Causes of Hypokalemia in Adults

Reviewed by:

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Hypokalemia: A Clinical Update

Hypokalemia, a condition where serum levels of potassium are lower than normal, is a common electrolyte disturbance. It usually results from increased potassium excretion or intracellular shift and less commonly from reduced potassium intake. An acceptable lower limit for normal serum potassium is 3.5 mmol/L. Severity is categorized as mild when the serum potassium level is 3 to 3.4 mmol/L, moderate when the serum potassium level is 2.5 to 3 mmol/L, and severe when the serum potassium level is less than 2.5 mmol/L. Values obtained from plasma and serum may differ. Compared to plasma levels, serum levels are usually slightly higher due to delay in processing and/or the effect of clotting.[1,2]

Symptoms and signs of hypokalemia can be subtle and easily overlooked without a carefully directed history and physical examination, and precise interpretation of the electrocardiogram (Box 1).[3] Hypokalemia is more commonly associated with cardiac diseases, renal failure, malnutrition, and shock. Hypothermia and increased blood cell production are additional risk factors for developing hypokalemia. It is prevalent in hospitalized patients, in particular, pediatric patients, those who have fever and those who are critically ill.[2]

Physiology of Potassium

Potassium is the major intracellular cation, with 98% of the total pool being inside the cells at a concentration of 140-150 mmol/L, and only 2% in the extracellular fluid, where it ranges between 3.5 and 5 mmol/L. Both internal and external homeostasis contributes in maintaining a normal potassium balance, by controlling its distribution (the first) and its excretion (the second) in either conditions of potassium loading and potassium depletion. External potassium balance is determined by the rate of potassium intake (normally 100 mEq/day) and rate of urinary (normally 90 mEq/day) and fecal excretion (normally 10 mEq/day). The distribution of potassium in muscles, bone, liver and red blood cells (RBC) and extracellular fluid (ECF) has a direct effect on internal potassium balance (Figure 1).[1,4]

Box 1: Clinical manifestations of hypokalemia

Cardiovascular System
- ECG changes: prominent U wave, flattened or inverted T waves, ST segment depression, T and U wave fusion giving appearance of QT interval prolongation with severe hypokalemia
- Arrhythmias: atrial tachycardia with or without block, premature ventricular contraction, ventricular tachycardia and/or fibrillation, torsades de pointes
- Worsening hypertension
- Sudden death

Kidney
- Polyuria due to decreased concentrating ability
- Hypokalemic nephropathy
- Chloride-depletion metabolic alkalosis
- Increased risk of nephrolithiasis

Neuromuscular
- Cramp, myalgia, rhabdomyolysis, weakness, paralysis, paresthesia

Gastrointestinal tract
- Altered gastrointestinal motility (nausea, vomiting, constipation, paralytic ileus)
- Worsening of hepatic encephalopathy

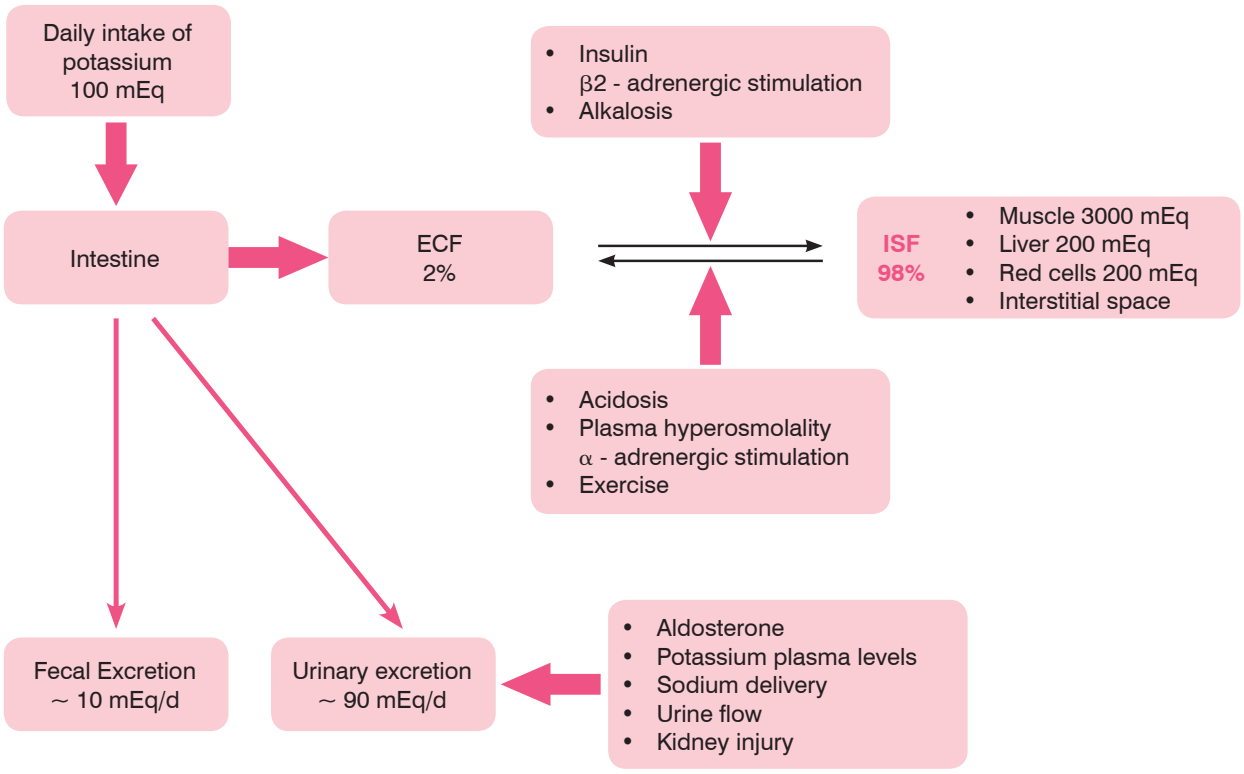
Genitourinary tract
- Hypotonic bladder

Respiratory System
- Respiratory acidosis secondary to respiratory muscle weakness

Endocrine System
- Insulin resistance and impairment in insulin release

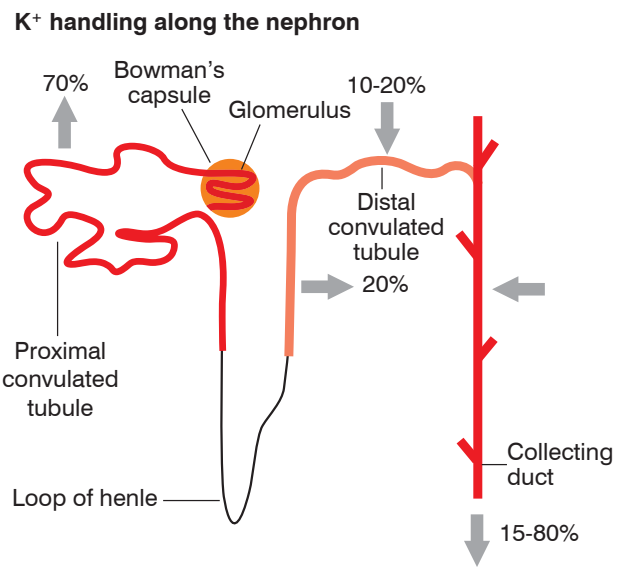
Adapted from: Asmar A, Mohandas R, Wingo CS. A Physiologic-Based Approach to the Treatment of a Patient With Hypokalemia. *Am J Kidney Dis.*2012;60(3):492-7.

Figure 1: Potassium homeostasis



Adapted from: Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect.* 2018;7(4):R135-R146.

Figure 2: Potassium reabsorption and secretion along the nephron



Adapted from: Zacchia M, Abategiovanni ML, Stratigis S, Capasso G. Potassium: From Physiology to Clinical Implications. *Kidney Dis (Basel)*. 2016; 2(2):72-79.

Intriguingly, various clearance studies demonstrated that the bulk of tubular potassium reabsorption occurs along the proximal tubule and the thick ascending limb on Henle's loop (Figure 2). Only 10% of the filtered load reaches the distal nephron. The evidence that the amount of potassium excreted could exceed the amount of potassium filtered suggested the presence of potassium secretion along the nephron.[4]

Causes of Hypokalemia

Hypokalemia can result from abnormal losses, transcellular shifts, or insufficient intake (Table 1). Abnormal losses are most common cause of hypokalemia. Excessive excretion of potassium in the urine (kaliuresis) may result from the use of diuretic drugs, endocrine diseases such as primary hyperaldosteronism, kidney disorders and genetic syndromes affecting the renal function. Gastrointestinal losses of potassium areusually due to prolonged diarrhea or vomiting, chronic laxative abuse, intestinal obstruction or infections. Insufficient intake is rarely the sole cause for hypokalemia, but it often contributes to hypokalemia in

Table 1: Causes of hypokalemia
Abnormal losses
• Medications • Diuretics • Laxatives and enemas • Corticosteroids • Gastrointestinal losses • Renal losses • Osmotic diuresis • Mineralocorticoid excess • Types I and II renal tubular acidosis • Polydipsia • Intrinsic renal transport defects • Hypomagnesemia • Dialysis/plasmapheresis
Transcellular shifts
• Medications • Insulin overdose • Beta 2 sympathomimetics • Decongestants • Xanthines • Amphotericin B • Verapamil intoxication • Chloroquine (Aralen) intoxication • Barium intoxication • Cesium intoxication • Alkalosis • Refeeding syndrome • Increased beta 2 adrenergic stimulation • Delirium tremens • Head injury • Myocardial ischemia • Thyrotoxicosis • Familial hypokalemic periodic • paralysis • Hypothermia
Inadequate intake
• Anorexia • Dementia • Starvation • Total parenteral nutrition
Pseudohypokalemia
• Delayed sample analysis • Significant leukocytosis • [> 75,000 cells per mm^3 (75.0 × 10^9 per L)]
Adapted from: Viera AJ, Wouk N. Potassium Disorders: Hypokalemia and Hyperkalemia. *Am Fam Physician.* 2015;92(6):487-95.

hospitalized patients. An intracellular shift of the potassium can also lead to severe hypokalemia. Insulin administration, stimulation of the sympathetic nervous system, thyrotoxicosis and familial periodic paralysis are some of the reasons for this phenomenon. Drugs, such as diuretics and penicillin can be often the underlying cause of hypokalemia. Finally, hypomagnesemia is very important, more than 50% of clinically significant hypokalemia has concomitant magnesium deficiency and is clinically most frequently observed in patients receiving loop or thiazide diuretic therapy. Concomitant magnesium deficiency has long been appreciated to aggravate hypokalemia. Hypokalemia associated with magnesium deficiency is often refractory to treatment with potassium supplementation alone.[1,5]

Treatment of Hypokalemia

The treatment of hypokalemia includes reduction in potassium losses, replenishment of potassium stores, evaluation for potential toxicities and determination of the cause. Management strategies vary depending on the severity of the imbalance (Box 2). Serum potassium concentrations between 3.5 and 4 mEq/L are a sign of early potassium depletion. No pharmacological therapy is recommended at this point, but the patient's diet should be assessed. Potassium levels of 2.5–3.5 mEq/L in patients may need only oral potassium replacement. Administration of oral Potassium should be accompanied with plenty of fluid (between 100 and 250 mL of water, depending on the

Box 2: Suggested management for hypokalemia
Mild to moderate hypokalemia (serum potassium concentration 3.0–3.5 mEq/L) • If possible, treat the underlying disorder with 60–80 mEq/d of potassium chloride orally in divided doses • Recheck serum potassium concentration after replacement therapy **Severe hypokalemia (serum potassium concentration < 3.0 mEq/L)** • Preferred: Potassium Chloride 40 mEq orally every 3–4 hours × 3 • If necessary: IV Potassium Chloride (10–20 mEq/hr) in the setting of cardiac arrhythmias, digitalis toxicity, and recent or ongoing cardiac ischemia. This should be done with continuous cardiac monitoring. Recheck serum potassium concentration every 2–4 hr to ensure that serum potassium concentration is > 3.5 mEq/L
Adapted from: Asmar A, Mohandas R, Wingo CS. A Physiologic-Based Approach to the Treatment of a Patient With Hypokalemia. *Am J Kidney Dis.*2012;60(3):492-7.

form of the tablet of potassium) and is better to be given with or after meals. Patients who have severe hypokalemia or who cannot take oral supplements require intravenous (i.v.) Potassium replacement therapy. Intravenous Potassium must be administered with caution to prevent serious complications, including potentially fatal cardiac arrhythmias. All infusions should be diluted and mixed thoroughly in adequate amounts of fluid; use premixed Potassium solutions when possible. To prevent or reduce toxic effects, i.v. infusion concentrations should not exceed 40 mEq/L and should be infused at a rate of 10 mEq per hour or less. A general rule for replacement in patients with normal renal function is 10 mEq Potassium supplement administration, which will raise the serum potassium level by 0.1 mmol/dL.[6]

Furthermore, a patient taking a thiazide or loop diuretic may be switched to a potassium-sparing agent like spironolactone, eplerenone or amiloride to prevent excessive urinary potassium loss. After the serum potassium level returns to normal, oral Potassium supplement may be required with daily dosages ranging from 20 mEq to 80 mEq.[6] A study[7] reported that co-administration of Potassium Citrate did not induce hypokalemia or hypochloremic metabolic alkalosis in thiazide-treated patient population of recurrent hypercalciuric nephrolithiasis. Lastly, patients may also need to increase their dietary intake of potassium-rich food.

Conclusion

Hypokalemia is a common electrolyte disorder caused by changes in potassium intake, altered excretion, or transcellular shifts. Management of the underlying disease or contributing factors constitutes the cornerstone of therapeutic approach. Potassium should be gradually replaced, preferably by oral administration if clinically feasible. In cases of severe/symptomatic hypokalemia and cardiac complications, i.v. administration with continuous ECG monitoring is recommended. In some patients, such as in endocrine related hypokalemia cases, multidisciplinary diagnostic and therapeutic approach is needed. Furthermore, daily supplementation with potassium is required for patients who continue to take medications that can lead to hypokalemia; such supplementation should be stopped when these medications are discontinued. Lastly, a through implementation of multiple interventions is entailed in order to improve awareness and understanding of the investigations, treatment, and monitoring of the hypokalemic patient.

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