Discussion

Clinical evidence shows that increased serum potassium above the normal range in patients with CKD is associated with a higher mortality rate, especially in patients with advanced age and comorbidities (Figures 3). Hyperkalemia is common in patients with CKD due to multiple risk factors. Management strategies should be based on the degree and cause of hyperkalemia. Conventional treatments focus on intermittent management of hyperkalemia and may pose safety risks. New agents in the potassium binder class may allow for improved management of hyperkalemia.

Figure 2. All-Cause Mortality Associated with Serum Potassium Levels in Patients with CKD Not on Dialysis

Multivariable adjusted log hazard ratios (solid line) and 95% confidence intervals (dashed lines) of all-cause predialysis mortality associated with serum potassium levels in the entire study population (n=1,273).


References


Clinical Update on HYPERKALEMIA

Diagnosis, Evaluation, and Treatment Options for Hyperkalemia in Patients with CKD

- Introduction
- Underlying Risk of Hyperkalemia in CKD
- Importance of RAS Blockade in CKD
- Diagnosis and Evaluation of Hyperkalemia
- Benefits and Risks of Conventional Management of Hyperkalemia
- Novel Treatment Options for the Treatment of Hyperkalemia
- Discussion

DECLARATION

Information contained in the National Kidney Foundation educational resources is based upon current data available at the time of publication. Information is intended to help clinicians become aware of new scientific findings and developments. This clinical bulletin is not intended to set out a systematized approach of care and should not be used as such. Readers should use the information in this document as a basis for discussion with healthcare professionals.

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Introduction
Hyperkalemia is a well-known complication of chronic kidney disease (CKD), since the kidneys are the main route for potassium excretion. Hyperkalemia is associated with increases in all-cause mortality and hospitalizations. Treatment with renin-angiotensin-aldosterone system inhibitors (RAASi) is often associated with increased risk of hyperkalemia in patients with CKD, which may lead to dose reduction or discontinuation. While the main objective for treating hyperkalemia is to reduce potassium loss, there have been limited treatment options to accomplish this safely and effectively.

Underlying Risk of Hyperkalemia in CKD
Patients with CKD have a high risk of hyperkalemia, due in part to the effects of kidney dysfunction on potassium homeostasis. Research shows that hyperkalemia is also frequently seen in patients with cardiovascular disease (CVD) who are taking RAASi. Independent predictors of hyperkalemia include advanced age, CVD, diabetes, heart failure, and perihilar vascular disease. Therefore, patients with CKD treated with RAASi, especially at a higher dose or treatment with more than one RAASi, are at very high risk for hyperkalemia. As a result, hyperkalemia is the major barrier against the optimal use of RAASi in patients with CKD.

Importance of RAAS Blockade in CKD
To prevent CKD progression clinical practice guidelines suggest that an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) be used in diabetic adults with CKD and urinary albumin-creatinine ratio 30-300 mg/g (or equivalent), and recommend that an ACE-I or ARB be used in both diabetic and non-diabetic adults with CKD and urinary albumin-creatinine ratio >300 mg/g (or equivalent). However, combination therapy with an ACE-I and ARB should not be used in diabetic or non-diabetic patients with CKD and hypertension since studies show more adverse events, including severe hyperkalemia, kidney dysfunction, and hypotension, without any increase in benefits.

Hyperkalemia and worsening kidney function can develop in some CKD patients after initiating an ACE-I or an ARB since RAASi can lower glomerular filtration rate and can decrease potassium secretion. Therefore, it is important to monitor serum potassium and estimated glomerular filtration rate (eGFR) within several weeks of starting or escalating a RAASi. Discontinuing these drugs is helpful in controlling or treating hyperkalemia, but the disadvantage to doing this is that it increases the risk for kidney disease progression and cardiovascular events.

Diagnosis and Evaluation of Hyperkalemia
The spectrum of hyperkalemia ranges from single episodes of hyperkalemia, sustained hyperkalemia, recurrent hyperkalemia, or severe cases that require dialysis, but what constitutes mild, moderate, or severe hyperkalemia is not consistently defined. Additionally, the toxic effects of a particular potassium concentration depend on the baseline value, the rate of increase in potassium concentration, as well as the acid base status, and serum calcium concentration. Pseudohyperkalemia must also be ruled out. Causes of pseudohyperkalemia include release of potassium from red blood cells in the test tube because of venepuncture trauma or prothrombinase before analysis, and very high platelet counts (>500,000 per microL). Pseudohyperkalemia is never accompanied by symptoms or electrocardiogram changes and must be confirmed by repeat analysis using plasma potassium and not urine potassium. This approach may not be effective in CKD patients with limited GFR.

The cause of hyperkalemia has to be determined to prevent future episodes. Figure 1 shows an etiologic workup of hyperkalemia based on GFR and aldosterone levels.

Benefits and Risks of Conventional Management of Hyperkalemia

Non-Emergent Treatment
Clinicians should individualize therapeutic strategies by considering the degree and cause of hyperkalemia and the urgency of emergent treatment. This therapy only has a moderate effect on hemodialysis patients when given as a single dose, and the duration of effect is about 4-6 hours or more. Concerns about dialysis associated with management of potassium include missed treatments and 2-day interdialytic intervals.

Potassium Redistribution
Treatment of metabolic acidosis with sodium bicarbonate may be beneficial to control elevated serum potassium levels. Sodium bicarbonate infusion can shift potassium from the extracellular to intracellular space by increasing blood pH. The onset of action is 5-10 minutes and the duration of effect is about 2 hours. In general, the efficacy of bicarbonate on hyperkalemia is controversial, and some studies suggest no effect at all. This therapy only has a moderate effect on hemodialysis patients when given as a single dose, and the duration of effect is about 4-6 hours. Concerns about dialysis associated with management of potassium include missed treatments and 2-day interdialytic intervals.

Potassium Excretion
Potassium removal can be achieved by enhanced renal excretion using loop or thiazide diuretics. Diuretics such as thiazides, which inhibit the reabsorption of potassium via Na-K-2Cl cotransporter (NKCC2) in the thick ascending limb (TAL) of Henle’s loop. The onset of action varies and the extent of the effect is until diuresis is present or longer. This approach may not be effective in CKD patients with limited GFR.

Another course of action to increase potassium excretion is ion exchange resins, such as sodium polystyrene sulfonate (SPS), which prevent enteral potassium from being reabsorbed. Oral treatment is more effective with onset of action of 1-2 hours, and lasts for hours to days or more. Concerns about the safety and efficacy of SPS have been raised. A double-blind, randomized clinical trial of 33 mildly hyperkalemia patients with CKD showed that SPS was superior to placebo in reducing serum potassium. In a retrospective chart review of 14 CKD patients, Chenin and colleagues showed that low-dose SPS was safe and effective as a secondary preventative measure for hyperkalemia induced by RAAS in CKD patients with heart disease. In contrast, a systematic review reported that SPS use, both with and without sorbitol, may be associated with fatal gastrointestinal injuries. According to the U.S. Food and Drug Administration (FDA), SPS should be avoided in patients taking medical interventions and occasionally hemodialysis. To reduce this potential risk, prescribers and patients should consider separating SPS dosing from other medications taken by mouth by at least 6 hours.

Potassium Removal
In patients without residual kidney function, maintenance dialysis is the principal means to control potassium balance. The onset of action takes place within minutes and duration of effect is until the end of the dialysis treatment or longer. Treatment duration, treatment frequency, and potassium dialysate concentration have an impact on potassium homeostasis. Daily dialysis or more frequent dialysis could enable more physiologic potassium homeostasis, since more frequent dialysis increases the efficiency of small solute clearance by spending more time dialyzing against high dialysate concentrations.

Emergency Treatment
The life-threatening nature of severe hyperkalemia requires immediate attention, which entails acute medical interventions and occasionally hemodialysis. Details regarding emergency treatment are described elsewhere.

Novel Treatment Options for the Management of Hyperkalemia
New potassium-lowering medications may provide renewed opportunities for improved management of hyperkalemia. A sodium-free, non-absorbed potassium binder for the treatment of hyperkalemia was recently approved by the FDA. A second potassium binder agent, which is insoluble, non-absorbed cation exchanger, is currently under clinical investigation.
Hyperkalemia is a well-known complication of chronic kidney disease (CKD), since the kidneys are the main route for potassium excretion. Hyperkalemia is associated with increases in all-cause mortality and hospitalizations. Treatment with renin-angiotensin-aldosterone system inhibitors (RAASi) is often associated with increased risk of hyperkalemia in patients with CKD, which may lead to dose reduction or discontinuation. While the main objective for treating hyperkalemia is to reduce potassium loss, there have been limited treatment options to accomplish this safely and effectively.

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Pseudohyperkalemia must also be ruled out. Causes of pseudohyperkalemia include release of potassium from red blood cells in the test tube because of venipuncture trauma or prolongation of time before analysis, and very high platelet counts (>500,000 per microliter). Pseudohyperkalemia is never accompanied by symptoms or electrocardiogram changes and must be confirmed by repeat analysis using plasma potassium and ARB should not be used in diabetic non-diabetic patients with CKD and hypertension since studies show more adverse events, including severe hyperkalemia, kidney dysfunction, and hypotension, without any increase in benefits.

Mild to moderate hyperkalemia is usually asymptomatic. Patients with moderate to severe hyperkalemia may complain of palpitations, nausea, muscle weakness, or paresthesia. However, moderate and especially severe hyperkalemia can lead to cardiac arrhythmias and conduction abnormalities, and may be fatal.

Emergency diagnostic workup:
1. Assessment of cardiac function, kidneys, and urinary tract
2. Assessment of hydration status
3. Electrocardiogram (ECG)
4. Elective/etiologic workup
1. Comprehensive laboratory workup
2. Review of medications

The cause of hyperkalemia has to be determined to prevent future episodes. Figure 1 shows an etiologic workup of hyperkalemia based on GFR and aldosterone levels.

Benefits and Risks of Conventional Management of Hyperkalemia

Non-Emergent Treatment: Clinicians should individualize therapeutic strategies by considering the degree and cause of hyperkalemia. For emergent treatment, strategies can be divided into four mechanisms of action: (1) restriction – diet, supplements, herbas, (2) excretion – diuretics or loop diuretics, cation exchange resins; (3) removal – dialysis; and (4) redistribution – sodium bicarbonate (does not affect total body potassium levels). Pseudohyperkalemia must also be ruled out. Causes of pseudohyperkalemia include release of potassium from red blood cells in the test tube because of venipuncture trauma or prolongation of time before analysis, and very high platelet counts (>500,000 per microliter). Pseudohyperkalemia is never accompanied by symptoms or electrocardiogram changes and must be confirmed by repeat analysis using plasma potassium and ARB should not be used in diabetic non-diabetic patients with CKD and hypertension since studies show more adverse events, including severe hyperkalemia, kidney dysfunction, and hypotension, without any increase in benefits.

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Potassium Restriction: The initial management of recurrent hyperkalemia associated with ACE-I or ARB treatment is assessment and restriction of dietary potassium. Potassium restriction has clinical importance, since high dietary potassium intake can counteract the benefits of therapeutic strategies to manage hyperkalemia. Guidelines recommend 2 to 3 grams (approximately 50 to 75 mEq) of potassium per day for patients with a history of hyperkalemia or an eGFR <30 ml/min/1.73m².

Clinicians should base the dietary potassium prescription on the serum potassium level. Many potassium-rich foods such as fruits and vegetables are part of a heart-healthy diet, and research shows that a low-potassium diet may contribute to the burden of cardiovascular disease in CKD patients.

A balanced and practical approach to dietary potassium management includes choosing the sources of potassium which provide the most benefit.

Potassium Excretion: Potassium removal can be achieved by enhanced renal excretion using loop or thiazide diuretics. Diuretics such as thiazides which prevent enteral potassium from being reabsorbed. Oral treatment is more effective with onset of action of 1-2 hours, and the last dose lasting for 24 hours. Concerns about the safety and efficacy of SPS have been raised. A double-blind, randomized clinical trial of 33 mildly hyperkalemia patients with CKD showed that SPS was superior to placebo in reducing serum potassium. In a retrospective chart review of 14 CKD patients, Chernin and colleagues showed that low-dose SPS was safe and effective as a secondary preventive measurement for hyperkalemia induced by RAAS in CKD patients with heart disease. In contrast, a systematic review reported that SPS use, both with and without sorbital, may be associated with fatal gastrointestinal injuries. According to the U.S. Food and Drug Administration (FDA), SPS can be used in other medications administered orally. To reduce this potential risk, prescribers and patients should consider separating SPS dosing from other medications taken by mouth by at least 6 hours.

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Emergency Treatment: The life threatening nature of severe hyperkalemia requires immediate attention, which entails acute medical interventions and subsequently hemodialysis. Details regarding emergency treatment are described elsewhere.

Novel Treatment Options for the Management of Hyperkalemia

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Clinical evidence shows that increased serum potassium above the normal range in patients with CKD is associated with a higher mortality rate, especially in patients with advanced age and comorbidities (Figure 3). Hyperkalemia is common in patients with CKD due to multiple risk factors. Management strategies should be based on the degree and cause of hyperkalemia. Conventional treatments focus on intermittent management of hyperkalemia and may pose safety risks. New agents in the potassium binder class may allow for improved management of hyperkalemia.

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