kidney K^+ wasting and hypertension. Increased distal Na^+ delivery is due to inhibition of proximal reabsorption brought about by volume expansion. Serum Na^+ concentration is often mildly increased in these conditions.

For patient 2-4, whose laboratory values indicate hypokalemic normal gap metabolic acidosis, the correct answer is (c). Loss of HCO_3^-, NaCl, and K^+ through chronic diarrhea brings about a normal gap hyperchloremic metabolic acidosis, hypokalemia, and extracellular fluid volume contraction. Acidosis and hypokalemia trigger ammoniagenesis in the kidney, which permits more secretion of distal H^+. The excreted ammonium is coupled to Cl^-, producing a negative urinary anion gap. Although there is substantial distal H^+ secretion, urine pH is not as acidic as might be expected because the free H^+ concentration is lowered by the buffering effect of urinary ammonium.

Complications and Treatment of Hypokalemia

Decreased extracellular K^+ concentration leads to cell membrane hyperpolarization, rendering the cell less sensitive to excitation and accounting for the association of muscle weakness with hypokalemia. In patients with distal (type 1) RTA, weakness progressing to complete flaccid quadriplegia can develop insidiously over 24 to 48 hours. Rhabdomyolysis complicated by acute kidney injury (AKI) and smooth muscle dysfunction leading to paralytic ileus are other potential complications. Disturbances in cell membrane voltage may also explain central nervous system manifestations such as confusion and affective disorders.

Disturbances in cell voltage can lead to cardiac complications. Depression of the ST segment, T wave flattening, and an increase in amplitude of the U wave are characteristic findings on the electrocardiogram. Hypokalemia in the setting of cardiac glycoside therapy is associated with increased risk for premature ventricular contractions and supraventricular and ventricular tachyarrhythmias.

Hypokalemia can present with polyuria and polydipsia due to decreased concentrating ability of the kidney. This effect is the result of decreased medullary tonicity and resistance of the tubule to the hydro-osmotic effect of vasopressin. Chronic hypokalemia can cause a chronic tubulointerstitial nephritis, referred to as kaliopenic nephropathy, which is characterized by the development of small kidney cysts and histologic changes of tubular atrophy, interstitial infiltration of macrophages, and interstitial fibrosis. Glucose intolerance can occur because insulin release is regulated partially by plasma K^+. In general, there is an ~10-mg/dL increase in glucose concentration for every 1-mEq/L decrease in plasma K^+ concentration.

Hypokalemia represents a total-body deficit in the absence of an intracellular shift. A decrease in plasma K^+ concentration from 4 to 3 mEq/L corresponds to a total-body deficit of 100 to 200 mEq, whereas a decline from 3 to 2 mEq/L signifies a deficit of 400 to 600 mEq/L. In patients with acidemia, total-body deficits are more profound still. K^+ can be administered orally or intravenously as KCl salt. Oral administration is safer and more effective and can be dosed at 100 to 150 mEq/d. Solutions of KCl taste bitter and the tablet can irritate the gastric mucosa; microencapsulated (wax-matrix) forms of KCl are more easily tolerated.

Administering K^+ intravenously may be needed for patients who are unable to take oral medications or if the K^+ deficit is substantial enough to cause cardiac arrhythmias, respiratory paralysis, or rhabdomyolysis. Intravenous KCl should be administered at no more than 20 mEq/h

and at a concentration no higher than 40 mEq/L; excessive concentrations cause phlebitis. In acidemic patients, K^+ should be given before HCO_3^- therapy because correction of metabolic acidosis will cause an intracellular shift of K^+, leading to a further decrease in the extracellular fluid concentration. After the patient is stabilized, the metabolic acidosis can be addressed by administering HCO_3^- along with K^+. With severe manifestations, such as paralysis and respiratory failure, intravenous K^+ should be given in a solution containing no glucose (due to the counter-regulatory insulin response) or HCO_3^- (to circumvent rapid shifts into the intracellular compartment).

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Hyperkalemia

Pseudohyperkalemia

Pseudohyperkalemia is a laboratory artifact in which there is marked elevation in serum K^+ concentration (>0.5 mEq/L) without clinical evidence of electrolyte imbalance. This phenomenon most commonly occurs during specimen collection when increased K^+ release from cells is caused by the application of tourniquets, fist clenching, use of small-bore needles, and mechanical trauma during pneumatic tube transport. Thrombocytosis (platelets > 500,000/μL) and marked leukocytosis (white blood cells, 70,000/μL) are pathologic causes of this disorder. Reverse pseudohyperkalemia refers to a false elevation in plasma K^+ concentration when serum K^+ concentration is normal. This condition most commonly occurs in the setting of hematologic malignancy and is due to heparin-induced cell membrane damage.

Increased Dietary Intake

Dietary intake contributes to hyperkalemia in the setting of decreased kidney function and/or decreased mineralocorticoid activity but rarely occurs in individuals with normal functioning kidneys. K^+ is listed as a nutrient of dietary concern in the most recent dietary guidelines because most individuals are not consuming recommended dietary intakes of K^+ and at the same time are exceeding the recommendations for Na^+ intake. Typical dietary sources enriched in K^+ include plant-based foods such as melons, citrus juice, and potatoes. It is important to note that some food sources high in K^+ are also high in carbohydrates, which would stimulate insulin release and thereby reduce the increase in plasma K^+ concentration. By contrast, animal products are high in K^+ but not carbohydrates, which may lead to higher plasma K^+ concentrations following consumption. Therefore, it is possible that not all K^+-enriched foods may lead to similar elevations in plasma K^+ concentrations.

Cell Shift

Case 3. *A 36-year-old woman presents with nausea and vomiting for 3 days. She reported polyuria and polydipsia during the last week. Physical examination show blood pressure of 110/70 mm Hg supine and 90/65 mm Hg seated. Laboratory examination show the following serum values: Na^+, 124 mEq/L; K^+, 6.4 mEq/L; Cl^-, 84 mEq/L; HCO_3^-, 10 mEq/L; anion gap, 30; glucose, 810 mg/dL; urea nitrogen, 46 mg/dL; creatinine, 2.1 mg/dL; pH 7.16; and P_{CO_2}, 25 mm Hg. A diagnosis of diabetic ketoacidosis is made and the patient is treated with intravenous insulin and isotonic saline solution. One day later, laboratory evaluation shows the following values: Na^+, 133 mEq/L; K^+, 2.9 mEq/L; Cl^-, 105 mEq/L; and HCO_3^-, 16 mEq/L.*

Question 3: Which one of the following is true regarding the hyperkalemia on admission?

a) Total-body K^+ content is normal
b) Total-body K^+ stores are low due to an osmotic diuresis, but plasma K^+ concentration is increased due to insulin deficiency
c) Total-body K^+ content is low due to an osmotic diuresis, but plasma K^+ concentration is increased because of cell shift due to metabolic acidosis
d) Total-body K^+ content is high due to volume contraction and concomitant oliguria

For the answer to the question, see the following text.

Although chronic hyperkalemia is almost always due to impaired kidney excretion, transient hyperkalemia suggests cell shift. The effect of metabolic acidosis and hypertonicity were previously discussed. Tissue damage (eg, rhabdomyolysis, trauma, massive hemolysis, and tumor lysis) are common causes of hyperkalemia resulting from cell shift. These conditions can cause sudden and severe hyperkalemia because only a 2% shift of intracellular K^+ to the extracellular space can double the normal extracellular K^+ concentration. Box 1 lists several factors that cause hyperkalemia due to cell shift.

In hyperkalemic periodic paralysis there are episodes of extreme muscle weakness or paralysis; in most cases, the cause is mutations in the sodium channel gene *SCN4A*. As opposed to familial hypokalemic periodic paralysis,

patients with the hyperkalemic form tend to be younger (<10 years vs 15-35 years), have more frequent attacks that usually last a shorter time (<24 vs >24 hours), and more commonly experience attacks in the morning (vs nighttime). Factors that can trigger attacks include rest after exercise, ingestion of K^+-rich foods, and exposure to cold temperatures.

Returning to case 3, given the patient's diagnosis of diabetic ketoacidosis, she can be expected to be total-body K^+ depleted due to renal K^+ wasting on account of increased distal Na^+ delivery coupled to increased circulating aldosterone level. This is the case even though such patients usually have increased plasma K^+ concentrations on admission. Distal Na^+ delivery is increased due to the osmotic diuretic effect of the glucose and excretion of Na^+-ketoacid salts. Volume depletion mediates the increase in aldosterone level. Even though there is total-body K^+ depletion, plasma K^+ concentration is frequently increased due to insulin deficiency and increased tonicity caused by the hyperglycemia. K^+ shifts do not occur because of metabolic acidosis because diabetic ketoacidosis is an organic acidosis. Mineral acidosis tends to cause much greater degrees of K^+ shift as compared to organic acidosis. Thus, the correct answer is (b).

Impaired Renal Excretion

Acute Kidney Injury

Hyperkalemia is a common occurrence in patients with AKI. Acute tubular necrosis or tubulointerstitial renal disease can lead to extensive injury to the late distal tubule and collecting duct, causing direct injury to cells that perform K^+ secretion. A rapid and severe reduction in glomerular filtration rate (GFR; <10 mL/min) per se is rate limiting for K^+ secretion. The speed of the GFR loss in AKI does not give sufficient time for normal renal and extrarenal adaptive mechanisms to come into force. Patients with oligo-anuria experience a pronounced decrease in distal delivery of salt and water, further contributing to reduced secretion of K^+. In those with nonoliguric AKI, hyperkalemia occurs more rarely because there is abundant distal delivery of salt and water. Severe acidosis, increased catabolism, and tissue breakdown are more likely to occur in AKI, and these processes all result in intracellular K^+ being released into the extracellular compartment. On account of increased cellular release along with impaired kidney K^+ secretion, life-threatening hyperkalemia occurs commonly in AKI.

Chronic Kidney Disease

Hyperkalemia is uncommon in patients with CKD until GFR declines to less than 15 to 20 mL/min. The ability to maintain a relatively normal plasma K^+ concentration despite a significant reduction in kidney mass is due to an adaptively accelerated rate of K^+ secretion in the remaining nephrons. This adaptation is believed to be analogous to what occurs in healthy persons subjected to high dietary K^+ intake. In animal models, long-term K^+ loading enhances the secretory capacity of the distal nephron, meaning that kidney K^+ excretion is substantially increased regardless of plasma K^+ concentration. This higher K^+ secretion happens along with cellular hypertrophy, higher mitochondrial density, and proliferation of the basolateral membrane in cells in the distal nephron and principal cells of the collecting duct. Higher plasma K^+ and mineralocorticoid concentrations separately trigger the amplification process, which occurs along with an increase in Na^+/K^+-ATPase activity. Flow, Na^+ delivery, and apical Na^+ transport are increased in the distal nephron of the remaining nephrons. Higher entry of apical Na^+ also stimulates Na^+/K^+-ATPase activity.

Gastrointestinal K^+ secretion plays an increasingly important role in the maintenance of total-body K^+ content with CKD progression. In hemodialysis patients, about 80 to 100 mEq of K^+ is removed with each treatment (up to 300 mEq/wk) while dietary K^+ intake is usually 400 to 500 mEq/wk. An adaptive increase in gastrointestinal K^+ secretion, primarily in the colon, allows for stabilization of total-body K^+ content. The process involves uptake over the basolateral membrane followed by secretion into the lumen by the large-conductance Ca^{2+}-activated ($K_{Ca}1.1$) BK channel. This channel is upregulated by aldosterone and other mediators that elevate cyclic adenosine monophosphate (cAMP) in the enterocyte. Decreased colonic secretion likely explains the development of hyperkalemia reported in anephric dialysis patients following the administration of renin-angiotensin-aldosterone system (RAAS) inhibitors.

Despite adaptations that occur in the kidney and gastrointestinal tract, patients with CKD have limited capacity to further increase K^+ secretion when there is an exogenous load; as a result, hyperkalemia can occur following even modestly increased K^+ intake. When GFR decreases to less than 15 to 20 mL/min, steady-state plasma K^+ concentration increases steeply with each incremental loss in GFR. The development of hyperkalemia when GFR is less severely reduced implies the superimposition of additional factors limiting K^+ secretion, including 1 or all of the following: decreased distal Na^+ delivery (as in decompensated heart failure or acute glomerulonephritis), disturbances in mineralocorticoid activity, or an abnormal collecting duct (Box 2).

Disease states or drugs can disrupt the RAAS and result in inadequate mineralocorticoid activity. A common cause of hyperkalemia with only a modest reduction in GFR and normal K^+ intake is the syndrome of hyporeninemic hypoaldosteronism. This syndrome is commonly present in the setting of diabetic nephropathy and interstitial renal disease.

In patients with lupus nephritis, urinary obstruction, or sickle cell disease, tubular injury often occurs early in the distal nephron and accounts for the development of hyperkalemia with only a mild decrease in GFR and

Box 2. Risk Factors for Hyperkalemia

- CKD: risk is inversely related to GFR, increasing substantially at <30 mL/min/1.73 m^2
- Acute kidney injury (particularly when oligo-anuric)
- Diabetes mellitus[a]
- Decompensated congestive heart failure
- Medications
  - ◇ Inhibition of renin release from juxtaglomerular cells
    - ▪ Nonsteroidal anti-inflammatory drugs
    - ▪ β-Blockers
    - ▪ Calcineurin inhibitors: cyclosporine, tacrolimus
  - ◇ Inhibition of aldosterone release from the adrenal gland
    - ▪ Heparin
    - ▪ Ketoconazole
  - ◇ Mineralocorticoid receptor blockade
    - ▪ Spironolactone
    - ▪ Eplerenone
    - ▪ Drospirenone (found in certain birth control pills)
  - ◇ Blockade of epithelial sodium channel blocker in kidney collecting duct
    - ▪ Amiloride
    - ▪ Triamterene
    - ▪ Trimethoprim
- K^+ supplements, some salt substitutes or herbal remedies, and K^+-enriched foods in the setting of diminished kidney excretion

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

[a]A spectrum of abnormalities in the renin-angiotensin-aldosterone system have been reported in patients with diabetes mellitus. These include hyporeninemic hypoaldosteronism and normal renin release alongside reduced capacity for aldosterone release. Hypoaldosteronism, together with collecting duct dysfunction on account of diabetic nephropathy and receipt of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, markedly increases the risk for hyperkalemia.

Adapted from Palmer & Clegg (*Adv Chromic Kidney Dis.* 2017;24:319-324).

normal aldosterone levels. Impaired renin release causing hyporeninemic hypoaldosteronism often coexists in these disease states. Hyperkalemia is common in kidney transplant recipients, for whom tubular injury and/or impaired release of renin is due to tubular injury resulting from immune-mediated damage, prior ischemia-reperfusion injury, or donor characteristics. Administration of drugs such as trimethoprim and RAAS blockers also play contributory roles. The calcineurin inhibitors tacrolimus and cyclosporine further increase the risk for hyperkalemia by processes similar to that of familial hyperkalemic hypertension. Calcineurin normally decreases NCC activity in the DCT1 through dephosphorylation. Calcineurin inhibition leads to unopposed phosphorylation and activation of the cotransporter. The retained NaCl causes hypertension and volume expansion, secondarily suppressing circulating levels of renin and aldosterone, while the decrease in Na^+ delivery to the ASDN impairs K^+ secretion.

The K^+-sparing diuretics lessen the K^+ secretory capacity of the cortical collecting tubule. Amiloride and triamterene block Na^+ reabsorption through the ENaC, causing the lumen to become less negative, thereby decreasing the driving force for K^+ secretion. Spironolactone and eplerenone are mineralocorticoid receptor antagonists. Certain birth control pills contain the non–testosterone-derived progestin drospirenone, which also has mineralocorticoid-blocking effects. Plasma K^+ concentration should be monitored closely if these drugs are used alongside other agents that interfere in the RAAS or nonsteroidal anti-inflammatory drugs.

Hyperkalemia and metabolic acidosis are key features of familial hyperkalemic hypertension (pseudohypoaldosteronism type II, Gordon syndrome). Mutations in the WNK4 and WNK1 kinases are most commonly the cause for this autosomal dominant form of hypertension. While an increase in plasma K^+ concentration normally stimulates aldosterone release from the adrenal gland, plasma aldosterone levels are generally low in this disorder. Thiazide diuretics are particularly effective in the treatment of this disorder, reflective of increased activity of the NCC in the DCT1.

Pseudohypoaldosteronism type I is characterized by hyperkalemia, metabolic acidosis, and renal salt wasting and is due to mineralocorticoid resistance. Homozygous mutations in the 3 subunits of ENaC are responsible for the autosomal recessive form of the disease. These patients typically present in the first few years of life and are prone to volume depletion. Excessive Na^+ loss in sweat and altered fluid transport in the lung may give rise to recurrent lung infections and/or lesions on the skin. There is an autosomal dominant form of the disease that arises as a result of mutations in the mineralocorticoid receptor. Clinical manifestations in this form of the disease are relatively mild and often improve in early childhood.

Clinical Features of Hyperkalemia

Hyperkalemia leads to a depolarizing effect on the heart, giving rise to changes on the electrocardiogram. Peaking of the T wave, ST-segment depression, widening of the PR interval, and widening of the QRS interval are sequential changes of progressively severe hyperkalemia. Appearance of a sine wave pattern is predictive of imminent ventricular fibrillation and asystole. Other reported changes attributable to hyperkalemia include a right bundle branch block and right precordial ST-segment elevations reminiscent of the Brugada syndrome and a pseudoinfarct pattern suggesting both an anteroseptal and inferior wall myocardial infarction.

The rapidity of the hyperkalemia is an important determinant as to whether electrocardiogram changes occur. For example, changes can be expected with a plasma K^+ concentration of 6 to 7 mEq/L when hyperkalemia occurs acutely. By contrast, the electrocardiogram

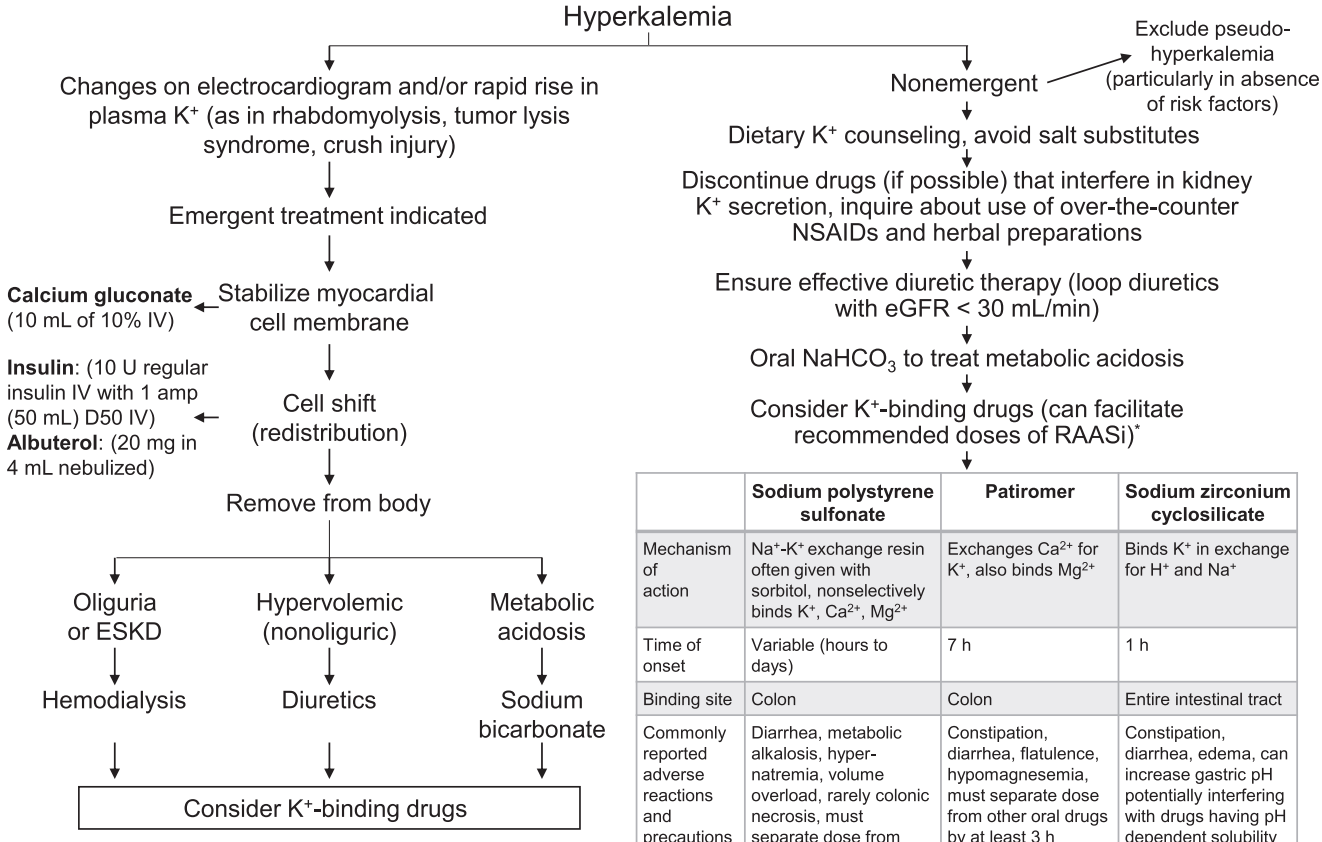
may be largely unchanged even at plasma concentrations of 8 to 9 mEq/L with chronic hyperkalemia. Overall, clinical studies show a poor correlation between cardiac manifestations and plasma K^+ concentration.

Hyperkalemia can also give rise to neuromuscular manifestations such as paresthesias and fasciculations in the arms and legs. In addition, some patients may present with weakness manifesting as an ascending paralysis and eventual flaccid quadriplegia. The trunk, head, and respiratory muscles are usually not affected.

Hyperkalemia impairs acidification in the kidney by lowering the amount of ammonium available to serve as a urinary buffer. Increased plasma K^+ concentration exerts a suppressive effect on ammonia production in the proximal tubule and interferes in the medullary transfer of ammonium in the thick ascending limb by competing with ammonium for transport on the $Na^+/K^+/2Cl^-$ cotransporter. Limited buffer availability for titration of secreted H^+ decreases net acid excretion.

Treatment of Chronic Hyperkalemia

Case 4. *A 55-year-old man with a 15-year history of hypertension, type 2 diabetes mellitus, and stage 3 CKD presents for follow-up. He was last evaluated 3 years ago. Six months ago, right knee osteoarthritis was diagnosed and he was given a prescription for ibuprofen by an outside physician. The patient brings empty medicine bottles for hydrochlorothiazide, losartan, metformin, and pravastatin. His only symptoms are fatigue, recent loss of appetite, and ankle swelling. On physical examination, temperature is 98.9°F, blood pressure is 146/92 mm Hg, pulse rate is 70 beats/min, and respiration rate 14 breaths/min. Body mass index is 31.5 kg/m². There is no jugular venous distention. Cardiac examination reveals distant heart sounds with no murmur. The lungs are clear to auscultation. There is trace bilateral lower-extremity edema. Laboratory examination shows the following serum values: Na^+, 142 mEq/L; K^+, 5.7 mEq/L; Cl^-, 108 mEq/L; HCO_3^-, 18 mEq/L; glucose, 230 mg/dL; and creatinine, 2.8 mg/dL. Urinary protein-creatinine ratio is 1.1 mg/mg.*



	Sodium polystyrene sulfonate	Patiromer	Sodium zirconium cyclosilicate
Mechanism of action	Na^+-K^+ exchange resin often given with sorbitol, nonselectively binds K^+, Ca^{2+}, Mg^{2+}	Exchanges Ca^{2+} for K^+, also binds Mg^{2+}	Binds K^+ in exchange for H^+ and Na^+
Time of onset	Variable (hours to days)	7 h	1 h
Binding site	Colon	Colon	Entire intestinal tract
Commonly reported adverse reactions and precautions	Diarrhea, metabolic alkalosis, hypernatremia, volume overload, rarely colonic necrosis, must separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, flatulence, hypomagnesemia, must separate dose from other oral drugs by at least 3 h	Constipation, diarrhea, edema, can increase gastric pH potentially interfering with drugs having pH dependent solubility

Figure 7. An approach to the treatment of emergent and nonemergent hyperkalemia. Abbreviations: eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IV, intravenously; NSAID, nonsteroidal anti-inflammatory drug; RAASi, renin-angiotensin-aldosterone system inhibitors. *In the management of patients with chronic kidney disease there is usually some K^+ restriction; this becomes more stringent in the transition to kidney failure and dialysis, if applicable. With the availability of new K^+-binding drugs, there may be opportunity for clinical trials focusing on liberalization of the diet to include sources of K^+, to see whether this leads to cardiovascular benefit and enhanced quality of life.

Question 4: In addition to initiating furosemide treatment, which of the following is the most appropriate initial step in managing this patient's CKD?

a) Begin hydrochlorothiazide treatment
b) Begin losartan treatment
c) Begin spironolactone treatment
d) Discontinue ibuprofen treatment

For the answer to the question, please see the following text.

Treatment of hyperkalemia is determined by the associated signs and symptoms, severity and rate of increase in plasma K^+ concentration elevation, and the underlying cause (Fig 7). Emergent treatment begins with stabilizing the myocardium to protect against arrhythmias, followed by shifting K^+ into cells. When the patient is stabilized, treatment focuses on lowering total-body K^+ content.

In patients without a hyperkalemic emergency, one should eliminate other sources of K^+ such as excessive dietary intake or dietary supplements (eg, some salt substitutes and herbal medications), discontinue treatment with drugs that impair renal K^+ excretion (nonsteroidal anti-inflammatory drugs), ensure effective diuretic therapy, and correct metabolic acidosis if present.

The increased risk for hyperkalemia with RAAS blockers creates a therapeutic dilemma because those at the greatest risk for this complication are often the same patients who gain the greatest cardiorenal benefit. K^+-binding agents may be useful to facilitate the continued use of recommended doses of these drugs. Long-term use of sodium polystyrene sulfonate for this purpose is poorly tolerated due to the sorbitol commonly used to promote osmotic diarrhea. Patiromer and sodium zirconium cyclosilicate are new K^+-binding drugs approved for the treatment of hyperkalemia. Clinical trials have demonstrated that both are well tolerated and can be used long term to lower the risk for hyperkalemia in people with diabetes or heart failure and/or who have CKD and are on RAAS blockade. Although not specifically tested, these drugs may also allow dietary liberalization of food enriched in K^+, potentially contributing to a better quality of life.

Returning to case 4, discontinuation of ibuprofen treatment and initiation of furosemide treatment are the most appropriate next steps in the initial management of this patient's CKD. Nonsteroidal anti-inflammatory drugs predispose to hyperkalemia by causing hyporeninemic hypoaldosteronism through inhibition of renin release at the juxtaglomerular apparatus. These drugs also limit distal Na^+ delivery by augmenting reabsorption along the ascending limb of Henle. The addition of a loop diuretic would help treat this patient's hypertension, control volume overload, and lower plasma K^+ concentration by increasing distal Na^+ delivery and flow rates. When the hyperkalemia is corrected, losartan treatment could be reinitiated with close monitoring of plasma K^+ concentration.

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Update

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Erratum Regarding "Managing Hyperkalemia to Enable Guideline-Recommended Dosing of Renin-Angiotensin-Aldosterone System Inhibitors" (*Am J Kidney Dis*. 2022;80[2]:159-160)

In the Editorial entitled "Managing Hyperkalemia to Enable Guideline-Recommended Dosing of Renin-Angiotensin-Aldosterone System Inhibitors" that appeared in the August 2022 issue of *AJKD* (Palmer and Clegg, volume 80, issue 2, pages 159-160), there was an error in the financial disclosure statement. The corrected statement is "Financial Disclosure: Dr Palmer reports receipt of consultancy and speaker fees from Relypsa and AstraZeneca. Dr Clegg is the spouse of Dr Palmer."

Erratum Regarding "Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019" (*Am J Kidney Dis*. 2019;74[5]:682-695)

In the Core Curriculum entitled "Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019" that appeared in the November 2019 issue of *AJKD* (Palmer and Clegg, volume 74, issue 5, pages 682-695), there was an error in the financial disclosure statement. The corrected statement is "Financial Disclosure: Dr Palmer reports receipt of consultancy and speaker fees from Relypsa and AstraZeneca. Dr Clegg is the spouse of Dr Palmer."

Erratum Regarding "Potassium Homeostasis in Health and Disease: A Scientific Workshop Cosponsored by the National Kidney Foundation and the American Society of Hypertension" (*Am J Kidney Dis*. 2017;70[6]:844-858)

In the Special Report entitled "Potassium Homeostasis in Health and Disease: A Scientific Workshop Cosponsored by the National Kidney Foundation and the American Society of Hypertension" that appeared in the December 2017 issue of *AJKD* (Kovesdy et al, volume 70, issue 6, pages 844-858), there was an error in the financial disclosure statement. The corrected statement is "Financial Disclosure: Dr Kovesdy is a consultant to Relypsa and Astra Zeneca. Dr Grams has a grant from the NKF. Dr Palmer reports receipt of consultancy and speaker fees from Relypsa and AstraZeneca. Dr Pitt is a consultant to Relypsa, KBP Pharmaceuticals, Ardelyx, Bayer, Davinci Therapeutics, Merck, Takeda, Boehringer Ingelheim, AstraZeneca, PharMain, Sarfez Pharmaceuticals, scPharmaceuticals, Tricidia, Aurasense, and Forest Laboratories; owns stock options in Relypsa, KBP Pharmaceuticals, Davinci Therapeutics, PharMain, scPharmaceuticals, and Aurasense; and has a patent pending for site-specific delivery of eplerenone to the myocardium. Dr Townsend is a consultant to Relypsa. The remaining authors declare that they have no other relevant financial interests."