

Physiology and pathophysiology of potassium homeostasis

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Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ* 40: 480–490, 2016 doi:10.1152/advan.00121.2016.—Total body potassium content and proper distribution of potassium across the cell membrane is of critical importance for normal cellular function. Potassium homeostasis is maintained by several different methods. In the kidney, total body potassium content is achieved by alterations in renal excretion of potassium in response to variations in intake. Insulin and beta-adrenergic tone play critical roles in maintaining the internal distribution of potassium under normal conditions. Despite homeostatic pathways designed to maintain potassium levels within the normal range, disorders of altered potassium homeostasis are common. The clinical approach to designing effective treatments relies on understanding the pathophysiology and regulatory influences which govern the internal distribution and external balance of potassium. Here we provide an overview of the key regulatory aspects of normal potassium physiology. This review is designed to provide an overview of potassium homeostasis as well as provide references of seminal papers to guide the reader into a more in depth discussion of the importance of potassium balance. This review is designed to be a resource for educators and well-informed clinicians who are teaching trainees about the importance of potassium balance.

POTASSIUM IS CRITICAL for maintaining cellular function. All cells possess a ubiquitous Na^+ - K^+ ATPase exchanger, which pumps Na^+ out of and K^+ into the cell, leading to a K^+ gradient across the cell membrane ($\text{K}^+_{\text{in}} > \text{K}^+_{\text{out}}$), which is partially responsible for maintaining the membrane potential. Excitable tissues, such as nerve and muscle, rely on maintenance of this gradient for normal function. The body has developed numerous mechanisms for maintenance of K^+ homeostasis which will be discussed below. Additionally, we have provided an updated reference list highlighting seminal papers published in this field to facilitate a more in-depth understanding of key concepts in potassium homeostatic mechanisms.

Overview of Potassium Homeostasis

There is ~50 mEq/kg of K^+ in the body such that total body K^+ in a 70-kg person is 3,500 mEq. K^+ (98%) is found mainly within cells, and ~2% of the body's K^+ is in the extracellular fluid. The normal concentration of K^+ in the extracellular fluid is 3.5–5.3 mEq/l. Large deviations from these values are not compatible with life. Approximately 90% of the daily K^+ intake is excreted in the urine, whereas a smaller percentage (10%) is excreted by the gastrointestinal tract. Therefore, within the body, the kidney is the major organ responsible for K^+ homeostasis. The kidney facilitates K^+ homeostasis by adjusting renal K^+ excretion over several hours in response to a K^+ load. Initial changes in extracellular K^+ concentration are

buffered by movement of K^+ into or out of skeletal muscle cells. Internal K^+ balance is a term used to refer to regulation of K^+ distribution between the intracellular and extracellular space. Insulin, catecholamines, and, to a lesser extent, aldosterone are critical factors responsible for maintaining the normal internal distribution of K^+ .

The amount of dietary K^+ required for normal homeostasis has been reviewed by the Food and Nutrition Board of the Institute of Medicine. In 2004, adequate intake levels for dietary K^+ intake were established at 4,700 mg/day (17). Data generated from the NHANES study conducted in 2007–2008 estimated that in the US both men and women were obtaining from their diet substantially lower levels of K^+ than recommended; specifically, the mean intake for women was estimated to be 2,290 mg/day, and 3,026 mg/day was estimated for men (57). Concern was initially raised about this relative “deficiency” in dietary K^+ intake, especially when these numbers were compared with what was consumed by prehistoric man, which was estimated to be 15,000 mg/day, suggesting that prehistoric man exceeded the NHANES recommendations by a factor >4 (14, 49). In fact, the most recent Dietary Guidelines for Americans and the Food and Drug Administration have now designated K^+ as a “nutrient of public health concern” because people are not meeting their estimated recommended dietary intake (13). It is important to note that eating diets high in K^+ has been linked to reducing blood pressure, decreasing the risk of stroke, improving bone health, and reducing the risk of nephrolithiasis more than taking K^+ supplements, suggesting that not only is K^+ critical, but also consumption of the foods enriched in K^+ provides benefits (39).

The normal kidney can maintain K^+ homeostasis even in the setting of high dietary intake. To demonstrate this, studies have shown serum K^+ levels are kept within the normal range even when there are increases to ~15 g daily of dietary K^+ intake sustained for 20 days (20, 43). Recent findings (discussed below) have identified the presence of an enteric K^+ sensing mechanism that initiates the renal secretory process upon K^+ entry into the gastrointestinal tract. The distal convoluted tubule has been identified as a site critical for K^+ homeostasis, where it acts as a K^+ sensor capable of initiating K^+ excretion independent of mineralocorticoid activity.

Overview of Renal K^+ Handling

K^+ is freely filtered across the glomerulus and then avidly reabsorbed by the proximal tubule and thick ascending limb of the kidney. Only a small amount of K^+ reaches the distal nephron. K^+ reabsorption in the proximal tubule is primarily through the paracellular pathway and is in rough proportion to the amount of Na^+ and water reabsorbed (Fig. 1). In the thick ascending limb, K^+ reabsorption occurs by both transcellular

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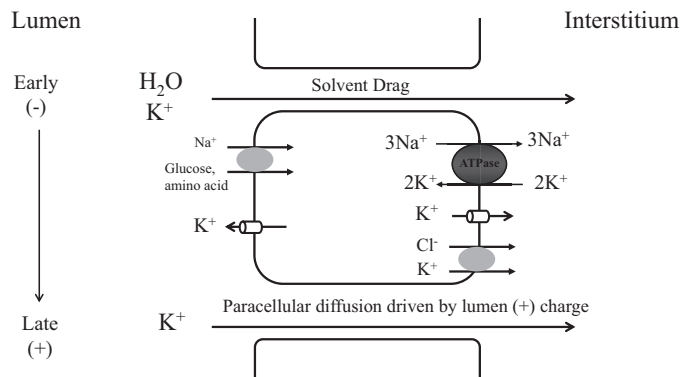


Fig. 1. A large component of filtered K^+ is reabsorbed by the proximal tubule primarily through the paracellular pathway driven by solvent drag. The shift in lumen potential from negative to positive in the later portions of the proximal tubule provides an additional driving force for K^+ reabsorption. On the basolateral surface, K^+ entry into the intracellular space by the $Na^+-K^+-ATPase$ exits coupled to Cl^- via a conductive pathway. A K^+ channel on the apical surface of the proximal tubule acts to stabilize cell voltage given the depolarizing effect of Na^+ -coupled glucose and amino acid reabsorption.

and paracellular pathways. Transcellular movement is mediated by the $Na^+-K^+-2Cl^-$ cotransporter located on the apical membrane. A component of K^+ that enters the cell back diffuses into the lumen through the ROMK (renal outer medullary K^+) channel, leading to the generation of a lumen positive charge which, in turn, drives a component of K^+ reabsorption through the paracellular pathway (Fig. 2). K^+ secretion begins within the early distal convoluted tubule and progressively increases in magnitude into the cortical collecting duct. Physiological needs regulate the secretory component of K^+ handling (36).

Electrogenic secretion through the ROMK channel is the major K^+ secretory mechanism in the distal nephron. Maxi- K^+ or BK channels are a second type of channel that also mediates K^+ secretion under conditions of increased flow. In addition to stimulating maxi- K^+ channels, tubular flow also augments electrogenic K^+ secretion by diluting luminal K^+ concentration and stimulating Na^+ reabsorption through the epithelial Na^+ channel (ENaC). This stimulatory effect can be traced to a mechanosensitive property whereby shear stress increases the open probability of the ENaC channel (30).

The biomechanical characteristics for Na^+ and K^+ transport in the distal nephron are ideally suited to buffer any increase in extracellular K^+ concentration following a protein-enriched meal, which is also high in K^+ content. In this setting there is an increase in glomerular filtration rate and tubular flow (48). High flow and increases in distal Na^+ delivery activate the maxi- K^+ channel and augment electrogenic K^+ secretion through ROMK, respectively. Increased flow also dilutes luminal K^+ concentration, keeping the gradient for K^+ secretion optimal, all of which provide a robust defense against development of hyperkalemia.

High K^+ intake leads to accumulation of K^+ in the interstitium of the kidney through medullary recycling. Older studies suggested that this increase in interstitial K^+ concentration would lead to an inhibitory effect on salt transport in the thick ascending limb and proximal tubule, which in turn would result in increased Na^+ and water delivery to the distal nephron, allowing for increased K^+ secretion (6, 53, 54). As discussed

below, recent studies have focused on how K^+ intake modulates transport in the low-capacity early distal convoluted tubule (DCT) as a way to adjust tubular flow to K^+ secretory sites. These studies suggest that the effect of dietary K^+ to modulate flow and delivery of Na^+ to K^+ secretory sites is more regionalized and confined to the lower capacity distal nephron.

The DCT as a K^+ sensor. The DCT comprises a proximal portion (DCT1) and a distal portion (DCT2). In the DCT1, salt transport is driven exclusively by the thiazide-sensitive $NaCl$ cotransporter (NCC), whereas in DCT2, electroneutral $NaCl$ transport coexists with electrogenic Na^+ and K^+ transport pathways (28). In the DCT2, aldosterone sensitivity, which is critical to facilitate K^+ homeostasis, begins and extends to the collecting duct. Cells of the early DCT exert a substantial, albeit indirect, role in K^+ secretion suggested by the fact that changes in transport in the early DCT control the delivery of $NaCl$ to the downstream connecting tubule and collecting duct, where the epithelial sodium channel (ENaC) mediates electrogenic Na^+ reabsorption and where K^+ is secreted (Fig. 3).

The location of the DCT1 immediately upstream from the aldosterone-sensitive distal nephron (ASDN) and its low capacity nature make this segment a more likely site for changes in dietary K^+ intake to modulate Na^+ transport and ensure that downstream delivery of Na^+ is precisely the amount needed to ensure maintenance of K^+ homeostasis without causing unwanted effects on volume. Dietary intake of K^+ , which causes changes in plasma K^+ concentration, leads to an inhibitory effect on NCC activity. As a result, Na^+ delivery and flow are increased to the aldosterone sensitive K^+ secretory segments located in the later portions of the DCT (DCT2) and collecting duct. At the same time, the increase in plasma K^+ concentration following intake stimulates aldosterone release from the adrenal gland, which in turn facilitates electrogenic K^+ secre-

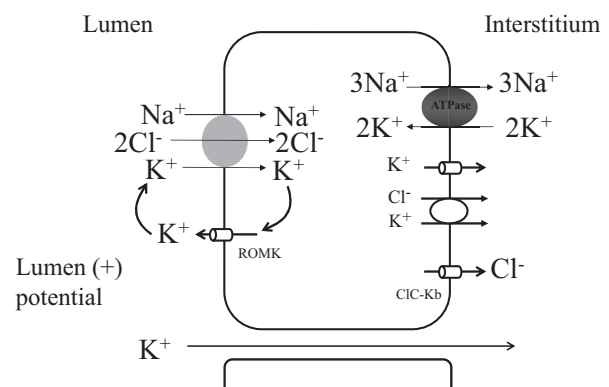
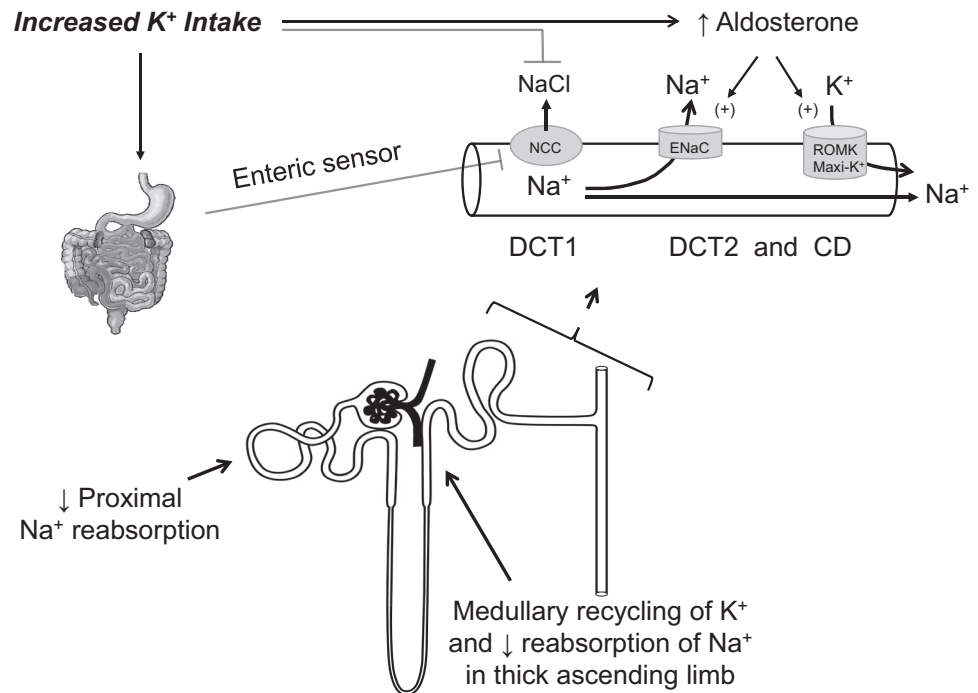


Fig. 2. The majority of filtered K^+ that escapes reabsorption in the proximal tubule is reabsorbed in the thick ascending limb by both transcellular and paracellular pathways. The transcellular pathway is an example of secondary active transport. Intracellular Na^+ is kept low by activity of the $Na^+-K^+-ATPase$. Luminal Na^+ enters the cell along with Cl^- and K^+ via the $Na^+-K^+-Cl^-$ cotransporter. An adequate amount of luminal K^+ for the cotransport step is ensured by K^+ movement from the intracellular space into the lumen via the apically located renal outer medullary potassium (ROMK) channel. This recycling of K^+ leads to generation of a lumen-positive charge, providing the driving force for a second component of K^+ reabsorption through the paracellular pathway. Intracellular K^+ can also exit the basolateral membrane in cotransport with Cl^- or by way of a conductive pathway. $ClC-Kb$, Cl^- channel.

Fig. 3. Older studies (6, 53, 54) have suggested that maintenance of K^+ homeostasis in the setting of high K^+ dietary intake was brought about by an inhibitory effect of K^+ on Na^+ reabsorption in the thick ascending limb and proximal tubule of the kidney, thereby facilitating increased delivery of Na^+ to portions of the distal nephron responsive to mineralocorticoid activity. Recent observations suggest that this process is more regionalized and implicate the distal convoluted tubule (DCT) as a renal K^+ sensor. High K^+ intake inhibits electroneutral $NaCl$ transport in the proximal portion of the distal convoluted tubule (DCT1). The resultant increase in Na^+ delivery and flow along with increased aldosterone facilitates electrogenic K^+ secretion through ROMK. Aldosterone and flow also increase K^+ secretion via the Maxi-K channel. Increased secretion can be initiated upon K^+ entry into the gastrointestinal tract through an enteric K^+ -sensing mechanism that inhibits Na^+-Cl^- cotransporter (NCC) activity in the absence of change in plasma concentration. ENaC, epithelial sodium channel; CD, collecting duct.



tion through ROMK. Both increased flow and aldosterone stimulate K^+ secretion through the Maxi-K channel (15, 28).

The inhibitory effect of increased plasma K^+ on NCC activity is mediated through changes in activity of the with-no-lysine (WNK) family of kinases and their regulatory proteins SPAK and OxSR1 (11, 19, 27). Studies suggest that fluctuations in extracellular K^+ concentration in response to dietary intake alter membrane voltage, leading to changes in intracellular Cl^- concentration, which in turn modulates the WNK axis (55, 56). Elevations in plasma K^+ concentration depolarize cells in the DCT1, resulting in an increase in intracellular Cl^- concentration. The increase in Cl^- alters WNK4 activity in such a way that activity of NCC is decreased. When plasma potassium is low, the opposite occurs; NCC activity is increased, thereby reducing Na^+ delivery and flow to the aldosterone-sensitive K^+ secretory segments. The unique sensitivity of WNK4 to Cl^- is consistent with this model. There is evidence suggesting that the Kir4.1/5.1 channel in the DCT may act as the sensor by which changes in plasma K^+ lead to changes in NCC activity (58).

K^+ -rich foods, such as fruit and vegetables, are also rich in precursors to bicarbonate ions, and the alkali content induced by consumption of these foods affects K^+ transport in the DCT so as to facilitate the renal excretion of the coingested K^+ load (3, 12). For example, when luminal or basolateral HCO_3^- and pH are elevated, ENaC abundance is increased. Additionally, increased activity of ENaC, ROMK, and maxi- K^+ channels is induced when intracellular pH increases. Therefore, the effects of an alkaline pH are additional mechanisms facilitating K^+ excretion following ingestion of such foods.

Enteric sensing of K^+ intake. K^+ homeostasis is also modulated in the gut. Upon K^+ entry into the gastrointestinal tract, urinary secretion of K^+ increases due to activation of an enteric sensing system. The ability to sense K^+ within the gastrointestinal tract may be an adaptive response to rapidly initiate a kaliuretic affect that facilitates K^+ homeostasis. It is important

to note that consumption of foods rich in K^+ differs from infusion of K^+ with respect to its impact on K^+ homeostasis. Specifically, the kaliuretic response to consumption of K^+ as a meal is greater than to an intravenous infusion, even in a setting where plasma K^+ concentrations are identical (26, 31, 60). Gastric delivery of K^+ leads to dephosphorylation of the Na^+-Cl^- cotransporter in the early DCT, resulting in decreased activity of the transporter and thereby enhancing delivery of Na^+ to the ASDN (50) (Fig. 3). Increased renal K^+ excretion results from a downstream shift in Na^+ reabsorption from the DCT to the ENaC in the ASDN as well as increased maxi-K channel K^+ secretion brought on by increased flow. Data suggest that splanchnic sensing of K^+ can initiate the renal excretory response independent of change in plasma K^+ concentration or mineralocorticoid activity (42). The blood pressure-lowering effect of K^+ -rich diets is induced by the rapid natriuretic response to increases in dietary K^+ intake.

Circadian rhythm of K^+ secretion. During a 24-h period, the timing and spacing of meals cause variations in K^+ excretion; however, there is also a circadian rhythm whereby K^+ excretion is lower at night and in the early morning hours and then increases in the afternoon (18). A circadian rhythm exists for gene transcripts that encode proteins involving K^+ secretion (62). Gene expression of ROMK is greater during periods of activity and daylight, whereas expression of the H^+-K^+ -ATPase is higher during rest and nighttime, corresponding to periods when renal K^+ excretion is greater and less, respectively (47). There is a pacemaker function regulating K^+ transport, as indicated by expression of clock genes within cells of the distal nephron. The circadian rhythm is such that during daytime hours, renal excretion is enhanced, when presumably K^+ intake is at its greatest.

Hypokalemia

Despite mechanisms to maintain K^+ homeostasis, hypokalemia is actually a frequent occurrence encountered in clinical

practice. Transient causes of hypokalemia are due to cell shift, whereas sustained hypokalemia can be manifested by either inadequate intake or excessive K^+ loss. Hypokalemia resulting from excessive K^+ loss can be due to renal or extrarenal losses. The cause and source of hypokalemia can be assessed by obtaining a clinical history and conducting a physical examination, with particular attention paid to volume and acid base status of the patient (Fig. 4).

Renal K^+ excretion assessment allows for determination as to whether hypokalemia is due to renal or extrarenal causes. A 24-h urine collection or a spot urine can be used to assess renal K^+ handling. A 24-h urinary K^+ of <20 mEq, or a spot urine K^+ (mmol)/creatinine (mmol) ratio <1 , suggests an extrarenal cause of hypokalemia. A useful tool to assess renal K^+ handling is the transtubular K^+ gradient (TTKG) formula since the equation takes into consideration the effect of renal water handling on urine K^+ concentration.

$$TTKG = [K_{\text{urine}} / (U_{\text{osmolality}} / S_{\text{osmolality}})] / K_{\text{serum}}$$

Normal TTKG ranges for a person consuming a typical Western diet are from 8 to 9, and this value will increase to >11 with increased K^+ intake. In patients with hypokalemia due to extrarenal K^+ losses, the TTKG should fall to values <3 . Calculation of the TTKG may prove useful in those patients in which the cause of a dyskalemia continues to remain in doubt; however, in most settings, a spot urine K^+ concentration and the clinical setting will be sufficient in determining the cause of K^+ disturbances.

Decreased potassium intake. Dietary restriction of K^+ can potentially lead to hypokalemia; however, in most cases dietary restriction exacerbates hypokalemia due to other causes. Although the kidney can elaborate urine virtually free of Na^+ in response to dietary Na^+ restriction, it can only reduce urinary K^+ to ~ 15 mEq/d in response to a K^+ -free diet.

Anorexia nervosa, crash diets, alcoholism, and intestinal malabsorption are clinical situations associated with K^+ deficiency. Magnesium deficiency (which is often present in these clinical situations) may contribute to the observed hypokalemia. In this setting, hypokalemia can be refractory to treatment due to a persistent increase in renal K^+ excretion, since intracellular Mg^{++} normally inhibits K^+ secretion through the ROMK channel in the distal nephron (21). The kaliuretic effect induced by magnesium deficiency is further exacerbated under conditions of increased distal Na^+ delivery and increased aldosterone.

Cellular distribution. Since adjustments in renal K^+ excretion can take several hours following a K^+ load, initial changes in extracellular K^+ concentrations are buffered by movement of K^+ into or out of skeletal muscle. Additionally, postprandial release of insulin functions not only to regulate the serum glucose concentrations but also to shift dietary K^+ into cells until the kidney excretes the K^+ load, thereby reestablishing normal total body K^+ content. During exercise, the release of catecholamines through β_2 -stimulation limits the increase in extracellular K^+ concentration that occurs as a result of the normal K^+ release by contracting muscle. Pathological stimulation of β_2 -receptors can result in symptomatic hypokalemia. For example, hypokalemia is a potential complication of the hyperadrenergic state that often times accompanies alcohol withdrawal syndromes or a myocardial infarction (35). Table 1 lists several factors that cause hypokalemia due to cell shift.

Hypokalemic periodic paralysis is a rare disorder characterized by muscle weakness or paralysis due to the sudden movement of K^+ into cells (25). These manifestations are normally precipitated in the rest period immediately following an exercise bout, during times of stress, or following a high-carbohydrate meal (8). There is an acquired form of this

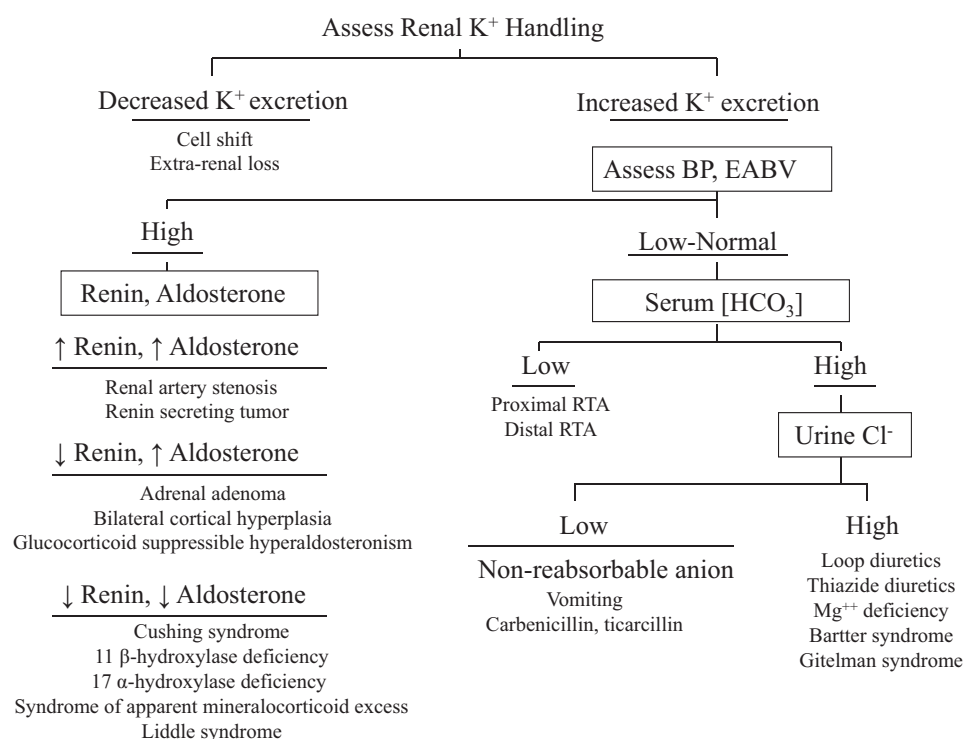


Fig. 4. Approach to the patient with hypokalemia. A primary increase in mineralocorticoid levels gives rise to disorders characterized by hypokalemia, metabolic alkalosis, and hypertension. Disorders characterized by a primary increase in distal Na^+ delivery are differentiated by acid base status and urinary Cl^- concentration. BP, blood pressure; EABV, effective arterial blood volume; RTA, renal tubular acidosis.

Table 1. *Factors which cause hypokalemia and hyperkalemia due to cell shift*

<i>Hypokalemia</i>	
Alkalosis (effect is trivial)	
Insulin administration	
B ₂ adrenergic stimulation	
Stress-induced epinephrine release	
Drugs: theophylline intoxication, ritodrine, terbutaline, albuterol, clenbuterol	
Anabolism	
Treatment of pernicious anemia	
Rapidly growing leukemias and lymphomas	
Hypokalemic periodic paralysis	
Acquired in association with hyperthyroid state	
Familial	
Drugs/toxins/herbs	
Barium intoxication	
Chloroquine intoxication	
Cesium salts (reported in herbal preparations marketed as anti-tumor agent)	
<i>Hyperkalemia</i>	
Metabolic acidosis (mineral and not 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	

disease that typically occurs in hyperthyroid men of either Asian or Mexican descent. Correction of the endocrine disorder leads to resolution of hypokalemia. There is a familial form of hypokalemic periodic paralysis that is inherited in an autosomal dominant pattern and has similar clinical features to the acquired form (10). However, the familial form is usually manifested in someone who is younger (usually <20 yr) and is most commonly seen in Caucasians. The familial disorder has been linked to mutations in the muscle calcium channel α_1 -subunit gene (*CACNA1S*) on chromosome 1q3132.

Extrarenal K^+ loss. Decreased total body K^+ can result from extrarenal or renal losses. Cutaneous loss of K^+ sufficient to cause hypokalemia is uncommon; however, this may occur under conditions of intense exercise in a hot, humid environment due to large volumes of sweat resulting in K^+ depletion. Gastrointestinal syndromes are actually the most common clinical disorders of extrarenal K^+ losses (2). Fecal K^+ wastage as a result of diarrhea is associated with a normal anion gap metabolic acidosis. Although usually associated with a low urinary K^+ concentration, the acidosis per se can lead to some degree of renal K^+ wasting through increased distal delivery of Na^+ (16). In addition, the acidosis will result in K^+ redistribution out of cells, leading to a degree of hypokalemia that underestimates the degree of total body K^+ depletion.

Renal K^+ wasting. The elaboration of aldosterone and distal delivery of Na^+ and water are two important factors in the renal excretion of K^+ . Although increased distal delivery of Na^+ and water as well as increased aldosterone activity can

each stimulate renal K^+ secretion, under normal circumstances there is a balanced reciprocal relationship between distal Na^+ delivery and circulating aldosterone that serves to maintain K^+ balance during normal volume regulation. It is only under pathophysiological conditions that distal Na^+ delivery and aldosterone become coupled. In this setting, renal K^+ wasting will occur (Fig. 5). When treating patients who are hypokalemic as a result of renal K^+ wasting, it must be determined whether there is a primary increase in mineralocorticoid activity or a primary increase in distal Na^+ delivery (36). A primary increase in mineralocorticoid activity can be due to primary increases in renin secretion, primary increases in aldosterone secretion, or increases in a non-aldosterone mineralocorticoid or increased mineralocorticoid-like effect. These conditions are observed when extracellular fluid volume is expanded and hypertension is typically present. These disorders represent the most common causes of curable hypertension; therefore, workup of these patients is extremely important. It is important for the clinician to remember that the differential diagnosis for the patient with hypertension, hypokalemia, and metabolic alkalosis relies on measurement of plasma renin activity and plasma aldosterone concentrations (Fig. 4) (35). Primary increases in distal Na^+ delivery are characterized by normal or low extracellular fluid volume and normal blood pressure. Distal Na^+ delivery is increased due to diuretics, which act proximal to the cortical collecting duct (33). Nonreabsorbed anions such as bicarbonate, as seen with active vomiting or a proximal renal tubular acidosis, are additional causes of increased delivery of Na^+ . Ketoanions and the Na^+ salts of penicillins are additional factors that influence distal Na^+ delivery. The inability to reabsorb these anions in the proximal tubule results in increased delivery of Na^+ to the distal nephron. Because the anions escape reabsorption in the distal nephron, this results in a more lumen negative voltage development, resulting in enhanced K^+ excretion into the tubular fluid. Disorders of hypokalemia, due to primary increases in distal Na^+ delivery, can best be categorized as to the presence of metabolic acidosis or metabolic alkalosis (Fig. 4). Within the category of metabolic acidosis, there are disorders that cause renal tubular acidosis. In proximal renal tubular acidosis, the threshold for bicarbonate reabsorption is reduced, resulting in a self-limited bicarbonaturia. The loss of $NaHCO_3$ in the urine leads to volume depletion that activates the renin-angiotensin-aldosterone system. The coupling of increased aldosterone levels to increased distal Na^+ delivery results in renal K^+ wasting. Renal K^+ wasting is minimal, and the degree of hypokalemia tends to be mild in the steady state when virtually all of the filtered HCO_3^- is reabsorbed in the proximal and distal nephron. Importantly, treatment of metabolic acidosis with bicarbonate improves the acidosis but worsens the degree of hypokalemia.

Distal renal tubular acidosis (dRTA) results in the development of hypokalemia due to several mechanisms (5). First, systemic acidosis in and of itself can lead to renal K^+ wasting. Metabolic acidosis is associated with decreased net proximal Na^+ reabsorption (3, 16). The subsequent increase in distal delivery of Na^+ leads to volume contraction and activation of the renin-angiotensin-aldosterone system. These changes lead to increased renal K^+ excretion. Second, dRTA may be secondary to a defect in the H^+-K^+ ATPase, which would increase renal K^+ excretion by directly impairing K^+ reabsorption in the distal nephron. Third, K^+ wasting can be the

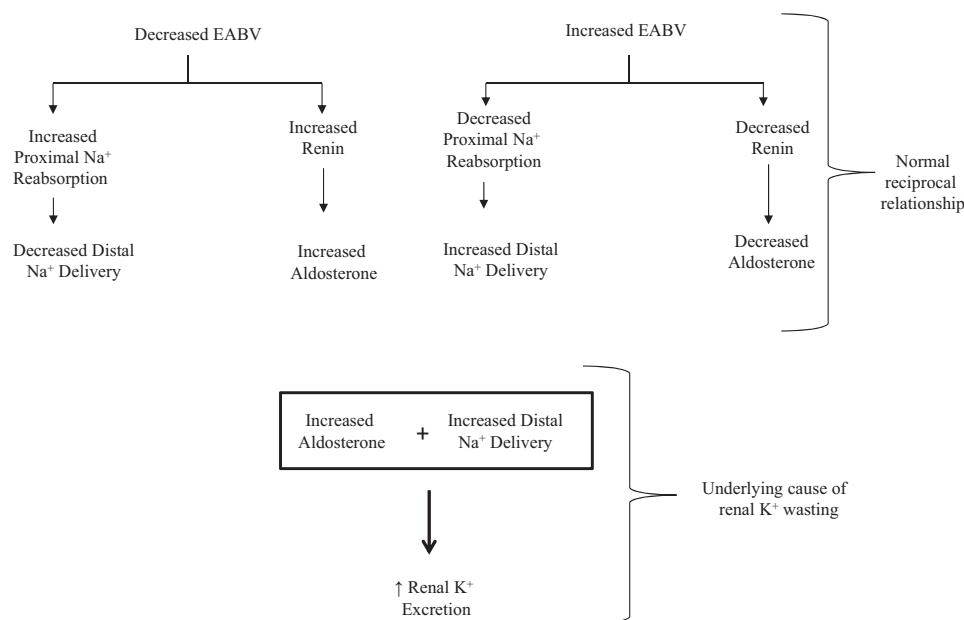


Fig. 5. *Top*: mineralocorticoids and distal delivery of Na⁺ normally have a reciprocal relationship, providing for the maintenance of K⁺ homeostasis despite wide variations in dietary Na⁺ intake and changes in extracellular fluid volume. *Bottom*: depicted are differing pathological states that couple increases in Na⁺ delivery to increased mineralocorticoid levels or activity that provides the basis of renal K⁺ wasting disorders. EABV refers to the adequacy of the arterial blood volume to “fill” the capacity of the arterial vasculature.

result of leakage into the tubular lumen as a result of an ionophoric effect, as seen in the gradient type of dRTA due to administration of amphotericin B.

Loop diuretics and Bartter syndrome fall into the category of causes of hypokalemia and metabolic alkalosis. Bartter syndrome is a hereditary disorder characterized by renal salt wasting and hypokalemic metabolic alkalosis, resembling the features of chronic loop diuretic therapy. In Bartter syndrome, hypokalemia can be severe and result in complications such as rhabdomyolysis and periodic paralysis. Gene defects that lead to decreased NaCl reabsorption in the thick ascending limb of Henle account for the clinical characteristics of Bartter syndrome (9), including significant salt wasting, an inability to maximally concentrate the urine, and increased 24-h urinary calcium excretion.

Gitelman syndrome, on the other hand, is also an inherited disorder, but individuals with this syndrome have clinical manifestations that mimic the chronic use of a thiazide diuretic. This disease is due to an inactivating mutation in the gene (SLC12A3) that encodes the thiazide-sensitive apical NaCl cotransporter (NCC) in the distal convoluted tubule (24, 28). In contrast to Bartter syndrome, individuals with Gitelman syndrome are more commonly hypomagnesemic, have less severe salt wasting, have decreased urinary calcium excretion, and retain the ability to concentrate the urine.

Complications and treatment of hypokalemia. A decrease in extracellular K⁺ concentration leads to hyperpolarization of the cell membrane and can result in muscle weakness occasionally severe enough to cause paralysis, as occurs in patients with hypokalemic dRTA. Muscle paralysis in this disorder can begin insidiously, with weakness evolving gradually over a 24- to 48-h time period, leading to complete flaccid quadriplegia. Attacks of flaccid paralysis in dRTA have been referred to as “RTA crisis” by some authors because this striking clinical manifestation may result in the clinician overlooking the underlying cause (7, 51). Treatment should be focused on correction of the K⁺ deficit and not the metabolic acidosis. Intravenous K⁺ should be administered in a solution devoid of

glucose as well as bicarbonate to avoid rapid shifts into the intracellular compartment. Once the patient is stabilized, bicarbonate can be given along with K⁺ to address the metabolic acidosis. A myopathy may also occur, which in its most severe form, can lead to frank rhabdomyolysis and renal failure. Hypokalemia can also lead to CNS changes with confusion and affective disorders and to smooth muscle dysfunction, including paralytic ileus.

Cardiac complications of hypokalemia may also be important. The typical electrocardiogram change is ST depression, T wave flattening, and an increase in the amplitude of the U wave. This change, often misread as a widened QT, is nonspecific, often absent, and of little clinical use. It is well known that patients on cardiac glycosides have an increased incidence of premature ventricular contractions and supraventricular and ventricular tachyarrhythmias when hypokalemic.

Hypokalemia also causes a renal concentrating defect due both to a decrease in the medullary gradient and resistance of the cortical collecting tubule to vasopressin. Kaliopenic nephropathy is characterized by polyuria, proteinuria, development of renal cysts, and loss of renal function and is histologically characterized by chronic tubulointerstitial renal disease (45, 46). Because insulin release is regulated partially by serum K⁺, hypokalemia can lead to glucose intolerance (61).

Hyperkalemia

Pseudohyperkalemia. Pseudohyperkalemia should be excluded before concluding that hyperkalemia is due to cell shift or abnormal renal K⁺ excretion. Pseudohyperkalemia is the result of release of K⁺ from cells during the phlebotomy procedure, or specimen processing, and is defined by a serum K⁺ concentration 0.5 mEq/l greater than the plasma K⁺ concentration. In addition to fist clenching, application of tourniquets, and use of small-bore needles, high cell counts such as thrombocytosis (>500,000/cm³) and pronounced leukocytosis (70,000/cm³) are risk factors for this disorder (37).

Increased dietary intake. It is difficult to ingest enough K^+ to become hyperkalemic in the presence of normal renal and adrenal function. Dietary intake as a contributor to hyperkalemia is usually in the setting of impaired kidney function. Melons, citrus juice, potatoes, avocado, and salt substitutes are just a few of the common dietary sources enriched in K^+ content that should be avoided in patients with hyperkalemia.

Cell shift. Cellular redistribution is a more important cause of hyperkalemia than hypokalemia. It is important to note that as little as a 2% shift of intracellular K^+ to the extracellular fluid will result in a serum K^+ of 8 mEq/l (Table 1). Disturbances in serum K^+ concentration due to cell shifts are generally transient in nature, whereas sustained hyperkalemia is due to impaired renal excretion. Metabolic acidosis promotes K^+ exit from cells dependent upon the type of acid present. Mineral acidosis (NH_4Cl or HCl) causes the greatest efflux of K^+ from cells, whereas organic acidosis (i.e., lactic, β -hydroxybutyric, or methylmalonic acid) results in no significant efflux of K^+ (Fig. 6). Hyperkalemia associated with lactic acidosis is the result of cell ischemia.

Cell shift is a potential complication of hypertonic states (38). Hyperglycemia leads to water movement from the intracellular to extracellular compartment. This water movement favors K^+ efflux through K^+ channels driven by solvent drag. In addition, cell shrinkage causes intracellular K^+ concentration to increase, creating a more favorable concentration gradient for K^+ efflux. This same phenomenon has been described in neurosurgical patients given large amounts of hypertonic

mannitol. Table 1 lists various causes of hyperkalemia due to cell shift.

Impaired renal excretion. Although redistribution of K^+ can result in hyperkalemia, the rise in K^+ is generally mild and not sustained. Prolonged and severe hyperkalemia implies the presence of concomitant decreases in renal K^+ excretion. In most instances, the clinical setting will allow the clinician to determine whether there is a disturbance in renal K^+ excretion or not. Decreased renal excretion of K^+ can be due to one or more of three abnormalities: decreased distal delivery of Na^+ , mineralocorticoid deficiency, and/or abnormal cortical collecting tubule function (34), which will be discussed in further detail below.

DECREASED DISTAL DELIVERY OF Na^+ . Acute decreases in glomerular filtration rate (GFR), as occurs in acute kidney injury, would not be expected to have a marked effect on K^+ excretion. However, acute decreases in GFR may lead to marked decreases in distal delivery of salt and water, which may secondarily decrease distal K^+ secretion. Thus, when acute kidney injury is oliguric, hyperkalemia is a frequent problem; when nonoliguric, distal delivery is usually sufficient, and hyperkalemia is unusual.

Chronic kidney disease is more complicated. In addition to the decreased GFR and secondary decreases in distal delivery, there is nephron dropout and less collecting tubule mass to secrete K^+ . However, this is counterbalanced by a K^+ adaptation, in which the remaining nephrons develop an increased ability to excrete K^+ (52). Although patients with chronic

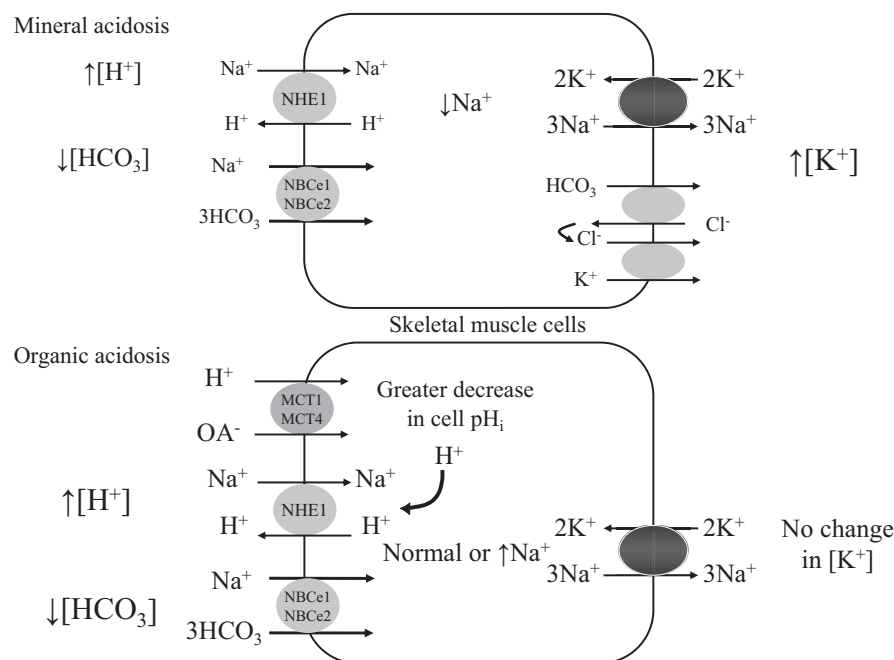


Fig. 6. Mineral acidosis (normal gap hyperchloremic acidosis) tends to cause a greater decrease in intracellular Na^+ compared with organic acidosis, and therefore, they are more likely to be accompanied by hyperkalemia. Decreased intracellular Na^+ leads to greater K^+ exit from the cell due to decreased activity of the Na^+-K^+ -ATPase. Sodium-hydrogen antiporter 1 (NHE1) and electrogenic sodium bicarbonate cotransporter 1 and 2 (NBCe1 and -2) are membrane transporters that serve to defend cell pH particularly in skeletal muscle. Mineral acidosis reduces the activity of NHE1 and NBCe1 and -2 due to increased extracellular H^+ concentration and reduced extracellular HCO_3^- concentration, respectively. In addition, the decrease in HCO_3^- concentration accompanied by an increase in Cl^- will favor movement of Cl^- into the cell by way of Cl^- - HCO_3^- exchange, secondarily enhancing K^+ efflux by K^+ - Cl^- cotransport. During organic acidosis, there is inward movement of H^+ and the accompanying organic anion on the monocarboxylate transporter 1 and 4 (MCT1 and -4), which results in a larger fall in cell pH in comparison to mineral acidosis. This more acidic intracellular pH allosterically increases activity of the Na^+-H^+ exchanger and provides a more favorable gradient for inward Na^+ - HCO_3^- cotransport. An adequate amount of intracellular Na^+ is available to better maintain activity of the Na^+-K^+ ATPase, thus minimizing any change in extracellular K^+ concentration.

kidney disease do not excrete a K^+ load as rapidly as individuals without chronic kidney disease, hyperkalemia is unusual until the GFR has fallen to <10 ml/min. The occurrence of hyperkalemia with a GFR of >10 ml/min should raise the clinician's question if there might be decreased mineralocorticoid activity or a specific lesion of the cortical collecting tubule.

DECREASED MINERALOCORTICOID ACTIVITY. Decreased mineralocorticoid activity can result from disturbances that originate at any point along the renin-angiotensin-aldosterone system. Such disturbances can be the result of a disease state or be due to effects of various drugs (Fig. 7). The syndrome of hyporeninemic hypoaldosteronism accounts for the majority of unexplained hyperkalemia in patients where the GFR and K^+ intake would not be expected to result in hyperkalemia (22). Diabetic nephropathy and interstitial renal disease are the most common clinical entities associated with this syndrome.

DISTAL TUBULAR DEFECT. Certain interstitial renal diseases can affect the distal nephron specifically and lead to hyperkalemia in the presence of mild decreases in GFR and normal aldosterone levels. Many of these diseases are the same ones associated with hyporeninemic hypoaldosteronism, and frequently, the impaired renin release and defect in tubular secretion coexist. Examples include renal transplant patients, lupus

erythematosus, amyloidosis, urinary obstruction, and sickle cell disease.

The K^+ sparing diuretics impair the ability of the cortical collecting tubule to secrete K^+ . The non-testosterone-derived progestin drospirenone contained in certain oral contraceptives possesses mineralocorticoid-blocking effects similar to what is seen with spironolactone. The serum K^+ should be monitored when these drugs are prescribed in patients receiving K^+ supplements, renin-angiotensin blockers, or nonsteroidal anti-inflammatory drugs (41).

Pseudohypoaldosteronism type II (Gordon syndrome) is an autosomal dominant form of hypertension in which hyperkalemia and metabolic acidosis are key features. Plasma concentrations of aldosterone are low despite the presence of hyperkalemia, which normally exerts a stimulatory effect on aldosterone released from the adrenal gland. The hypertension and hyperkalemia are particularly responsive to the administration of thiazide diuretics. Mutations in the WNK4 and WNK1 protein kinases and their regulatory proteins SPAK and OxsR1 are responsible for this disease (40).

Pseudohypoaldosteronism type I is a disorder characterized by mineralocorticoid resistance that typically presents in newborns. Clinical findings include hyperkalemia, metabolic acidosis, and a tendency toward volume depletion due to renal salt

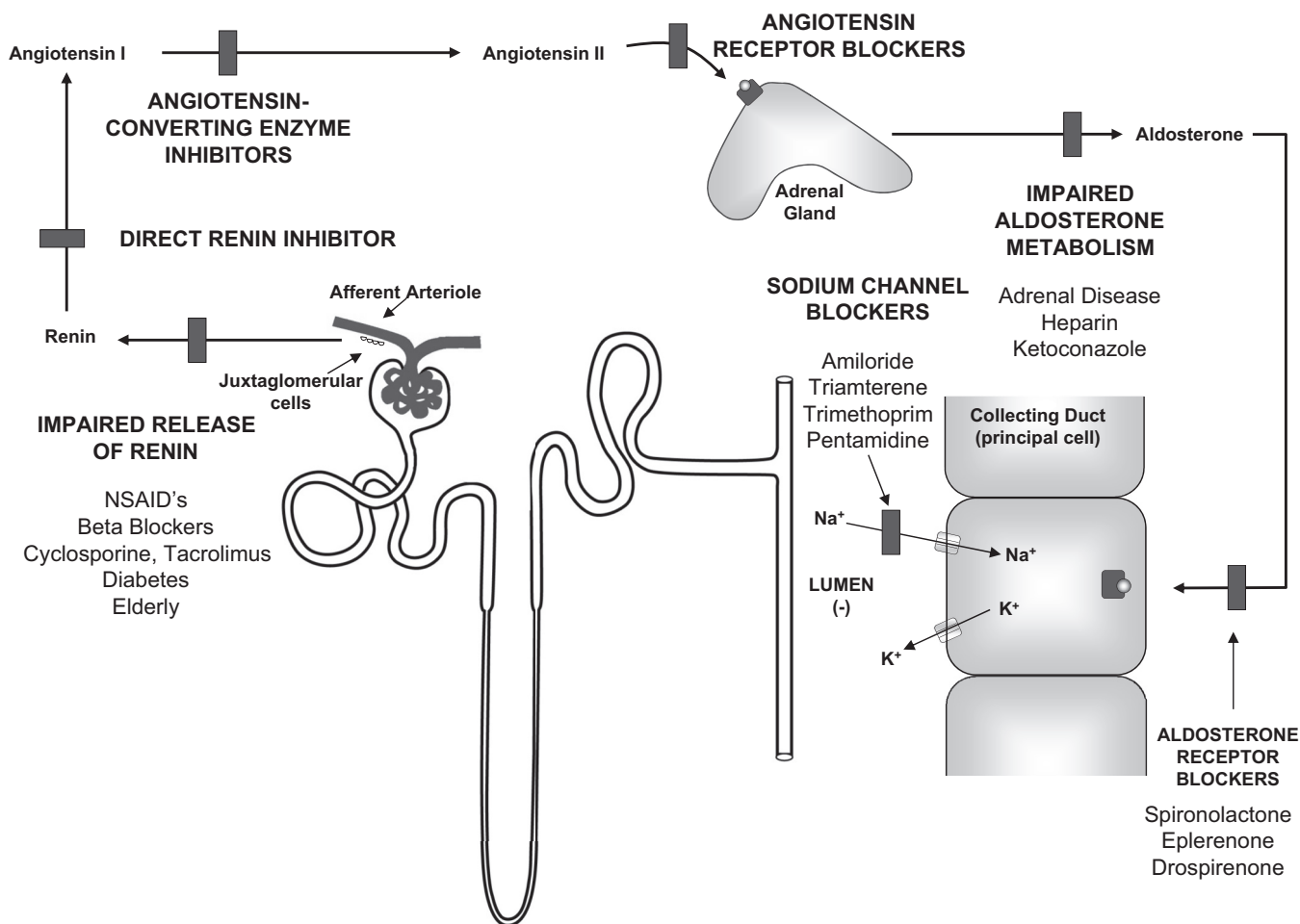


Fig. 7. Disease states or drugs that interfere in the renin-angiotensin-aldosterone axis interfere in the mechanisms of renal K^+ secretion. In many clinical settings, the system is disrupted at multiple sites, magnifying the risk of hyperkalemia. NSAIDs, nonsteroidal anti-inflammatory drugs.

wasting (44). In the autosomal-recessive form of the disease, the defect has been localized to homozygous mutations in the three subunits of the epithelial sodium channel. The autosomal-dominant form of the disease results from mutations in the mineralocorticoid receptor that in turn result in mineralocorticoid resistance.

Clinical features of hyperkalemia. All of the clinically important manifestations of hyperkalemia occur in excitable tissues. Neuromuscular manifestations include paresthesias and fasciculations in the arms and legs. As the serum K^+ continues to rise, an ascending paralysis with eventual flaccid quadriplegia supervenes. Classically, trunk, head, and respiratory muscles are spared; however, respiratory failure also can occur, albeit rarely.

The depolarizing effect of hyperkalemia on the heart is manifested by changes observable in the electrocardiogram (ECG). The progressive changes of hyperkalemia are classically listed as peaking of T waves, ST segment depression, widening of the PR interval, widening of the QRS interval, loss of the P wave, and development of a sine-wave pattern. The appearance of a sine-wave pattern is ominous and is a harbinger of impending ventricular fibrillation and asystole.

Less common patterns on the ECG include a right-bundle branch block and right precordial ST segment elevations reminiscent of the Brugada syndrome. The tall, narrow, and symmetrical peaked T waves typical of hyperkalemia can occasionally be confused with the hyperacute T-wave change associated with a ST segment elevation myocardial infarction. A pseudoinfarct pattern has also been described, resembling both an anteroseptal and inferior wall myocardial infarction.

The correlation of ECG changes and serum K^+ concentration depend on the rapidity of the hyperkalemia onset. Generally, with acute onset of hyperkalemia, ECG changes appear at a serum K^+ of 6–7 mEq/l. However, with chronic hyperkalemia, the ECG may remain normal up to a concentration of 8–9 mEq/l. Despite these generalities, clinical studies show a poor correlation between serum K^+ concentration and cardiac manifestations (29).

Treatment of chronic hyperkalemia. The initial approach is to review the patient's medication profile and whenever possible discontinue drugs that can impair renal K^+ excretion (32). Patients should be questioned specifically as to the use of over-the-counter, nonsteroidal, anti-inflammatory drugs as well as herbal remedies since herbs may be a hidden source of dietary potassium. Patients should be placed on a low K^+ diet, with specific counseling against the use of K^+ containing salt substitutes. Diuretics are particularly effective in minimizing hyperkalemia. In patients with an estimated glomerular filtration rate >30 ml/min, thiazide diuretics can be used, but with more severe renal insufficiency, loop diuretics are required.

In patients with chronic kidney disease and metabolic acidosis, administration of sodium bicarbonate is an effective strategy to minimize increases in the serum K^+ concentration. Ensuring that the patient is first on effective diuretic therapy will lessen the likelihood of developing volume overload as a complication of sodium bicarbonate administration.

The development of hyperkalemia after the administration of renin-angiotensin blockers is of particular concern because patients at highest risk for this complication are often times the same ones who derive the greatest cardiovascular benefit. In addition to the steps mentioned previously, the risk of hyper-

kalemia with these drugs can be minimized by initiating therapy at low doses. The serum K^+ should be checked within 1 wk of starting the drug. If the K^+ is normal, then the dose of the drug can be titrated upward. With each increase in dose, the serum K^+ should be remeasured 1 wk later. For increases in the serum K^+ concentration of ≤ 5.5 mEq/l one can lower the dose, and in some cases the K^+ concentration will improve, allowing the patient to remain on the renin-angiotensin blocker, albeit at a lower dose. Angiotensin receptor blockers and direct renin inhibitors should be used with the same caution as ACE inhibitors in patients at risk for hyperkalemia.

Sodium polystyrene sulfonate is commonly used to treat hyperkalemia in the acute setting. However, chronic use is poorly tolerated because the resin is usually given in a suspension with hypertonic sorbitol to promote an osmotic diarrhea. In addition, chronic use has been associated with mucosal injury in the lower and upper gastrointestinal tract (1). There are new oral K^+ binding drugs that have been shown to be effective in preventing development of hyperkalemia. Patiromer is approved for clinical use, and ZS-9 is pending approval. Both agents exhibit good tolerability and are not associated with serious adverse effects. Clinical trials demonstrate that these compounds lower the risk of incident hyperkalemia associated with renin-angiotensin-aldosterone system blockade in people with diabetes and heart failure and/or who have chronic kidney disease (4, 23, 59).

Summary

Disorders of K^+ balance are common in clinical practice and are generally the result of disturbances that affect the internal distribution of K^+ (cell shift) or total body K^+ content. Disorders of total body K^+ content can result from variations in dietary K^+ intake or alterations in renal or gastrointestinal K^+ handling. Using a systematic and diagnostic approach to the patient with dyskalemia will enable the clinician to determine the underlying cause of the K^+ disturbance and institute appropriate treatment. For more in-depth information about potassium homeostasis, the reader is encouraged to utilize the reference list provided below, which highlights seminal articles written on this important subject matter.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

B.F.P. and D.J.C. drafted manuscript; B.F.P. and D.J.C. edited and revised manuscript.

REFERENCES

1. Abraham SC, Bhagavan BS, Lee LA, Rashid A, Wu TT. Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol* 25: 637–644, 2001. doi:10.1097/0000478-200105000-00011.
2. Agarwal R, Afzalpurkar R, Fordtran JS. Pathophysiology of potassium absorption and secretion by the human intestine. *Gastroenterology* 107: 548–571, 1994. doi:10.1016/0016-5085(94)90184-8.
3. Aronson PS, Giebisch G. Effects of pH on potassium: new explanations for old observations. *J Am Soc Nephrol* 22: 1981–1989, 2011. doi:10.1681/ASN.2011040414.
4. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, Stasiv Y, Zawadzki R, Berman L, Bushinsky DA; AMETHYST-DN Investigators. Effect of Patiromer on Serum Potassium Level in Patients

- With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. *JAMA* 314: 151–161, 2015. doi:10.1001/jama.2015.7446.
5. **Batlle D, Moorthi KM, Schlueter W, Kurtzman N.** Distal renal tubular acidosis and the potassium enigma. *Semin Nephrol* 26: 471–478, 2006. doi:10.1016/j.semnephrol.2006.12.001.
 6. **Brandis M, Keyes J, Windhager EE.** Potassium-induced inhibition of proximal tubular fluid reabsorption in rats. *Am J Physiol* 222: 421–427, 1972.
 7. **Bresolin NL, Grillo E, Fernandes VR, Carvalho FL, Goes JE, da Silva RJ.** A case report and review of hypokalemic paralysis secondary to renal tubular acidosis. *Pediatr Nephrol* 20: 818–820, 2005. doi:10.1007/s00467-005-1833-9.
 8. **Cannon SC, Mi W, Wu F.** Proposed Mechanism for Post-Exercise Weakness in Hypokalemic Periodic Paralysis. *FASEB J* 30, Suppl: 1224–1249, 2016.
 9. **Castrop H, Schiefl IM.** Physiology and pathophysiology of the renal Na-K-2Cl cotransporter (NKCC2). *Am J Physiol Renal Physiol* 307: F991–F1002, 2014. doi:10.1152/ajprenal.00432.2014.
 10. **Cheng CJ, Kuo E, Huang CL.** Extracellular potassium homeostasis: insights from hypokalemic periodic paralysis. *Semin Nephrol* 33: 237–247, 2013. doi:10.1016/j.semnephrol.2013.04.004.
 11. **Cheng CJ, Truong T, Baum M, Huang CL.** Kidney-specific WNK1 inhibits sodium reabsorption in the cortical thick ascending limb. *Am J Physiol Renal Physiol* 303: F667–F673, 2012. doi:10.1152/ajprenal.00290.2012.
 12. **Cornelius RJ, Wen D, Hatcher LI, Sansom SC.** Bicarbonate promotes BK- α / β -mediated K excretion in the renal distal nephron. *Am J Physiol Renal Physiol* 303: F1563–F1571, 2012. doi:10.1152/ajprenal.00490.2012.
 13. **DeSalvo KB, Olson R, Casavale KO.** Dietary Guidelines for Americans. *JAMA* 315: 457–458, 2016. doi:10.1001/jama.2015.18396.
 14. **Eaton SB, Konner M.** Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med* 312: 283–289, 1985. doi:10.1056/NEJM198501313120505.
 15. **Ellison DH, Terker AS, Gamba G.** Potassium and Its Discontents: New Insight, New Treatments. *J Am Soc Nephrol* 27: 981–989, 2016. doi:10.1681/ASN.2015070751.
 16. **Faroqui S, Sheriff S, Amlal H.** Metabolic acidosis has dual effects on sodium handling by rat kidney. *Am J Physiol Renal Physiol* 291: F322–F331, 2006. doi:10.1152/ajprenal.00338.2005.
 17. **Food and Nutrition Board.** *Institute of Medicine. Potassium. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate.* Washington, DC: National Academies Press, 2005, p. 186–268.
 18. **Gumz ML, Rabinowitz L.** Role of circadian rhythms in potassium homeostasis. *Semin Nephrol* 33: 229–236, 2013. doi:10.1016/j.semnephrol.2013.04.003.
 19. **Hadchouel J, Ellison DH, Gamba G.** Regulation of Renal Electrolyte Transport by WNK and SPAK-OSR1 Kinases. *Annu Rev Physiol* 78: 367–389, 2016. doi:10.1146/annurev-physiol-021115-105431.
 20. **Hené RJ, Koomans HA, Boer P, Dorhout Mees EJ.** Adaptation to chronic potassium loading in normal man. *Miner Electrolyte Metab* 12: 165–172, 1986.
 21. **Huang CL, Kuo E.** Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol* 18: 2649–2652, 2007. doi:10.1681/ASN.2007070792.
 22. **Karet FE.** Mechanisms in hyperkalemic renal tubular acidosis. *J Am Soc Nephrol* 20: 251–254, 2009. doi:10.1681/ASN.2008020166.
 23. **Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, Roger SD, Yang A, Lerma E, Singh B.** Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA* 312: 2223–2233, 2014. doi:10.1001/jama.2014.15688.
 24. **Koulouridis E, Koulouridis I.** Molecular pathophysiology of Bartter's and Gitelman's syndromes. *World J Pediatr* 11: 113–125, 2015. doi:10.1007/s12519-015-0016-4.
 25. **Kung AW.** Clinical review: Thyrotoxic periodic paralysis: a diagnostic challenge. *J Clin Endocrinol Metab* 91: 2490–2495, 2006. doi:10.1210/jc.2006-0356.
 26. **Lee FN, Oh G, McDonough AA, Youn JH.** Evidence for gut factor in K⁺ homeostasis. *Am J Physiol Renal Physiol* 293: F541–F547, 2007. doi:10.1152/ajprenal.00427.2006.
 27. **Liu Z, Xie J, Wu T, Truong T, Auchus RJ, Huang CL.** Downregulation of NCC and NKCC2 cotransporters by kidney-specific WNK1 revealed by gene disruption and transgenic mouse models. *Hum Mol Genet* 20: 855–866, 2011. doi:10.1093/hmg/ddq525.
 28. **McCormick JA, Ellison DH.** Distal convoluted tubule. *Compr Physiol* 5: 45–98, 2015.
 29. **Montague BT, Ouellette JR, Buller GK.** Retrospective review of the frequency of ECG changes in hyperkalemia. *Clin J Am Soc Nephrol* 3: 324–330, 2008. doi:10.2215/CJN.04611007.
 30. **Morimoto T, Liu W, Woda C, Carattino MD, Wei Y, Hughey RP, Apodaca G, Satlin LM, Kleyman TR.** Mechanism underlying flow stimulation of sodium absorption in the mammalian collecting duct. *Am J Physiol Renal Physiol* 291: F663–F669, 2006. doi:10.1152/ajprenal.00514.2005.
 31. **Oh KS, Oh YT, Kim SW, Kita T, Kang I, Youn JH.** Gut sensing of dietary K⁺ intake increases renal K⁺ excretion. *Am J Physiol Regul Integr Comp Physiol* 301: R421–R429, 2011. doi:10.1152/ajpregu.00095.2011.
 32. **Palmer BF.** Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 351: 585–592, 2004. doi:10.1056/NEJMr035279.
 33. **Palmer BF, Naderi AS.** Metabolic complications associated with use of thiazide diuretics. *J Am Soc Hypertens* 1: 381–392, 2007. doi:10.1016/j.jash.2007.07.004.
 34. **Palmer BF.** A physiologic-based approach to the evaluation of a patient with hyperkalemia. *Am J Kidney Dis* 56: 387–393, 2010. doi:10.1053/j.ajkd.2010.01.020.
 35. **Palmer BF.** A physiologic-based approach to the evaluation of a patient with hypokalemia. *Am J Kidney Dis* 56: 1184–1190, 2010. doi:10.1053/j.ajkd.2010.07.010.
 36. **Palmer BF.** Regulation of potassium homeostasis. *Clin J Am Soc Nephrol* 10: 1050–1060, 2015. doi:10.2215/CJN.08580813.
 37. **Palmer BF, Clegg DJ.** Hyperkalemia. *JAMA* 314: 2405–2406, 2015. doi:10.1001/jama.2015.9230.
 38. **Palmer BF, Clegg DJ.** Electrolyte and Acid-Base Disturbances in Patients with Diabetes Mellitus. *N Engl J Med* 373: 548–559, 2015. doi:10.1056/NEJMr1503102.
 39. **Palmer BF, Clegg DJ.** Achieving the Benefits of a High-Potassium, Paleolithic Diet, Without the Toxicity. *Mayo Clin Proc* 91: 496–508, 2016. doi:10.1016/j.mayocp.2016.01.012.
 40. **Pathare G, Hoenderop JG, Bindels RJ, San-Cristobal P.** A molecular update on pseudohypoaldosteronism type II. *Am J Physiol Renal Physiol* 305: F1513–F1520, 2013. doi:10.1152/ajprenal.00440.2013.
 41. **Perazella MA.** Drug-induced hyperkalemia: old culprits and new offenders. *Am J Med* 109: 307–314, 2000. doi:10.1016/S0002-9343(00)00496-4.
 42. **Preston RA, Afshartous D, Rodco R, Alonso AB, Garg D.** Evidence for a gastrointestinal-renal kaliuretic signaling axis in humans. *Kidney Int* 88: 1383–1391, 2015. doi:10.1038/ki.2015.243.
 43. **Rabelink TJ, Koomans HA, Hené RJ, Dorhout Mees EJ.** Early and late adjustment to potassium loading in humans. *Kidney Int* 38: 942–947, 1990. doi:10.1038/ki.1990.295.
 44. **Riepe FG.** Pseudohypoaldosteronism. *Endocr Dev* 24: 86–95, 2013.
 45. **Reungjui S, Roncal CA, Sato W, Glushakova OY, Croker BP, Suga S, Ouyang X, Tungsanga K, Nakagawa T, Johnson RJ, Mu W.** Hypokalemic nephropathy is associated with impaired angiogenesis. *J Am Soc Nephrol* 19: 125–134, 2008. doi:10.1681/ASN.2007030261.
 46. **Reungjui S, Hu H, Mu W, Roncal CA, Croker BP, Patel JM, Nakagawa T, Srinivas T, Byer K, Simoni J, Wesson D, Sitprija V, Johnson RJ.** Thiazide-induced subtle renal injury not observed in states of equivalent hypokalemia. *Kidney Int* 72: 1483–1492, 2007. doi:10.1038/sj.ki.5002564.
 47. **Salhi A, Centeno G, Firsov D, Crambert G.** Circadian expression of H,K-ATPase type 2 contributes to the stability of plasma K⁺ levels. *FASEB J* 26: 2859–2867, 2012. doi:10.1096/fj.11-199711.
 48. **Satlin LM, Carattino MD, Liu W, Kleyman TR.** Regulation of cation transport in the distal nephron by mechanical forces. *Am J Physiol Renal Physiol* 291: F923–F931, 2006. doi:10.1152/ajprenal.00192.2006.
 49. **Sebastian A, Frassetto LA, Sellmeyer DE, Morris RC Jr.** The evolution-informed optimal dietary potassium intake of human beings greatly exceeds current and recommended intakes. *Semin Nephrol* 26: 447–453, 2006. doi:10.1016/j.semnephrol.2006.10.003.
 50. **Sorensen MV, Grossmann S, Roessinger M, Gresko N, Todkar AP, Barmettler G, Ziegler U, Odermatt A, Loffing-Cueni D, Loffing J.** Rapid dephosphorylation of the renal sodium chloride cotransporter in response to oral potassium intake in mice. *Kidney Int* 83: 811–824, 2013. doi:10.1038/ki.2013.14.
 51. **Soy M, Pamuk ON, Gerenli M, Celik Y.** A primary Sjögren's syndrome patient with distal renal tubular acidosis, who presented with symptoms of hypokalemic periodic paralysis: Report of a case study and review of the literature. *Rheumatol Int* 26: 86–89, 2005. doi:10.1007/s00296-005-0587-9.

52. **Stanton BA.** Renal potassium transport: morphological and functional adaptations. *Am J Physiol* 257: R989–R997, 1989.
53. **Stokes JB.** Consequences of potassium recycling in the renal medulla. Effects of ion transport by the medullary thick ascending limb of Henle's loop. *J Clin Invest* 70: 219–229, 1982. doi:[10.1172/JCI110609](https://doi.org/10.1172/JCI110609).
54. **Sufit CR, Jamison RL.** Effect of acute potassium load on reabsorption in Henle's loop in the rat. *Am J Physiol* 245: F569–F576, 1983.
55. **Terker A, Zhang C, Erspamer K, Gamba G, Yang C, Ellison D.** Unique chloride-sensing properties of WNK4 permit the distal nephron to modulate potassium homeostasis. *Kidney Int* 89: 127–134, 2016.
56. **Terker AS, Zhang C, McCormick JA, Lazelle RA, Zhang C, Meermeier NP, Siler DA, Park HJ, Fu Y, Cohen DM, Weinstein AM, Wang WH, Yang CL, Ellison DH.** Potassium modulates electrolyte balance and blood pressure through effects on distal cell voltage and chloride. *Cell Metab* 21: 39–50, 2015. doi:[10.1016/j.cmet.2014.12.006](https://doi.org/10.1016/j.cmet.2014.12.006).
57. **USDA/Agricultural Research Service.** *Nutrient intakes from food. Mean amounts consumed per individual, by gender and age. What we eat in America, NHANES 2007–2008* (Online). www.ars.usda.gov/ba/bhnrc/fsrg [Updated 14 April 2011].
58. **Wang WH.** Basolateral Kir4.1 activity in the distal convoluted tubule regulates K secretion by determining NaCl cotransporter activity. *Curr Opin Nephrol Hypertens* 25: 429–435, 2016. doi:[10.1097/MNH.0000000000000248](https://doi.org/10.1097/MNH.0000000000000248).
59. **Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B; OPAL-HK Investigators.** Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 372: 211–221, 2015. doi:[10.1056/NEJMoa1410853](https://doi.org/10.1056/NEJMoa1410853).
60. **Youn JH.** Gut sensing of potassium intake and its role in potassium homeostasis. *Semin Nephrol* 33: 248–256, 2013. doi:[10.1016/j.semnephrol.2013.04.005](https://doi.org/10.1016/j.semnephrol.2013.04.005).
61. **Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL.** Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 48: 219–224, 2006. doi:[10.1161/01.HYP.0000231552.10054.aa](https://doi.org/10.1161/01.HYP.0000231552.10054.aa).
62. **Zuber AM, Centeno G, Pradervand S, Nikolaeva S, Maquelin L, Cardinaux L, Bonny O, Firsov D.** Molecular clock is involved in predictive circadian adjustment of renal function. *Proc Natl Acad Sci USA* 106: 16523–16528, 2009. doi:[10.1073/pnas.0904890106](https://doi.org/10.1073/pnas.0904890106).

