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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 common\(^21\) 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.
Roberto Pecoits-Filho (professor of nephrology at the School of Medicine, Pontifical Catholic University of Paraná, Curitiba, Brazil) and Catherine M. Clase (associate professor of medicine, McMaster University, Hamilton, Canada) 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 outline in the Appendix: Scope of Coverage. We also seek to describe how basic science advances have translated and may translate in 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.

References


Appendix: Scope of Coverage

**Group 1: Potassium Homeostasis**

1. 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?

2. 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?

3. 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?

4. 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?

5. What is the role of aldosterone in determining systemic potassium homeostasis? Is it primarily to regulate internal balance?

6. 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?

7. How does calcineurin inhibitor therapy affect these processes? Might knowledge of this new information provide insight as to the relationship between dietary intake and disease such as hypertension?

8. 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?
9. 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.

10. Is there a sexual dimorphism in kidney potassium homeostasis? What might be the clinical relevance of such a difference?
Group 2: Serum Potassium, Potassium Intake & Outcomes in Health and Disease

1. **Dietary potassium.** What are the dietary sources of potassium? Is high dietary potassium part of a healthy or an unhealthy eating pattern (association with Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diets, Healthy Eating Index)? 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 of 24-hour urinary potassium excretion as a marker of dietary potassium intake in normal subjects and in those with CKD? What are the pitfalls of 24-hour urinary potassium excretion (circadian variation, single vs multiple collections, treatment with RAAS blockade and/or long-term potassium-binding agents, etc.)?

3. **Circulating potassium.** How strongly do dietary and circulating potassium associate? Which is the preferred source to quantify potassium in circulation (plasma/serum)? How do these measurements approximate/differ from each other?

4. **Health effects of dietary potassium.** What are the health effects of dietary potassium in persons with normal function and in persons with CKD?
   a. Is there any trial/interventional evidence that dietary potassium intake influences serum/plasma potassium levels potentially leading to hyperkalemia?
   b. What are the effects of dietary potassium (alone or in combination with dietary sodium) on blood pressure?
   c. What are the associations between dietary potassium (alone or in combination with dietary sodium) and cardiovascular event risk?
   d. What are the associations/effects of dietary potassium and other outcomes (e.g., kidney stones, CKD progression, neuropathy, death)?
   e. Does the source of dietary potassium (i.e., plant vs animal origins) have an effect on the clinical consequences of hyperkalemia? Is there any clinical trial evidence indicating that changes in dietary potassium intake are associated with improved clinical outcomes?
5. **Recommended dietary intake of potassium.** Based on the above, what is the current daily recommended intake and the usual potassium intake in the general population? Should recommendations for dietary potassium intake be adjusted in high-risk populations such as in patients with differing severity of CKD?

6. **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 risk of hyper- and hypokalemia (i.e., causes and risk factors)? At what level of estimated glomerular filtration (eGFR) is renal potassium excretion significantly affected such as to meaningfully modify circulating potassium? Does dietary intervention for dyskalemia change serum potassium levels?

7. **Clinical outcomes associated to circulating potassium.** What is the association between serum/plasma potassium and the risk of cardiovascular outcomes or death? At what level of circulation do these associations become clinically important? Does the shape or strength of the association differ in high-risk populations? What other clinical outcomes have been associated with abnormal circulating potassium (e.g., CKD progression, kidney stones)?

8. **Reference/optimal ranges of circulating potassium.** Based on the above, do we need to reconsider current normokalemia ranges (4-5 mmol/L)? Do we need to consider serum- versus plasma-specific thresholds?
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?

Hypokalemia in Patients Treated with Peritoneal Dialysis

6. What is the prevalence of hypokalemia among peritoneal dialysis patients?

7. What are risk factors for hypokalemia among peritoneal dialysis patients?

8. What are the consequences of hypokalemia among peritoneal dialysis patients, including cardiovascular and residual renal function, and is there any difference by chronicity of the hypokalemia?

9. What are the optimal treatment strategies (e.g., diet vs supplements vs medications)?
Group 4: Chronic Hyperkalemia

1. How should we define chronic hyperkalemia?
   a. Potassium threshold (e.g., > 5 mmol/L, > upper limit of normal): Should threshold be the same for all patients? (e.g., differences in CKD vs ESKD patients; serum vs plasma, presence of comorbidities)
   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
   b. Methods of measurement (e.g., chemistry lab vs. point-of-care devices vs. need for other novel methods)

3. How can chronic hyperkalemia be predicted?
   a. Causes and risk factors
   b. Risk scores for prediction

4. 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. Are there characteristics that modify the association of hyperkalemia with outcomes (e.g., CKD, left ventricular hypertrophy, and other electrolyte and acid-base disorders)?

5. What are the risks and benefits 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, reduced use of otherwise indicated medication such as ACEi/ARBs)
   b. Cost-benefit considerations
6. 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. Dietary restrictions: pros and cons
   d. Discontinuation of relevant medications, effect of therapeutic compromises (e.g., discontinuation of RAAS inhibitors in CKD/HF patients)
   e. Enhancement of renal potassium excretion (e.g., mineralocorticoid agonists)
   f. Decreasing potassium absorption (e.g., different types of binders)
7. Special considerations in ESKD
   a. Modality considerations (hemodialysis [HD] vs. peritoneal dialysis 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
   c. Monitoring frequency (can also be discussed under Q2)
Group 5: Acute Hyperkalemia and Hyperkalemia in AKI (acute kidney injury)

Epidemiology and etiology

1. What is the prevalence of acute hyperkalemia in AKI?
2. What is the prevalence of hyperkalemia overall (e.g., in emergency department patients)?
3. What are the risk factors for development of acute hyperkalemia in AKI?
4. What are the risk factors/associated factors for development of acute hyperkalemia overall?
   a. Medications associated with/leading to hyperkalemia?
   b. Co-morbidities associated with/leading to hyperkalemia?
   c. Sociodemographic factors (e.g., age distribution, ethnicity, sex)
5. What are the causes of hyperkalemia in AKI (in both common and rare conditions)?
6. What is the prevalence of concurrent electrolyte disorders (e.g., dysnatremias)?

Diagnosis

7. 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)
8. Value of additional diagnostic tests such as venous blood gas analysis, ECG?
9. What is the evidence on symptoms of hyperkalemia: are further studies indicated?
10. Are thresholds to define mild/moderate/severe hyperkalemia useful? Does symptomatology depends on tolerance of patients? If so, what potassium thresholds should be used to define:
    a. Severe hyperkalemia
    b. Mild/moderate hyperkalemia

Management

11. What arrhythmias are associated with hyperkalemia, and at what potassium threshold?
12. What are the indications for use of intravenous calcium/sodium-bicarbonate, insulin and glucose, loop diuretics in hyperkalemia?
13. What ECG changes warrant calcium administration?
    a. What is the evidence of the effectiveness of intravenous calcium to prevent arrhythmia in hyperkalemia?
14. What is the comparative effectiveness of the various agents for acute management of hyperkalemia to shift potassium:
   a. Timing of onset
   b. Duration of effect
15. What is the comparative effectiveness of the various agents for acute management of hyperkalemia to bind/excrete potassium:
   a. Timing of onset
   b. Duration of effect
16. What is the optimal algorithm for the management of severe hyperkalemia
   a. Setting for management
   b. Treatment
   c. Ongoing monitoring (i.e., frequency and duration)
   d. Evaluation of current medication and potential changes in medication
17. What is the optimal algorithm for the management of mild/moderate hyperkalemia
   a. Setting for management
   b. Treatment
   c. Ongoing monitoring (i.e., frequency and duration)

Consequences

18. What are the adverse consequences of acute hyperkalemia, and at what potassium thresholds:
   a. Cardiovascular effects
   b. Non-cardiovascular effects
19. Messages for patients (and follow-up doctors) with acute hyperkalemia:
   a. Information concerning caution with concomitant medication use (e.g., aldosterone-antagonists, NSAIDs, etc...)