Pathophysiology and management of hypokalemia: a clinical perspective

Robert J. Unwin, Friedrich C. Luft and David G. Shirley

Abstract | Potassium (K^+) ions are the predominant intracellular cations. K^+ homeostasis depends on external balance (dietary intake [typically 100 mmol per day] versus excretion [95% via the kidney; 5% via the colon]) and internal balance (the distribution of K^+ between intracellular and extracellular fluid compartments). The uneven distribution of K^+ across cell membranes means that a mere 1% shift in its distribution can cause a 50% change in plasma K^+ concentration. Hormonal mechanisms (involving insulin, β-adrenergic agonists and aldosterone) modulate K^+ distribution by promoting rapid transfer of K^+ across the plasma membrane. Extrarenal K^+ losses from the body are usually small, but can be marked in individuals with chronic diarrhea, severe burns or prolonged sweating. Under normal circumstances, the kidney's distal nephron secretes K^+ and determines final urinary excretion. In patients with hypokalemia (plasma K^+ concentration <3.5 mmol/l), after the exclusion of extrarenal causes, alterations in sodium ion delivery to the distal nephron, mineralocorticoid status, or a specific inherited or acquired defect in distal nephron function (each of which affects distal nephron K^+ secretion), should be considered. Clinical management of hypokalemia should establish the underlying cause and alleviate the primary disorder. This Review aims to inform clinicians about the pathophysiology and appropriate treatment for hypokalemia.

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Introduction

Hypokalemia is one of the most common electrolyte disturbances seen in clinical practice and, although more prevalent than hyperkalemia, most cases are mild. Although thresholds for the definition of hypokalemia vary slightly, a widely quoted lower limit for a normal serum potassium (K^+) ion concentration is 3.5 mmol/l. A serum K^+ level of 2.5–3.0 mmol/l is considered moderate hypokalemia and a level <2.5 mmol/l is regarded as severe hypokalemia. Around 3% of unselected hospitalized patients may be hypokalemic on admission to the clinic,[1] but >20% are likely to develop hypokalemia during their hospital stay, commonly for iatrogenic reasons related to prescribed drugs[2] or to infection.[3] One-fifth of these patients will exhibit moderate to severe hypokalemia.[4] Psychiatric patients seem to be at particular risk of hypokalemia,[5] perhaps because of their drug therapy (discussed later) rather than their underlying psychiatric illness, and patients on peritoneal dialysis are also at increased risk of hypokalemia, possibly owing to a combination of K^+ loss into peritoneal fluid, infection and poor nutrition.[6] Hypokalemia is common in patients who are ill, have a fever or are malnourished, including those with eating disorders, alcoholism or AIDS. Women develop hypokalemia more often than men,[7] especially when given thiazide diuretics;[8] the increased susceptibility of women to hypokalemia is probably related to reduced muscle mass and a smaller pool of exchangeable K^+. A form of pseudohypokalemia has also been described that is related to seasonal (summer) changes in ambient temperature, and has been attributed to metabolic increases in Na^+,K^+-ATPase ('sodium pump') activity and cellular uptake of K^+.[9]

This Review describes the pathophysiology and management of hypokalemia and is aimed at clinicians and clinical trainees, rather than those who conduct research in this field. Consequently, some aspects of physiology and debate with regard to hypokalemia will not be covered in depth; however, these aspects have been discussed elsewhere.[10]

General considerations

When treating a patient with hypokalemia, it is helpful to consider normal K^+ homeostasis and how a stable plasma or serum K^+ concentration is maintained through a combination of adjustments in acute cellular shifts of K^+ between extracellular and intracellular fluid compartments and more long-term renal excretion. Knowledge of whether K^+ concentration has been measured in plasma or serum is important, as these values may not always match; serum K^+ values are often slightly higher than plasma K^+ concentrations owing to delays in sample processing and/or the effect of clotting. Unlike total levels of sodium (Na^+) ions in the body, K^+ is predominantly intracellular (~3,600 mmol), where it is the most abundant cation. Intracellular K^+ neutralizes fixed anions and is involved in the regulation of cell volume, pH, enzyme activity, DNA and protein synthesis, and growth. The

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The authors declare no competing interests.

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Key points

- Hypokalemia is common and generally limited; however, the condition can be life threatening
- Understanding the basis of potassium (K^+) distribution in the body is the first step in the diagnosis of hypokalemia
- Levels of insulin, adrenergic activity, aldosterone, Na^+,K^+-ATPase activity, pH and osmolality can shift the internal distribution of K^+ ions
- Extrarenal losses, such as diarrhea or excess sweating, are generally (though not always) obvious
- Renal losses of K^+ ions are often an adverse effect of therapy
- Successful treatment of hypokalemia requires the primary cause to be established and the underlying problem to be addressed

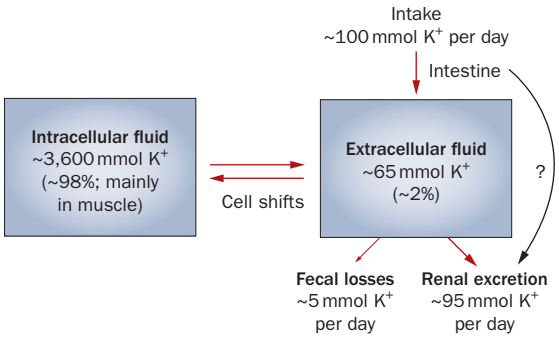

Figure 1 | Distribution of K^+ in the body. Approximately 98% of the body's K^+ is located in the intracellular fluid, mainly in skeletal muscle, and only approximately 2% is located in the extracellular fluid. The pool of K^+ in the extracellular fluid is determined by input from the gastrointestinal system and output in the urine and stools, as well as the distribution between the extracellular fluid and the intracellular fluid compartments. A novel hypothesis is that the gut can somehow signal to the kidneys to excrete K^+ abruptly when sudden gastrointestinal K^+ loads occur. Abbreviation: K^+, potassium.

steep K^+ concentration gradient across cell membranes, which are permeable to K^+, is largely responsible for the membrane potential of excitable and nonexcitable cells. Any change in this gradient can disturb cell excitation.

As the fraction of K^+ in the extracellular fluid is so small (~2% of total K^+ levels in the body) and as it is highly sensitive to cellular shifts, plasma or serum K^+ concentration is not a reliable index of deficits in body K^+. However, for every decrease in serum K^+ concentration of 0.3 mmol/l, as much as a ~100 mmol deficit in total body K^+ levels could exist. A serum K^+ concentration of <3 mmol/l or <2 mmol/l generally indicates deficits of at least 200 mmol or 500 mmol, respectively. Although these indices can be a useful clinical guide to corrective treatment, accurate quantification is difficult. Cellular shifts in K^+ levels occur because cell membranes are permeable to K^+ via a family of K^+ channels.[11] The extent of any shift of K^+ into cells is difficult to determine in a given patient because this shift is a function of muscle mass, adrenergic activity, insulin receptor signaling, and alterations in acid–base balance.

Maintenance of K^+ balance involves three key elements: cellular shifts, renal excretion and (to a lesser extent) gastrointestinal losses (Figure 1). K^+ concentrations in gastrointestinal secretions are between 5 mmol/l and 20 mmol/l along the small intestine and can be as high as 70 mmol/l or more in the colon. Yet, despite colonic secretion of K^+, which is stimulated by aldosterone, the volume of normal stool is low and so fecal K^+ losses are usually small.

Dietary K^+ restriction alone is rarely a cause of hypokalemia, as renal K^+ excretion can decrease to <15 mmol per day. Therefore, even if K^+ intake were reduced to zero, it would take 2–3 weeks for the serum K^+ concentration to decrease to ~3 mmol/l, which could only occur in starvation or severe eating disorders (such as anorexia nervosa). Indeed, even in these situations K^+ deficiency is almost always the result of additional renal, gastrointestinal or skin losses—the cause of the K^+ deficit must therefore be investigated.

The way in which humans have adapted to maintain K^+ balance and to control K^+ in the extracellular fluid within a fairly narrow range (3.5–5 mmol/l) is necessary for normal cellular function, especially for excitable cells, and is quite remarkable. The mechanisms are probably related to the habits of our early ancestors who, according to experts, consumed a 'hunter–gatherer' diet of chiefly berries and nuts (which have a relatively high K^+ content), as well as intermittent surfeits of K^+-rich meat when available. Such a chronic K^+ load, with sudden excesses from ingesting meat, would require mechanisms of acute internal adaptation, as well as an ability for subsequent and long-term excretion, namely cellular shifts versus renal excretion.

Cellular shifts in K^+

Cellular uptake of K^+ is promoted by alkalemia, insulin, β-adrenergic stimulation, and xanthines such as caffeine.[12] Evidence indicates that aldosterone also promotes cellular uptake of K^+.[12] After eating, insulin stimulates K^+ uptake—most importantly in skeletal muscle—by stimulation of Na^+,K^+-ATPase. Indeed, insulin is probably as vital for normal postprandial K^+ regulation as it is for glucose control. Several mechanisms account for the short-term effects of insulin on Na^+,K^+-ATPase. One of these is insulin-mediated translocation of Na^+,K^+-ATPase from intracellular stores to the cell surface. This rapid translocation is considered to be the main mechanism of Na^+,K^+-ATPase stimulation in skeletal muscle.[13] Although insulin also stimulates Na^+/H^+ exchanger activity, secondary stimulation of Na^+,K^+-ATPase in this way is unlikely to be as important as its direct stimulation. Skeletal muscle loses K^+ during exercise, which leads to transient hyperkalemia that promptly recovers when exercise stops. Catecholamines activate α_1-adrenergic and β_2-adrenergic receptors to decrease or increase, respectively, K^+ uptake by directly affecting Na^+,K^+-ATPase activity[14] in both muscle and liver.[15] α-Adrenergic-receptor stimulation is increased in patients with end-stage renal disease (possibly as a result of increased renal afferent nerve activity from diseased and ischemic native kidneys), which exacerbates exercise-related and fasting-related hyperkalemia.[16] β_2-Adrenergic-receptor stimulation and insulin can act synergistically to shift

K^+ into cells, as insulin secretion by pancreatic β cells is increased not only by direct stimulation of β_2-adrenergic receptors but also as a result of increased glycolysis and a rise in blood glucose concentration.[17] The hormone aldosterone seems to fulfill a major role in controlling K^+ balance, not only because it stimulates renal K^+ secretion (see below), but also because it can alter the transcellular distribution of K^+ in muscle. The latter action is a nongenomic effect that increases Na^+,K^+-ATPase activity as a result of enhanced Na^+ entry through Na^+/H^+ or Na^+–K^+–$2Cl^-$ transporters.[18,19]

Although an elevated systemic pH (alkalemia) was originally reported to cause potentially serious hypokalemia in anesthetized patients during acute respiratory alkalosis,[20] in fact a slight rise (~0.3 mmol/l) in plasma K^+ concentration occurs, followed by a post-hyperventilation fall, which reflects the balance of the initial inhibitory α-adrenergic, and later stimulatory β-adrenergic, activities.[21] In a given patient, the mechanisms of K^+ changes attributable to pH-related shifts are difficult to discern because changes in adrenergic tone and other confounders commonly occur simultaneously. A simplified, but clinically helpful, view of cellular K^+ shifts is given in Figure 2.

Several case reports have described hypokalemia after overdoses of chloroquine,[22] the antipsychotic agents risperidone or quetiapine,[23] cesium[24] and barium.[25] Barium and cesium are poisons that block K^+ channels, thereby preventing K^+ exit from cells (although it should be noted that barium sulfate does not dissociate appreciably and is harmless when used as a contrast agent for radiography). The mechanism by which hypokalemia occurs after administration of chloroquine or antipsychotic medications is less clear, but might relate to changes in adrenergic activity. The danger of these agents lies in the induction of a prolonged QT interval and potentially fatal cardiac dysrhythmias (torsade de pointes).[26] Treatment is symptomatic and supportive, and includes K^+ and magnesium supplements to correct any dysrhythmia; emergency hemodialysis can be effective in removing barium,[27] and probably cesium too, but not chloroquine, risperidone or quetiapine. Hypokalemia can also, albeit rarely, result from rapid cell growth (for example, after vitamin B_{12} treatment for pernicious anemia). Autosomal dominant hypokalemic periodic paralysis (HPP), caused by loss-of-function mutations in Na^+ or calcium (Ca^{2+}) ion channels in skeletal muscle that cause aberrant depolarization (typically after exercise or a large carbohydrate-rich meal), and thyrotoxicosis (which may present in a similar way to HPP but is often 'silent' in young Asian males), are other rare causes of hypokalemia.[28] The hypokalemia of thyrotoxicosis is caused in part by increased catecholamine sensitivity and also by a direct effect of thyroxine on Na^+,K^+-ATPase activity; patients with the thyrotoxic form of HPP are sometimes also hypophosphatemic and can respond to nonselective β-blockade.[29] The mechanistic link between a Ca^{2+} or Na^+ channel mutation in familial HPP and K^+ influx into muscle is still unknown. HPP treatment is empirical and anecdotal, and includes Na^+ restriction, K^+ supplementation, K^+-sparing diuretics (amiloride, triamterene or spironolactone), and the use of carbonic-anhydrase inhibitors, which may work by activating Ca^{2+}-activated K^+ channels, but can also cause hypokalemia (presumably from increased renal K^+ losses) in some cases.[30] Although not caused by cellular shifts in K^+, distal renal tubular acidosis, especially the autoimmune form, can sometimes present with a flaccid muscle paralysis that resembles HPP.[31] Indeed, one might ask why muscle paralysis is not more common in hypokalemic states. One possible reason is the difference in K^+ concentration gradients across cell membranes between acute (HPP) and chronic hypokalemia.

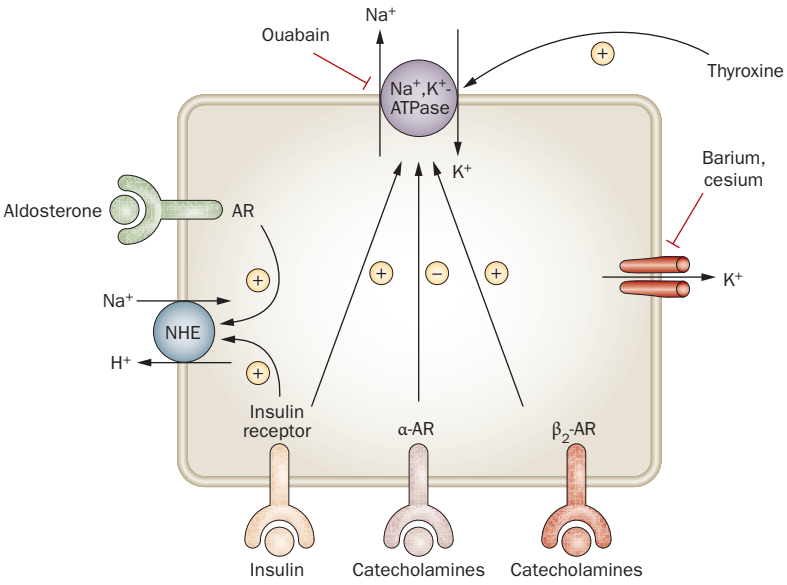

Figure 2 | Cellular shifts in K^+. A simplified diagram showing the important transporters involved in K^+ distribution across cell membranes, including the Na^+,K^+-ATPase 'sodium pump', K^+ channels and NHE. Substances that act on these channels and transporters to induce cellular shifts in K^+ are also shown. Abbreviations: α-AR, α-adrenergic receptor; β_2-AR, β_2-adrenergic receptor; AR, aldosterone receptor; H^+, hydrogen; K^+, potassium; Na^+, sodium; NHE, Na^+/H^+ exchanger.

K^+ loss

Extrarenal causes

Gastrointestinal loss of K^+ owing to severe or chronic diarrhea (including that caused by laxative abuse) is the most common extrarenal cause of hypokalemia, but it can also occur in celiac disease[32] and in patients with a villous (secreting) adenoma.[33] In these settings, urinary K^+ excretion should be <15 mmol per day (U_K:U_{Cr} ratio <1.5). Hypokalemia owing to prolonged vomiting is partly the result of renal K^+ losses from a combination of secondary hyperaldosteronism (because of volume depletion) and an alkalosis-related increase in filtered bicarbonate load, which exceeds the reabsorptive capacity of the proximal tubule and acts as a nonreabsorbable anion that, together with a reduced delivery of chloride (Cl^-) as a consequence of vomiting and hypovolemia, increases distal nephron K^+ secretion and urinary excretion (see below).

Another potential source of extrarenal K^+ loss is through the skin: exceptionally in severe burns, but

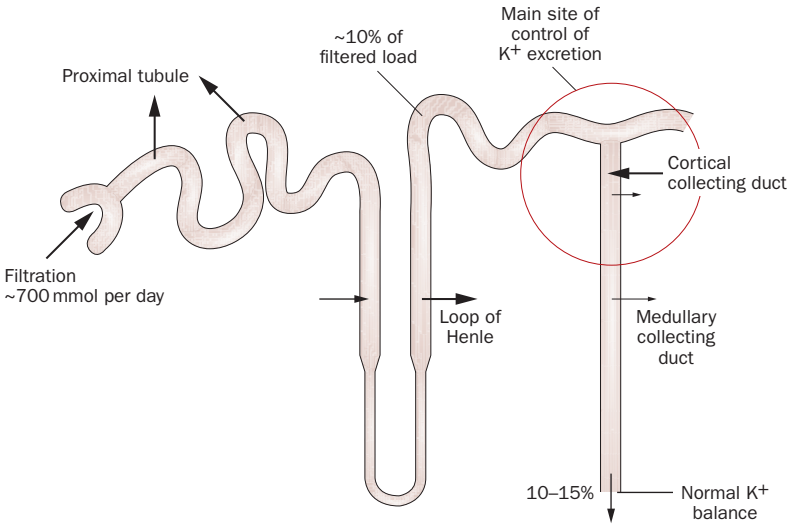

Figure 3 | Renal K^+ handling. Most filtered K^+ is reabsorbed in the proximal tubule and loop of Henle, so that approximately 10% of the filtered load arrives at the distal tubule, regardless of the state of K^+ balance. Control over the amount of K^+ excreted resides mainly in the connecting tubule and cortical collecting duct, where connecting tubule and principal cells secrete K^+ and A-type intercalated cells can reabsorb K^+ (at least during K^+ depletion). Under normal circumstances, the amount of K^+ secreted by the connecting tubule and principal cells determines how much K^+ is excreted in the urine. Abbreviation: K^+, potassium.

more usually in sweat, which, when thermally induced, contains K^+ at a concentration of 5–8 mmol/l.[34] During intense and prolonged exercise, substantial amounts of K^+ can be lost in sweat. For example, an American football player can lose up to 5 l of sweat during a 2 h practice session, which would be expected to contain up to 40 mmol of K^+.[35] The K^+ level in sweat can also have a concealed role in some underlying diseases associated with hypokalemia. For example, in one report, a young man presented with hypokalemia, prerenal failure, and metabolic alkalosis after unaccustomed exercise on a hot day. The investigators established that the patient had cystic fibrosis and explained that a partially functional cystic fibrosis transmembrane conductance regulator (CFTR) may, perhaps not uncommonly, be associated with only mild pulmonary and gastrointestinal signs and symptoms.[36] However, a dysfunctional CFTR in the sweat ducts of patients with cystic fibrosis can be responsible for excessive electrolyte losses, especially in hot weather. The hypokalemia seen with heat stress and after exercise is probably secondary to sweat losses, as well as renal K^+ wasting, similar to the pathophysiology outlined above for vomiting.

Renal causes

Normal renal K^+ handling

Under normal circumstances, most filtered K^+ is reabsorbed in the proximal convoluted tubule, although some secretion of K^+ occurs in the pars recta and the descending limb of the loop of Henle (Figure 3). Reabsorption of K^+ in the thick ascending limb of the loop of Henle means that approximately 10% of the filtered load arrives at the distal tubule. Control over the amount of K^+ appearing in the urine is mostly regulated within the connecting tubule and cortical collecting duct. Here, K^+ is normally secreted by the connecting tubule cells and by the principal cells of the cortical collecting duct, the extent of secretion being determined by K^+ balance. These nephron sites also contain A-type intercalated cells that have an apical H^+/K^+-ATPase that effects a certain amount of K^+ reabsorption and is stimulated in states of K^+ depletion.[37] Finally, some K^+ is normally reabsorbed in the medullary collecting duct. Renal K^+ excretion can vary from ~2% to ~150% of the filtered load, depending on the dietary intake of K^+ (normally ~100 mmol per day).

The mechanism of K^+ secretion by principal cells is shown in Figure 4. Because the efflux of K^+ from cell to tubular lumen is greatly influenced by the apical membrane and transepithelial potential difference, factors that affect Na^+ entry via amiloride-sensitive epithelial Na^+ channels (ENaCs) will also affect K^+ secretion. Thus, aldosterone, which increases insertion of ENaCs into the apical membrane and upregulates expression of the basolateral Na^+,K^+-ATPase, stimulates K^+ secretion. In addition, evidence indicates that aldosterone increases the membrane expression of apical K^+ channels by increasing serine/threonine protein kinase (also known as serum-glucocorticoid-induced kinase 1).[38] Despite unequivocal evidence for a stimulatory effect of aldosterone on K^+ secretion, doubts have been expressed as to whether this hormone has a major effect on K^+ excretion.[39] Such doubts arise from experiments in which aldosterone infusions cause a decrease in plasma K^+ levels, but without discernible kaliuresis.[40] However, an analysis by Young[41] provided an explanation by showing that aldosterone and plasma K^+ levels interact to control K^+ excretion, and that an aldosterone-induced decrease in plasma K^+ concentration resulting from a redistribution of K^+ between extracellular and intracellular compartments could negate the kaliuretic effect of the hormone.

Increased flow rate along the connecting tubule and cortical collecting duct stimulates K^+ secretion by two mechanisms: by stimulating reabsorption of some of the extra Na^+ in the tubular fluid, thereby further depolarizing the apical membrane, and by rapidly sweeping the secreted K^+ downstream, thereby maintaining the concentration gradient for further K^+ efflux. Under normal circumstances, K^+ secretion by principal cells is mediated by low-conductance renal outer medullary K^+ (ROMK) channels,[42] but flow-induced increases in K^+ secretion are thought to be mediated by large-conductance big K^+ (BK or Maxi-K) channels.[37] In addition to ROMK and BK channels, a K^+–Cl^- cotransporter has been identified in the apical membrane throughout most of the distal nephron.[43] This transporter might have a role in K^+ secretion, particularly when intraluminal Cl^- ion concentrations are low, which may partly explain the enhanced K^+ secretion observed when nonreabsorbable anions are present in tubular fluid (see below).

Effects of hormones, tubular flow and drugs

Once a renal loss of K^+ has been established in hypokalemia (urinary K^+ excretion >15 mmol per day; urinary K^+ concentration [U_K]:urinary creatinine concentration

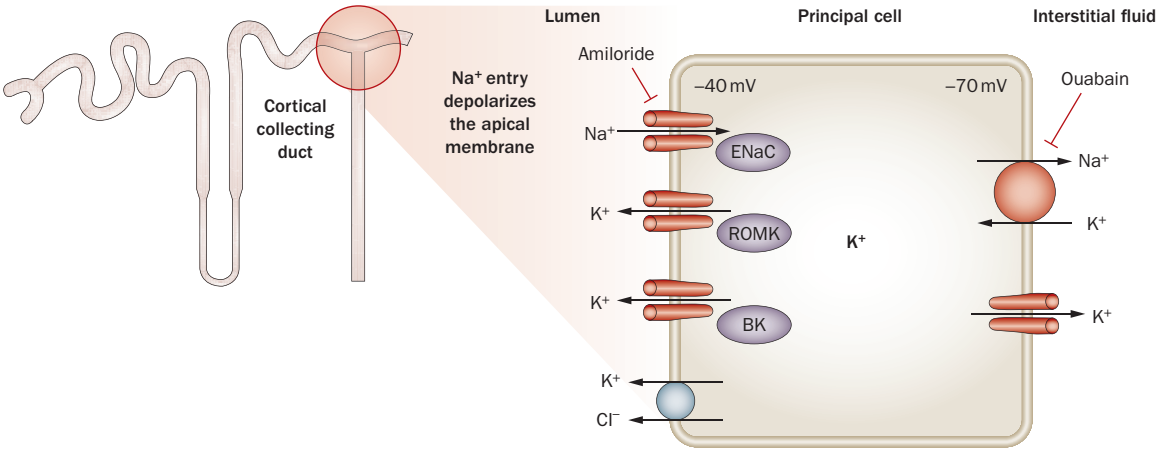

Figure 4 | K^+ secretion by principal cells. Entry of Na^+ through ENaCs depolarizes the apical membrane, with the result that K^+ efflux through apical K^+ channels (mainly ROMK channels) is greater than K^+ efflux through basolateral K^+ channels. Flow-induced increases in K^+ secretion are mediated by BK channels. Some K^+ secretion occurs via K^+–Cl^- cotransporters. Abbreviations: BK, big potassium; Cl^-, chloride; ENaC; epithelial sodium channel; K^+, potassium, Na^+, sodium; ROMK, renal outer medullary potassium.

[U_{Cr}] ratio >1.5), the main factors to consider clinically when investigating its cause are: increased mineralocorticoid-receptor stimulation (Box 1), increased distal nephron delivery of Na^+ and fluid and/or the presence of a nonreabsorbable anion (Box 1), or low intratubular Cl^- concentration. The balance between mineralocorticoid activity and distal nephron delivery of Na^+ and fluid explains why acute volume expansion or contraction does not usually affect renal K^+ excretion and why hyperkalemia tends not to occur in nonoliguric, as opposed to oliguric, glomerulonephritis and acute kidney injury (Table 1). Diuretics that act upstream of the connecting tubule and collecting duct will increase Na^+ and fluid delivery to these sites and promote K^+ secretion.[44] By reducing medullary osmolality, loop diuretics such as furosemide reduce fluid absorption in the descending limb of the loop of Henle (particularly in long-looped nephrons), thereby increasing fluid delivery from the loop to the distal tubule—an effect augmented by the ability of most loop diuretics to inhibit fluid reabsorption in the proximal tubule. These diuretics also directly inhibit K^+ reabsorption by cells of the thick ascending limb and may even induce net K^+ secretion by these cells.[45] Thiazide diuretics act on cells of the distal convoluted tubule to inhibit Na^+–Cl^- cotransport. As indicated above, these cells may secrete K^+ via K^+–Cl^- cotransport, a process that might be expected to be reduced when intraluminal Cl^- concentrations are raised by thiazides. However, the major effect of thiazides on K^+ excretion is to increase it, as a result of increased Na^+ delivery to the collecting duct. Loop and thiazide diuretics can also cause a degree of secondary hyperaldosteronism, adding to their stimulatory effect on tubular K^+ secretion.

Drugs that inhibit carbonic anhydrase (for example, acetazolamide) act on the proximal tubule to inhibit Na^+ and bicarbonate reabsorption, increasing distal delivery of Na^+, but also increasing the delivery of bicarbonate. This situation also occurs in proximal renal tubular acidosis (type 2) and inherited or acquired renal Fanconi syndrome; although in contrast to distal (type 1) renal tubular acidosis, hypokalemia only occurs in proximal renal tubular acidosis when bicarbonate is replaced in ample amounts. Some penicillins, as well as ketoacids in diabetic ketoacidosis and organic anions during fasting, also behave as nonreabsorbable anions that can stimulate K^+ secretion.[46] This stimulatory effect does not seem to depend on any associated increase in Na^+ delivery, and thus ROMK-mediated K^+ secretion, but depends instead on a low intratubular Cl^- concentration and enhanced electroneutral K^+–Cl^- cotransport.[47] Alkaline luminal fluids also have a direct stimulatory effect on this transporter.[48]

Acid–base disturbances and hypomagnesemia

The renal effects of acid–base disturbances on K^+ excretion are not readily predictable, as they can be both direct (pH-related) and indirect, occurring together with altered tubular fluid flow rate and composition. Although hypokalemia is frequently associated with metabolic alkalosis, it can occur in chronic metabolic acidosis (Box 1). Acute alkalosis directly affects principal cells of the collecting duct, specifically acting on ROMK channels to increase K^+ secretion, whereas acidosis has the opposite effect.[49] In chronic metabolic alkalosis and compensated respiratory acidosis, filtered bicarbonate is increased, which itself promotes K^+ secretion. Moreover, in chronic metabolic acidosis, reduced proximal tubular reabsorption of Na^+ increases its distal delivery, as well as tubular fluid flow rate, to enhance K^+ secretion and excretion.[50]

Hypokalemia commonly occurs in both proximal and distal forms of renal tubular acidosis but not, of course, in the less common hyperkalemic (type 4) form that is caused by a real or apparent deficiency in mineralocorticoid. In proximal renal tubular acidosis, as already discussed, hypokalemia largely occurs as a result of impaired bicarbonate reabsorption, which can be exacerbated by treatment with oral bicarbonate. However,

Box 1 | Clinical factors for renal K^+ loss

Increased mineralocorticoid-receptor stimulation

Primary hyper-reninism (characterized by elevated renin and aldosterone levels, which cannot be suppressed by saline)

- Malignant hypertension (~50% of cases of primary hyper-reninism)
- Renal artery stenosis (~15% of cases of primary hyper-reninism)
- Renin-secreting tumors, Page kidney, or postlithotripsy

Primary aldosteronism (characterized by suppressed renin levels and elevated aldosterone levels)

- Conn syndrome
- Adrenal hyperplasia (aldosterone levels increase further with standing)
- Glucocorticoid-remediable aldosteronism (sensitive to adrenocorticotropic hormone)

A primary increase in the effectiveness and/or amount of nonaldosterone mineralocorticoid-receptor agonist

- Cushing syndrome
- Congenital adrenal hyperplasia
- Apparent mineralocorticoid excess

Increased distal Na^+ delivery and/or nonreabsorbable ions in the distal nephron

- Diuretics acting upstream of the connecting tubule and cortical collecting duct
- An increase in nonreabsorbable anions (e.g. caused by vomiting, nasogastric suction, ketoacidosis, starvation and/or low protein intake, high-alkaline ash diet, hippurate from glue sniffing, carbenicillin)
- Magnesium deficiency
- Bartter syndrome
- Gitelman syndrome
- Chronic metabolic acidosis

Abbreviation: K^+, potassium; Na^+, sodium.

the explanation for renal K^+ wasting in distal renal tubular acidosis is much less clear.[51] It may result from a combination of: chronic acidosis *per se*; the presence of relatively alkaline tubular fluid containing little ammonium;[52] secondary hyperaldosteronism and increased vasopressin levels[53] caused by increased Na^+ and water losses; and/or treatment with oral bicarbonate or citrate supplements.

Hypomagnesemia often occurs with, and may worsen, hypokalemia, particularly in the presence of chronic diarrhea, alcoholism, long-term diuretic treatment after administration of tubulotoxic chemotherapeutic agents (such as aminoglycosides, amphotericin B and platinum-based anticancer drugs), as well as with some genetic tubular disorders such as Gitelman syndrome. An important cause of hypomagnesemia has only become apparent since the use of proton-pump inhibitors has become widespread for gastric protection. These compounds have been associated with hypomagnesemia that might occur after months or even years of treatment, and the site of magnesium ion loss seems to be the gastrointestinal tract, although the mechanism by which this occurs is still unknown.[54]

Intracellular magnesium deficiency can affect K^+ excretion in at least two ways: by reducing Na^+,K^+-ATPase activity, which may modestly decrease Na^+ reabsorption in nephron segments upstream of the collecting duct, thereby increasing distal Na^+ and fluid delivery and K^+ secretion; and by reducing magnesium-dependent inhibition of ROMK channels in collecting duct principal cells, which also increases K^+ secretion.[55] However, reduced basolateral uptake of K^+ by principal cells (owing to inhibition of Na^+,K^+-ATPase) counters the capacity for increased K^+ secretion, which may be why magnesium deficiency alone rarely causes hypokalemia.

The gut and renal K^+ excretion

The factors that can affect the cellular redistribution of K^+ and renal K^+ excretion, particularly in preventing postprandial hyperkalemia, are often coordinated. Insulin and glucagon have both been shown to cause a modest increase in K^+ excretion, and aldosterone levels also increase shortly after a meal.[56–58] Nevertheless, adaptation to sudden K^+ gluttony remains a mystery from the time of our Neolithic ancestor who hunted the woolly mammoth to the present day fast food consumer. A novel argument is that K^+ intake can be 'sensed' in the splanchnic vascular bed or in the gastrointestinal tract, and that signals can be sent to the kidney to rapidly adjust renal K^+ excretion, independent of somewhat 'sluggish' feedback mechanisms such as the stimulation of aldosterone release.[12] Sheep ingesting a K^+-rich meal over a 1 h period have a rapid and appropriate increase in renal K^+ excretion, which cannot be accounted for by changes in plasma K^+ and aldosterone concentrations alone.[39] Studies in adrenalectomized rats confirmed that this rapid urinary K^+ excretion was not mediated by aldosterone because much greater than physiological doses of aldosterone were required to mimic the response.[59,60] Studies in healthy humans undergoing a water diuresis have corroborated these findings by showing that ingestion of K^+ salts promotes urinary K^+ excretion within 20 min, before any detectable increases in plasma K^+ or aldosterone levels.[61]

What could be the sensor for this novel feed-forward mechanism? In contrast to the systemic or portal vein route, an intragastric K^+ infusion given with a K^+-deficient meal to fasted rats led to an increase in the renal clearance of K^+ in the absence of any change in plasma K^+ concentration.[62] The finding that K^+ clearance was enhanced in response to a K^+ load only when food was present in the stomach strongly suggests that the sensor in this feed-forward pathway is in the gastrointestinal tract itself.[63] Whether or not mechanical factors associated with the bulk of food have a role in K^+ sensing in the gut, and how such mechanical sensors might initiate the kaliuretic reflex signal, remain to be established. A hepatoportal K^+ sensor might also participate in the kaliuretic reflex. Morita and colleagues[64] found that an intraportal infusion of potassium chloride (KCl) in rats caused greater urinary excretion of K^+ than did an equivalent intravenous infusion. Furthermore, the acute infusion of KCl directly into the hepatoportal circulation stimulated hepatic afferent nerve activity and increased urinary K^+ excretion in the absence of changes in plasma K^+ levels; severing the periarterial hepatic nervous plexus attenuated the kaliuresis.[64] Whatever the mechanism may

Table 1 | K^+ secretion in the connecting tubule and cortical collecting duct related to changes in ECFV

Disorder	Aldosterone	Distal Na^+ delivery	K^+ secretion
High ECFV	Decreased	Increased	No change
Low ECFV	Increased	Decreased	No change
Conn syndrome (increased ECFV)	Increased	Increased	Increased
Diuretics (decreased ECFV)	Increased	Increased	Increased
Addison syndrome (decreased ECFV)	Decreased	Decreased	Decreased
Acute nephritis (increased ECFV)	Decreased	Decreased*	Decreased

*Overall distal Na^+ delivery is reduced as a consequence of the fall in overall glomerular filtration rate (distal Na^+ delivery per functioning nephron is unlikely to be reduced). Abbreviations: ECFV, extracellular fluid volume; K^+, potassium; Na^+, sodium.

be, the gut somehow senses K^+ intake during a meal and enhances the renal clearance of K^+. This response should theoretically minimize increases in plasma K^+ levels during or after a meal.[65]

Consequences of hypokalemia

The consequences of acute and chronic hypokalemia include muscle weakness, palpitations and cardiac dysrhythmias, as well as worsening diabetic control (a result of impaired insulin release and reduced tissue sensitivity to insulin). In addition, polyuria commonly occurs, through an impaired ability to concentrate urine.[66] Cardiovascular risks and adverse effects of anesthesia in patients with hypokalemia have always been a particular clinical concern. In contrast to the response of skeletal muscle, hypokalemia-induced hyperpolarization increases excitability in cardiac muscle (although why is unclear) and delays repolarization, causing atrial and ventricular dysrhythmias. Changes observed in the electocardiogram of patients with hypokalemia are characterized by an early T-wave flattening followed by an ST-T depression and a U wave that can sometimes be difficult to distinguish from the T wave, with prolongation of the QU or QT interval.[67] Although hypokalemia in the setting of an acute myocardial infarct poses the particular risk of a life-threatening dysrhythmia and requires prompt recognition and correction, routine K^+ supplementation is not necessary in patients with hypertension, or with a history of stable cardiovascular disease, who are being treated with diuretics. However, animal and human data do support a role for K^+ repletion and supplementation in reducing hypertension, risk of stroke, and morbidity and mortality in patients with congestive heart failure,[68] as well as other potential benefits such as reduced risk of kidney stones and improved diabetic control.[69] In patients receiving general anesthesia, concern with regard to hypokalemia relates to the risk of dysrhythmias and impaired cardiac contractility. The danger of these adverse events is, however, associated with acute, rather than chronic, hypokalemia. Indeed, the risk of such events occurring under general anesthetic is much lower than was originally believed and the threshold serum K^+ concentration for cancellation of elective surgery is now <2.6 mmol/l.[70,71] Caution should still be exercised in the use of intraoperative glucose solutions (owing to the risk of insulin-mediated hypokalemia) and anesthetic agents that are known to be cardiac depressants.

Early observations of a link between hypokalemia and renal lesions were reviewed more than 50 years ago by Conn and Johnson.[72] 'Vacuolar degeneration' in the kidneys of patients dying from chronic dysentery was first described in 1919 and was attributed to intestinal losses of unspecified 'nutritional substances'. Similar descriptions linked to chronic intestinal disease followed, but it was not until the early 1950s that evidence began to implicate chronic K^+ deficiency as the underlying cause.[72] In fact, similar tubular lesions had already been described in the 1930s and 1940s in rats maintained on a K^+-deficient diet.[72] Over the past decade, descriptions of hypokalemic (or kaliopenic) nephropathy have typically been made in patients taking excess laxatives and/or diuretics, individuals with eating disorders (anorexia nervosa and bulimia),[73] or those with primary hyperaldosteronism. A disturbing and perhaps underappreciated study regarding hypokalemia was published by Bock and colleagues.[74] These investigators argued that chronic hypokalemia caused nephropathy leading to end-stage renal disease. However, the patients in this study had many confounding factors (their hypokalemia was caused by malnutrition associated with anorexia, vomiting and/or laxative and/or diuretic abuse) and were prone to self-destructive behavior. Interestingly, with the advent of genetic testing and better characterization of patients found to be hypokalemic, we have found that nephropathy, as evidenced by a reduced glomerular filtration rate and/or proteinuria, is not a feature of Gitelman syndrome. Moreover, the nephropathy of Bartter syndrome (when evident) seems to be related to more severe and episodic Na^+ and water losses, and perhaps increased aldosterone levels, rather than hypokalemia *per se* (R. Unwin, unpublished work).

Investigation of hypokalemia

A clinical algorithm can be used in suspected cases of hypokalemia;[75] our own example is shown in Figure 5. It is crucial that clinicians recognize any renal loss of K^+ that could be responsible for the hypokalemia. Two tests are commonly used to assess increased or inappropriate renal K^+ losses from a 'spot' urine sample: fractional K^+ excretion (FE_K; expected value in hypokalemia <2%) and transtubular K^+ gradient (TTKG; which is calculated by dividing the urine:plasma K^+ concentration ratio by the urine:plasma osmolality ratio, to provide an index of K^+ secretion;[76] expected value in hypokalemia <2).

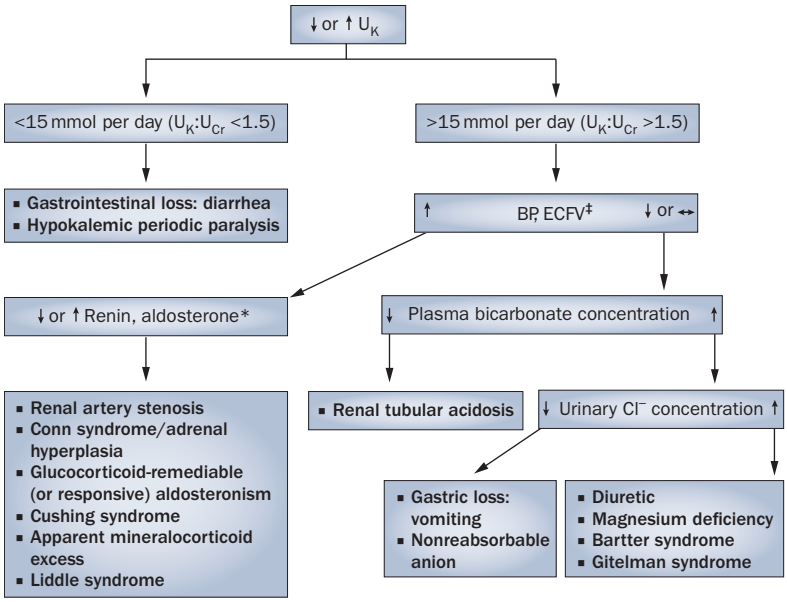

Figure 5 | A clinical algorithm for investigating hypokalemia. *See Box 1 for details. ‡Assessed clinically. Abbreviations: BP, systemic arterial blood pressure; ECFV, extracellular fluid volume; U_{Cr}, urinary creatinine content; U_K, urinary K^+ content.

According to a retrospective analysis by Lin and colleagues,[29] a low value for TTKG in hypokalemia strongly suggests a redistribution of K^+ as seen in HPP, given that gastrointestinal losses are not usually substantial. Nevertheless, both of these indices have their limitations. Neither is particularly sensitive to increased mineralocorticoid activity[77] and the TTKG is probably more useful to detect impaired renal K^+ secretion in hyperkalemia. In the case of unexplained or seemingly isolated or incidental hypokalemia, or if an underlying renal tubulopathy is suspected, a potentially useful screening test is the 'thiazide test'.[78] This is designed to identify patients with Gitelman syndrome without necessarily requiring genetic testing.[79] Although the presence of hypocalciuria with hypokalemia may be suggestive of Gitelman syndrome, it can also be found in those patients with an underlying eating disorder and poor nutrition as a cause of hypokalemia.

Treatment of hypokalemia

Optimum treatment of hypokalemia requires that the cause be established and the underlying disorder alleviated. This strategy is successful in the majority of cases. Establishing whether hypokalemia is caused by a cellular shift or by a K^+ deficit is essential. Furthermore, as K^+ disturbances almost invariably feature acid–base disorders (HPP is an exception), the acid–base status should be investigated. If the patient has metabolic acidosis (for example, from distal renal tubular acidosis), the hypokalemia should be treated before the acidosis is addressed. K^+ can be given orally in liquid or tablet form, or intravenously, usually as KCl. The approximate K^+ deficit can be estimated from the plasma or serum K^+ concentration, as stated earlier. If replacement needs to be given intravenously, it is safer not to exceed a dose of 20 mmol/h, as there is a danger of rebound hyperkalemia. This danger is of particular concern in HPP, in which spontaneous recovery will lead to a reversal of the redistribution of K^+; in these patients, K^+ supplementation should therefore not exceed 10 mmol/h.[80] As indicated earlier, modest K^+ replacement can be supplemented with nonselective β-blockers in patients with the thyrotoxic form of HPP.[81] One cautionary note about KCl tablets (which typically contain ~8 mmol K^+) is that they can irritate the gastrointestinal mucosa to cause bleeding and ulceration, especially if taken in large quantities. Importantly, KCl tablets must be taken with plenty of fluid and avoided just before going to bed, as they can remain for a substantial amount of time in the lower esophagus and could cause ulceration. Potassium citrate tablets, which in Europe provide 40 mmol K^+, are an alternative to KCl, particularly in patients with an accompanying metabolic acidosis. In treating chronic hypokalemia, K^+-sparing diuretics (such as amiloride, triamterene or spironolactone) can be useful, but again there is an increased risk of hyperkalemia in patients with reduced renal function or in those taking angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers or NSAIDs, which can reduce glomerular filtration rate. Ingestion of foods particularly rich in K^+ (for example, artichokes, avocados, bananas, grapes and pineapples) should be encouraged in patients with hypokalemia, although, if weight gain is to be avoided, potassium citrate tablets are an alternative to sugar-rich juices and foods. Finally, we again underscore the fact that most cases of hypokalemia can be fully explained if a systematic and physiological approach to diagnosis is adopted.

Conclusions

Although most cases are mild, hypokalemia is a common electrolyte disorder that can sometimes be life threatening. Proper management and treatment of hypokalemia requires an understanding of the factors that affect K^+ distribution within the body and the causes of renal and extrarenal K^+ losses from the body. Daily K^+ intake averages ~100 mmol per day; ~95% of this amount is usually excreted in the urine, which is regulated largely by the degree of K^+ secretion by connecting tubule cells and by principal cells in the cortical collecting duct. The remaining ~5% is normally lost in feces. K^+ is unevenly distributed within the body, ~98% being intracellular; as a result, very small changes in the distribution of K^+ between intracellular and extracellular compartments can lead to major changes in plasma K^+ concentration.

Once hypokalemia has been identified and confirmed, the physician must pursue a diagnostic course of action before administering any therapy. A clinical history is often sufficient, because many patients with hypokalemia are taking one or more drugs that could be responsible, or they can tell the clinician what the problem is, as long as the appropriate questions about losses or (rarely) reduced intake are asked. Physical examination can sometimes provide helpful clues, suggesting extrarenal losses from skin or bowel, or signs pointing to an underlying eating disorder (for example, damaged teeth and gums, angular

cheilitis, calluses on the hands). Collecting simultaneous plasma and urine samples to test whether renal excretion is increased in the presence of hypokalemia is the best way to document inappropriate renal K^+ losses. If these measurements are not performed at the outset, the opportunity for establishing a precise cause may well be lost. If renal losses are not obviously increased, it is necessary to consider possible causes of K^+ redistribution (such as HPP) and/or of excessive extrarenal K^+ losses. If an extrarenal cause has been excluded, it is usually sufficient to think in terms of factors that increase K^+ secretion in the connecting tubule and cortical collecting duct, such as increased Na^+ delivery to the distal nephron (as in diuretic treatment), increased aldosterone levels or mineralocorticoid-like activity, increased distal delivery of nonreabsorbable anions, or an inherited or acquired defect in distal nephron function.

Although moderate oral and intravenous K^+ replacement is sometimes necessary, the ideal approach to the successful management of hypokalemia requires the cause of the disturbance to be established and the underlying disorder alleviated. Finally, one electrolyte deficiency is commonly accompanied by another, and a brief check of plasma Na^+, K^+, magnesium and hydrogen ion concentrations (acid–base balance) is always warranted.

Review criteria

We searched PubMed and Google Scholar for full-length, English-language publications on potassium homeostasis using the search terms "potassium" and "hypokalemia". We also consulted experts in the field, whom we know personally, for additional references.

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Author contributions

R. J. Unwin, F. C. Luft and D. G. Shirley contributed equally to all aspects of this manuscript.