Clinical Update on HYPERKALEMIA

A Chronic Risk for CKD Patients and a Potential Barrier to Recommended CKD Treatment

National Kidney Foundation®

Introduction

Hyperkalemia is a serious medical condition that can cause severe cardiac electrophysiology alterations, such as cardiac arrhythmias, and sudden death. Hyperkalemia is defined as a serum potassium level above the reference range and arbitrary thresholds are used to indicate degree of severity, such as >5.0, >5.5 or >6.0 mmol/L.[1] Patients with chronic kidney disease (CKD) (especially advanced CKD) are at high risk for hyperkalemia, especially when other factors and comorbidities that interfere with renal potassium excretion are present. The prevalence of hyperkalemia in CKD patients is considerably higher than in the general population. A recent review reports hyperkalemia frequency as high as 40-50% in the CKD population compared to 2-3% in the general population.[1] Those at highest risk are patients with diabetes and advanced CKD, kidney transplant recipients, and patients treated with renin-angiotensin aldosterone system (RAAS) inhibitors. Moreover, an episode of hyperkalemia in patients with CKD increases the odds of mortality within one day of the event.[2] There may also be racial differences for hyperkalemia outcomes. According to a retrospective observational study of 1227 patients, white patients with CKD have a consistent association between hyperkalemia and increased mortality, while African American/black patients with CKD appear to have a better tolerance of high potassium levels; but these results need to be confirmed by prospective studies.[3]

Potassium Homeostasis

The kidneys play a major role in maintaining potassium homeostasis by matching potassium intake with potassium excretion. Potassium is freely filtered by the glomerulus and 90-95% is reabsorbed in the proximal tubule and loop of Henle. Urinary excretion of potassium begins in the distal convoluted tubule and is further regulated by the distal nephron and collecting duct.[4,5] Therefore, loss of nephron function due to kidney disease results in renal retention of potassium. The main regulators of this process are aldosterone and serum potassium level.

Increases in serum potassium level correlate with worsening kidney function.[6] As glomerular filtration rate (GFR) declines, potassium excretion is maintained by changes in the remaining nephrons that increase efficacy of potassium excretion. Due to this adaptive response, under normal conditions hyperkalemia rarely occurs at GFR >15 mL/min, unless aldosterone secretion or function is impaired. But there is a limit to renal compensation and as the GFR falls below 15 mL/min, extrarenal handling of potassium, especially gastrointestinal excretion, becomes critical in dissipating an acute potassium load.[7]

Importantly, the capacity of the colon to secrete potassium increases as kidney function declines and makes a substantial contribution to potassium homeostasis in patients with CKD. Research shows that under basal conditions, fecal potassium excretion was almost three-fold greater in kidney failure patients, compared to patients with normal kidney function.[8] In a case report of a hemodialysis patient, severe hyperkalemia was seen due to reduced colonic potassium secretion following colon diversion surgery. This was evidenced by changes in fecal potassium before and after restored bowel continuity, without dietary modification.[9]

Hyperkalemia in CKD

In addition to a decrease in GFR and disturbances in renal handling of potassium, CKD patients often have other factors and comorbidities that worsen hyperkalemia. These factors described below explain why hyperkalemia is commonly seen in the CKD population:[1,10]

- *Dietary modifications for CKD* – Increased dietary potassium intake from salt substitute (potassium chloride), potassium-rich heart-healthy diets, and herbal supplements (noni, alfalfa, dandelion, etc.)
- *Metabolic acidosis* – Potassium shift from the intracellular to the extracellular space
- *Anemia requiring blood transfusion* – High acute potassium load (large transfusions, outdated blood)
- *Kidney transplant* – Effects of calcineurin inhibitors are the prime offenders in this category. Renal tubular acidosis contributes to a lesser extent.
- *Acute kidney injury* – Rapid decrease in GFR and tubular flow; often accompanied by a hypercatabolic state, tissue injury, and high acute potassium loads
- *Diabetes* – Insulin deficiency and hypertonicity caused by hyperglycemia contribute to an inability to disperse high acute potassium load into the intracellular space. Hyporeninemic hypoaldosteronism results in the inability to upregulate tubular potassium secretion.
- *Cardiovascular disease (CVD) and associated conditions* – Require medical treatments that have been linked to hyperkalemia (eg mineralocorticoid-receptor blockers, cardiac glycosides)
- *Advanced stages of heart failure* – Reductions in renal perfusion

Other reported independent risk factors for hyperkalemia in patients with CVD and CKD include coronary artery disease and peripheral vascular disease. This association could be due to the role of aldosterone in regulating potassium homeostasis, oxidative stress, and atherosclerosis.[11]

The most common cause of increased potassium levels as related to morbidity and mortality is drug-induced hyperkalemia, triggered either by inhibiting renal potassium excretion or by blocking extrarenal removal (Table 1).[12] In an observational retrospective study of nondialyzed patients with serum potassium of 6.5 mmol/L or greater on admission or during hospital stay, more than 60% were taking at least one drug known to cause or worsen hyperkalemia.[13]

Treatment with RAAS inhibitors, such as angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB), is widely used for managing CKD progression, but linked with an increased risk of hyperkalemia, especially when administered in combination.[14] In a study of veterans with proteinuric diabetic kidney disease, the risk of hyperkalemia was more than double in the combination-therapy group (ACE inhibitor and ARB) compared to the monotherapy group, and the study was stopped early due to safety concerns.[15]

In a cohort study of patients with possible CKD who started an ACE inhibitor, investigators identified seven patient characteristics that predicted 90-day risk of hyperkalemia: advanced age (80-89 years), declining kidney function, diabetes, heart failure, high starting dose of ACE inhibitor (>10 mg/day), current use of potassium supplements, and current use of ARB or potassium-sparing diuretics.[16] Of course, for RAAS blockade therapy, the higher the baseline serum potassium the higher the risk of hyperkalemia. Risk predictors may be useful for more intensive potassium monitoring and subsequent intervention in CKD patients on RAAS inhibitors.

There is a high prevalence of nonsteroidal anti-inflammatory drug (NSAID) use, especially by the elderly, and approximately 14 million people in the U.S. are treated with both antihypertensive drugs and NSAIDs.[17] The strongest risk factors for NSAID-induced hyperkalemia include prior episode of hyperkalemia, CKD, diabetes, acute kidney injury, and use of potassium-sparing diuretics.[18] Risk of hyperkalemia with use of selective cyclo-oxygenase (COX)-2 inhibitors versus nonselective NSAIDS is not clear. Aljadhey et al report clinically important increases in serum potassium in patients prescribed selective COX-2 inhibitors, putting them at risk for hyperkalemia or cardiovascular events.[19] Whereas Lafrance et al suggest that certain NSAIDs may increase the risk of hyperkalemia, not in relation to COX-2 selectivity of the NSAID, but may depend on concurrent use of other agents.[18] Larger studies are needed to confirm these results.

Table 1. Drugs known to induce hyperkalemia [12]

Medication	Mechanism
Drug-inducing transmembrane potassium movement	
• Non-selective beta blockers	Decrease activity of Na^+/K^+-ATPase pump and renin release
• Digoxin intoxication	Inhibition of Na^+/K^+-ATPase pump activity
• Intravenous cationic amino acids	Increase in extracellular potassium shifts
• Mannitol	Hyperosmolality with increase of extracellular potassium shifts
• Suxamethonium	Prolonged depolarization of cell membrane
Drugs that affect aldosterone secretion	
• ACE inhibitors	Blockade of angiotensin II synthesis with decreased aldosterone secretion; impaired delivery of sodium to the distal nephron
• ARBs	Competitive binding to the angiotensin II receptor with decrease of aldosterone synthesis
• Direct renin inhibitors	Inhibition of the conversion of angiotensinogen to angiotensin I with decrease of aldosterone formation
• NSAIDs and COX-2 inhibitors	Decrease of prostaglandin-mediated renin release, renal blood flow, and GFR
• Calcineurin inhibitors	Decrease aldosterone synthesis and Na^+/K^+-ATPase pump activity
Drugs that cause tubular resistance to the action of aldosterone	
• Aldosterone antagonists	Blockade of mineralocorticoid receptors
• Potassium-sparing diuretics	Blockade of luminal sodium channels
• Trimethoprim, pentamidine	Blockade of luminal sodium channels
Potassium-containing agents	
• Salt substitutes and alternatives	Potassium source
• Penicillin G, stored blood products	

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ATPase, adenoisine triphosphatase; COX-2, cyclo-oxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.
Ben Salem C, Badreddine A, Fathallah N, et al. Drug-induced hyperkalemia. *Drug Saf.* 2014;37:677-692.

Managing Hyperkalemia in CKD

Hyperkalemia is not an "all or nothing" event and cannot be established by occasional or solitary determinations of serum potassium. Repetitive serial determinations are mandated to ascertain if the hyperkalemia is sustained, or at times merely constitutes a transient event.[20]

Acute Management

There are several differences in the etiology and management of acute versus chronic hyperkalemia (Table 2). Acute or severe hyperkalemia (serum potassium >6 mmol/L and/or evidence of EKG changes consistent with hyperkalemia) usually require immediate attention, such as cardiac monitoring, acute medical interventions, and possibly emergency dialysis. The goals of acute management are to induce potassium transport into the intracellular space and remove potassium from the body, in order to quickly restore the normal electrophysiology of the cell membrane and prevent cardiac arrhythmia.[1] Details regarding acute hyperkalemia management are described elsewhere.

Table 2. Acute versus chronic hyperkalemia

Acute Hyperkalemia[a]	Recurrent (periodic or persistent) Hyperkalemia[a,b]
• Singular event; requires no ongoing management	• >1 event per year; requires ongoing management
• Caused by abnormal net release of K^+ from cells, often due to trauma, metabolic acidosis, hemolytic states	• Caused by impairment of K^+ excretory process

[a] Alvo M, Warnock DG. Hyperkalemia. *West J Med.* 1984.

[b] Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med.* 2009;169:1156-1162.

Chronic Management

The goal of chronic management of hyperkalemia is to prevent the development or recurrence of hyperkalemia by correcting the underlying disturbances in potassium balance. The first step is to identify and eliminate modifiable causes, such as high potassium intake, hyperkalemia-inducing medications or metabolic acidosis.

As mentioned previously, RAAS inhibitors are associated with an increased risk for hyperkalemia, with no relevant differences found between ACEs or ARBs.[21] For this reason physicians frequently reduce or discontinue RAAS regimens, even though maintaining therapy is beneficial for the preservation of renal function.[22] The following is a suggested approach to enable continuation of RAAS inhibitors in patients at high risk for hyperkalemia:[23]

1. Estimate GFR (≤30 ml/min is the threshold for the likelihood of hyperkalemia).
2. Closely monitor serum potassium levels.
3. Avoid NSAIDs (including COX-2 inhibitors) and herbal remedies.
4. Prescribe a low-potassium diet and avoid potassium-containing salt substitutes.
5. Prescribe thiazide or loop diuretics (loop diuretics are indicated for GFR <30 ml/min).
6. Correct metabolic acidosis with sodium bicarbonate.
7. Start with a low-dose ACE inhibitor or ARB.
8. Monitor serum potassium within one week of ACE or ARB initiation and dose increase to determine dose titration or discontinuation of drug (discontinue if potassium >5.5 mmol/L persists) after interventions above.

Failure to manage hyperkalemia with the above measures may necessitate the need for potassium-binding resins.[1]

Sodium polystyrene sulfonate is a common treatment for acute hyperkalemia, but there is limited data on its safety and efficacy for the chronic management of hyperkalemia. Long-term use of sorbitol-containing sodium polystyrene sulfonate has been associated with colonic necrosis and mucosal injury of the upper gastrointestinal tract.[24,25] Researchers also question the efficacy of sodium polystyrene sulfonate in treating hyperkalemia. Sterns et al found no convincing evidence that sodium polystyrene sulfonate increases fecal losses of potassium in animal or human studies, and no evidence that adding sorbitol to the resin increases its effectiveness in managing hyperkalemia.[26] Conflicting data are reported in a retrospective chart review of 14 CKD patients on RAAS inhibitors treated with daily low-dose sorbitol-free sodium polystyrene sulfonate after episodes of hyperkalemia. In this small case series, no patients developed colonic necrosis or life-threatening events that could be attributed to sodium polystyrene sulfonate and no recurrences of serum potassium ≥6.0 mEq/L were reported.[27] However, larger systematic studies are needed to evaluate the safety and efficacy of sodium polystyrene sulfonate.[1]

Conclusion

Patients with reduced kidney function due to advanced CKD are at chronic risk for hyperkalemia, and as kidney disease progresses and renal function declines, the ability to maintain potassium homeostasis is increasingly impaired. Hyperkalemia occurs frequently in patients with CKD treated with RAAS inhibitors, yet these are the same patients who receive the greatest benefit from this treatment. Currently, therapies indicated for hyperkalemia may have safety and efficacy issues. Therefore, there is a growing need for safe and effective therapies to manage the risk of chronic hyperkalemia. As we learn more about this condition in patients with CKD, we are beginning to better understand the increasing importance of managing hyperkalemia over the long term.

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