



KDIGO Controversies Conference on Potassium Management Scope of Work

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Relevance of the topic and the conference

Because of the kidney's central role in potassium homeostasis, potassium disorders are common in patients with chronic kidney disease (CKD) and acute kidney injury (AKI), particularly in those with severe kidney function impairment and those with concomitant comorbidities, such as diabetes, hypertension and heart failure.^{1, 2} Other disorders of the kidney not associated with CKD, including tubular, endocrine and nutritional disorders, may also lead to alterations in serum potassium.³ The consequences of serum potassium disorders can be severe and may include arrhythmias and death; furthermore, disturbances of serum potassium also associate with adverse outcomes even when direct causality is not proven.¹ However, physiologists and other basic scientists have made recent gains in the understanding of intestinal and renal mechanisms in potassium homeostasis in health and disease.^{4, 5} In healthy people, these homeostatic mechanisms enable tight regulation of serum potassium levels across a wide range of dietary potassium intake. Cardiac and kidney outcomes, blood pressure in children and adults, and hyperkalemia are all, however, intricately associated with dietary potassium intake.⁶⁻⁹ As such, dietary intake potassium is a potential therapeutic target for clinically important outcomes, as well as maintaining optimal serum potassium and avoiding the direct adverse outcomes associated with hyper- and hypokalemia. In addition to modification of other medications and dietary advice on potassium intake, pharmacologic potassium supplementation may be indicated in patients with, or at risk of, hypokalemia; and therapeutic interventions such as myocardial stabilizers (calcium), glucose/insulin, bicarbonate, diuretics, and potassium binders may also be warranted in patients with, or at risk of, hyperkalemia.¹⁰

In addition, medications commonly employed in the management of cardiac and kidney diseases, such as inhibitors of the renin-angiotensin-aldosterone system (RAAS), and the use of immunosuppressants, such as calcineurin inhibitors in kidney transplant recipients, may also affect serum potassium levels.^{1, 2, 11-14} As a result, other medications are often prescribed in order to restore abnormal serum potassium levels to a normal range, either acutely or chronically, and maintaining it there.¹⁵⁻²⁰

Patients with CKD or AKI who have abnormal serum potassium are common²¹ and are often referred to nephrologists and pediatric nephrologists. However, specialists from other disciplines such as cardiology, endocrinology, general internal medicine, pediatric/geriatric medicine, transplantation, emergency/intensive care medicine, dietary medicine and pharmacology may in fact be the first point of contact for many patients, with and without CKD or AKI, who have disturbances in serum potassium.^{22, 23}

Beyond the management of potassium of individual patients, the issue of regulating potassium intake also has broad implications on health and food policies.

We plan to examine the evidence base covering five broad areas in potassium management, identify and delineate relevant controversies, offer practical guidance for common patient scenarios, identify knowledge gaps, articulate a research agenda and assess whether formal guidelines could be established for this topic area.

Conference overview

The KDIGO Controversies Conference on Potassium Management will gather a global panel of multidisciplinary clinical and scientific expertise spanning nephrology, cardiology, endocrinology, general internal medicine, pediatric, geriatric and family medicine, transplantation, emergency, anesthesia, pharmacology, dietary medicine, basic science, and epidemiology that will identify key issues in potassium management. The objective of this conference is to identify optimal management of disturbances in serum potassium (both hypo- and hyperkalemia, acutely and chronically) either as a kidney disease itself, or in the context of other kidney diseases, and to describe what is known about diet and health outcomes, including dietary interventions and potassium supplementation. We anticipate that in many of these areas evidence will be lacking or may be derived from non-randomized observations. Still, we hope that the explicit inclusion of a basic science component in the conference will identify potential translational approaches between basic and clinical sciences in both directions. Finally, we will identify knowledge gaps and describe research priorities.

Catherine M. Clase (associate professor of medicine, McMaster University, Hamilton, Canada) and Roberto Pecoits-Filho (professor of nephrology at the School of Medicine, Pontifical Catholic University of Paraná, Curitiba, Brazil) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. Invited participants and speakers will include worldwide experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. We also seek to describe how basic science advances have translated and may translate in the future into advances in patient care. Our task is to explicitly articulate controversies and to critically and rigorously dissect issues to identify the evidence that underlies disagreements. The conference output will include publication of a Controversies Conference Report that will help guide KDIGO and other organizations on potassium management and future research.

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Appendix: Scope of Coverage

Group 1: Potassium Homeostasis

1. What determines the internal distribution of potassium and internal potassium homeostasis? What is the role of aldosterone in mediating potassium uptake by extrarenal tissues? How does organic versus mineral acidosis affect potassium distribution?
2. What is the role of aldosterone in determining systemic potassium homeostasis? Is it primarily to regulate internal balance?
3. What is the special role of the distal convoluted tubule in systemic potassium homeostasis? How does the distal nephron sense potassium and regulate sodium-chloride co-transporter (NCC)? Does increased distal sodium delivery mediate the kaliuretic effects of diuretics? Are there novel channels that might represent future therapeutic targets?
4. How do therapeutic drugs affect these processes? Might knowledge of this new information provide insight as to the relationship between dietary intake and disease such as hypertension?
5. What is known about the diurnal variability in potassium homeostasis? What is the known about clock genes and how they might be involved in potassium secretion at the tubular level and in regulating aldosterone secretion?
6. What is known about the mineralocorticoid receptors particularly at extrarenal sites? This has relevance to new receptor blockers that are said not to cause hyperkalemia.
7. Is there a sexual dimorphism in kidney potassium homeostasis? What might be the clinical relevance of such a difference?
8. What is known about gastric renal signaling with regards to potassium homeostasis? What is the evidence favoring a 'feed forward' versus a 'feedback' system for potassium homeostasis?

9. What is known about potassium transport along the gastrointestinal (GI) tract?
What is known about transport in each segment of the GI tract? Might differences in transport characteristics relate to differences in potassium lowering observed with new potassium-binding drugs? How does fecal potassium excretion change in patients with low glomerular filtration rate (GFR)?

10. How is this transport altered in the setting of advancing CKD? Does the use of inhibitors of the RAAS system affect GI transport and cause increased potassium in the setting of anuric patients on dialysis?

Group 2: Potassium Intake & Epidemiology of Dyskalemias

1. **Dietary potassium.** What are the dietary sources of potassium? Is high dietary potassium part of a healthy or an unhealthy eating pattern (e.g., association with Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diets, Healthy Eating Index)? How does potassium intake vary around the globe (geographical, socioeconomic and cultural differences)? What other nutrients with salutary effects accompany diets high or low in potassium? How much do potassium additives add to daily potassium intake?
2. **Measuring dietary potassium.** How can dietary potassium intake be estimated or measured? What is the reliability and/or pitfalls of 24-hour urinary potassium excretion as a marker of dietary potassium intake in normal subjects and in those with CKD? How strongly do dietary and circulating potassium associate (in general and in persons with CKD)?
3. **Health effects of dietary potassium.** What are the health effects of dietary potassium in persons with normal function **and in persons with CKD?**
 - a. Dietary potassium (alone or in combination with dietary sodium) and blood pressure?
 - b. Dietary potassium (alone or in combination with dietary sodium) and cardiovascular event risk?
 - c. Dietary potassium and other outcomes (e.g., kidney stones, CKD progression, neuropathy, death)?
 - d. Does the source of dietary potassium (i.e., plant vs animal origins) have an effect on the clinical consequences of hyperkalemia?
4. **Dyskalemia incidence and determinants in healthcare.** How common are hyperkalemia and hypokalemia in healthcare (incidence)? What are the patient characteristics, comorbidities and medications that predict the risk of hyper- and hypokalemia (i.e., causes and risk factors)? Presuming kidney function as one of the strongest predictors, at what level of eGFR is renal potassium excretion significantly affected, such as to meaningfully modify circulating potassium?

- 5. Modifying serum/plasma potassium with diet.** Is there any trial/interventional evidence that dietary potassium intake influences serum/plasma potassium in healthy persons or those with CKD? Is there any trial/interventional evidence indicating that changes in dietary potassium intake are associated with improved clinical outcomes (in healthy persons or those with CKD)? What is the evidence behind dietary potassium restriction recommendations for hyperkalemia prevention in CKD?

- 6. Recommended dietary intake of potassium.** What is the current daily recommended intake and the usual potassium intake in the general population? How does this recommendation align with the evidence shown above? How does this recommendation and above evidence align with the classic dietary potassium restrictions for persons with CKD? How large is the problem of potassium additives for persons with CKD?

Group 3: Hypokalemia

Hypokalemia in Patients without End-Stage Kidney Disease (ESKD)

1. How should chronic hypokalemia be investigated in the stable, hypertensive patient?
2. How should chronic hypokalemia be investigated in the stable, normotensive patient?
3. How should acute hypokalemia be investigated in the emergency room? Can an overall treatment algorithm be developed to address Q1, Q2 and Q3?
4. How should hypokalemia in the stable, chronic hypertensive patient be treated (e.g., diet vs supplements vs medications)? At what level is hypokalemia life-threatening? How should acute, severe but undifferentiated hypokalemia be treated?
5. Who should diagnose and treat chronic hypokalemia? Does hypokalemia require specialist referral or can it be managed by primary care physicians? Is there any evidence on when magnesium should be measured and when it should be replaced?
6. Is there a threshold for low potassium levels that should lead to cancelling elective or emergency procedures?
7. Is chronic hypokalemia a risk factor for low GFR or progression of CKD?

Hypokalemia in Patients Treated with Peritoneal Dialysis (PD)

8. What is the prevalence of hypokalemia among PD patients?
9. What are risk factors for hypokalemia among PD patients?
10. What are the consequences of hypokalemia among PD patients, including peritonitis, obstipation, cardiovascular and residual kidney function, and is there any difference by chronicity of the hypokalemia?
11. What are the optimal treatment strategies (e.g., diet vs supplements vs medications)?

Hypokalemia in Patients Treated with Hemodialysis (HD)

12. Does end-of-treatment hypokalemia, or rate of change of serum potassium during dialysis, contribute to morbidity or mortality for patients on HD?

Group 4: Chronic Hyperkalemia

1. How should we define chronic hyperkalemia?
 - a. Potassium threshold (how to define: e.g., > 5 mmol/L, > upper limit of normal, etc.) Should threshold be the same for all patients? (e.g., differences in normal kidney function vs low GFR vs ESKD patients; adults vs. pediatric patients, serum vs plasma; presence of comorbidities and etiology of CKD (e.g., DM, PKD, others); acute vs chronic; acid-base status)
 - b. Absolute number of measurements vs. percent of measurements with abnormal values
 - c. Need for chronic therapy (e.g., binder use; use of co-interventions that incidentally might reduce potassium, such as bicarbonate therapy, loop or thiazide diuretics; alteration in co-interventions that are otherwise indicated, such as RAAS blockade, sacubitril/valsartan, potassium-sparing diuretics?)
2. What is the ideal monitoring strategy for chronic hyperkalemia?
 - a. Frequency of measurements, including after initiating drugs that lead to hyperkalemia or drugs that treat hyperkalemia.
 - b. Methods of measurement (e.g., chemistry lab vs. point-of-care devices vs. need for other novel methods)

How can chronic hyperkalemia be predicted?

- c. Causes and risk factors
 - d. Risk scores for prediction (see also Q3e)
3. What is the significance of chronic hyperkalemia?
 - a. Does chronicity confer protection from cardiovascular or other effects?
 - b. Is there a potassium threshold for cardiovascular or other effects?
 - c. Is there a threshold for high potassium above which should lead to cancellation of elective or emergency procedures?
 - d. Are there characteristics that modify the association of hyperkalemia with outcomes (e.g., CKD, left ventricular hypertrophy, and other electrolyte and acid-base disorders)?
 - e. Can the risk of hyperkalemia be assessed and individualized via use of prediction models, risk scores?

4. What are the risks and benefits for controlling chronic hyperkalemia?
 - a. Impact on outcomes of interest (e.g., all-cause/cardiovascular deaths, malignant arrhythmias, initiation of kidney replacement therapy, hospitalizations, emergency room visits, patient-centered outcomes, satisfaction with diet, quality of life, gastrointestinal side effects)
 - b. Impact on use of otherwise indicated medications such as ACEi/ARBs (see Q1c)
 - c. Cost-benefit considerations
 - d. Patient reported outcomes (e.g., patient perspectives on different strategies to control chronic hyperkalemia)
5. What are the options for management of chronic hyperkalemia? What is the evidence for the effectiveness of these in reducing hyperkalemia? What is the evidence for the effectiveness of following strategies in preventing adverse clinical outcomes?
 - a. Treatment of exacerbating conditions (e.g., metabolic acidosis, hyperglycemia) and use of ancillary treatments with effect on serum potassium (e.g., diuretics)
 - b. Is there any evidence on the safety and effectiveness of allowing a higher than normal range of potassium without treatment (a permissive strategy)?
 - c. Discontinuation of relevant medications, effect of therapeutic compromises (e.g., decreasing dose or discontinuation of RAAS inhibitors in CKD/HF patients)
 - d. Enhancement of renal potassium excretion (e.g., mineralocorticoid agonists)
 - e. Decreasing potassium absorption (e.g., different types of binders)
 - f. Special considerations (e.g., pediatric issues, LMICC issues)
 - g. Is anything known about the patient perspective on different strategies for management of chronic hyperkalemia?
6. Special considerations in ESKD
 - a. Modality considerations (HD vs. PD vs. frequent HD); role of residual kidney function/diuretic use; mass balance vs. electrophysiologic balance
 - b. HD bath composition: e.g., potassium, calcium, magnesium, bicarbonate; gradients vs. absolute values. Discuss specifics for LMICC where flexibility to adjust HD bath composition is limited.
 - c. Monitoring frequency (can also be discussed under Q2) and timing (e.g., pre-, post-, or interdialytic, day of week)
 - d. Liberalization of RAASi/MRA therapy

Group 5: Acute Hyperkalemia and Hyperkalemia in AKI (acute kidney injury)

Epidemiology and etiology

1. What is the prevalence of acute hyperkalemia in AKI and overall (e.g., in emergency department patients)?
2. What are the risk factors for development of acute hyperkalemia in AKI and overall (i.e., medications, comorbidities, etc.)?

Diagnosis

3. What are the optimal methods for measurement of acute hyperkalemia, and their accuracy (e.g., studies on accuracy of point-of-care testing versus laboratory [serology] measurement)
4. Are thresholds to define mild/moderate/severe hyperkalemia useful? Does symptomatology depend on tolerance of patients? If so, what potassium thresholds should be used to define:
 - a. Severe hyperkalemia
 - b. Mild/moderate hyperkalemia

Management

5.
 - a. What arrhythmias are associated with hyperkalemia, and at what potassium threshold?
 - b. What measurement properties from ECG could be used to predict clinically important acute adverse outcomes (e.g., arrhythmia)?
6. What are the indications for use of intravenous calcium/sodium-bicarbonate, insulin and glucose, β -agonists, loop diuretics in hyperkalemia?
7. What ECG changes warrant calcium administration?
 - a. What is the evidence of the effectiveness of intravenous calcium to prevent arrhythmia in hyperkalemia?
8. What is the comparative effectiveness of the various agents for acute management of hyperkalemia to *shift* potassium:
 - b. Timing of onset
 - c. Duration of effect

9. What is the comparative effectiveness of the various agents for acute management of hyperkalemia to *bind/excrete* potassium (including dialysis):
 - d. Timing of onset
 - e. Duration of effect

10. What is the optimal algorithm for the management of hyperkalemia with respect to:
 - f. Setting for management
 - g. Treatment
 - h. Ongoing monitoring (i.e., frequency and duration)
 - i. Evaluation of current medications and potential changes in medications
 - j. Indication for dialysis

11. Is anything known about the patient perspectives on emergency room visits for management of acute hyperkalemia?

Consequences

12. What are the adverse consequences of acute hyperkalemia, and at what potassium thresholds in relation to:
 - k. Cardiovascular effects
 - l. Non-cardiovascular effects

13. Messages for patients (and follow-up doctors) with acute hyperkalemia:
 - m. Information concerning caution with concomitant medication use (e.g., aldosterone-antagonists, NSAIDs, etc.)