Epidemiology of hyperkalemia: an update

Csaba P. Kovesdy[1,2]

[1]University of Tennessee Health Science Center, Memphis, Tennessee, USA; and [2]Memphis Veterans Affairs Medical Center, Memphis, Tennessee, USA

Hyperkalemia represents one of the most important acute electrolyte abnormalities, due to its potential for causing life-threatening arrhythmias. In individuals with normal kidney function hyperkalemia occurs relatively infrequently, but it can be much more common in patients who have certain predisposing conditions. Patients with chronic kidney disease are the most severely affected group, by virtue of their decreased ability to excrete potassium and because they commonly have additional predisposing conditions that often cluster within patients with chronic kidney disease. These conditions include comorbidities (e.g., diabetes mellitus) and the use of various medications, of which the most important are renin–angiotensin–aldosterone system inhibitors (RAASis). Hyperkalemia is associated with increased risk for all-cause mortality and for malignant arrhythmias such as ventricular fibrillation. The increased risk for adverse outcomes is observed even in serum potassium ranges that are often not considered targets for therapeutic interventions. The heightened risk of mortality associated with hyperkalemia is present in all patient populations, even those in whom hyperkalemia occurs otherwise rarely, such as individuals with normal kidney function.

Kidney International Supplements (2016) **6,** 3–6; http://dx.doi.org/10.1016/j.kisu.2016.01.002

KEYWORDS: chronic kidney disease; epidemiology; hyperkalemia; mortality

Correspondence: *Csaba P. Kovesdy, University of Tennessee Health Science Center, 956 Court Avenue, Room B222, Memphis, Tennessee 38163, USA. E-mail: ckovesdy@uthsc.edu*

Received 18 December 2015; revised 5 January 2016; accepted 5 January 2016

Hyperkalemia is one of the most common acute electrolyte abnormalities, and it usually triggers heightened therapeutic response due to its potential for causing cardiac arrhythmias. Understanding the risk factors underlying the development of hyperkalemia and the outcomes associated with elevations in serum potassium is paramount toward instituting proper preventive strategies, with the ultimate goal being the achievement of improved clinical outcomes. This paper reviews the frequency and the risk factors of hyperkalemia and discusses the clinical consequences of elevated serum potassium levels.

Frequency and predictors of hyperkalemia

Little is known about the true incidence and prevalence of hyperkalemia in the general population, as there are no population-wide studies that examine it. Studies that have examined hyperkalemia in large, unselect samples suggest that its overall incidence and prevalence are relatively low. In a study of 129,076 hospital admissions among elderly patients (aged >65 years) in Ontario, Canada, hyperkalemia diagnosed by ICD10 codes was present in 2.6% of emergency room visits and 3.5% of hospital admissions.[1] The specificity of the hyperkalemia diagnosis was high (99%), but its sensitivity was very low (14.6%), suggesting that the true frequency of hyperkalemia may be higher. Similarly low frequencies of hyperkalemia were reported in 2 large studies performed in US veterans, at 3.2%[2] and 2.6%.[3]

The frequency of hyperkalemia may vary according to the case mix of the studied population. Indeed, studies examining patients with chronic kidney disease (CKD) have reported a significantly higher incidence of hyperkalemia. In a small, single-center study performed using data from an advanced CKD clinic, among 238 patients with a mean estimated glomerular filtration rate (eGFR) of 14.6 ml/min/1.73 m^2, the incidences of serum potassium levels above 5.0 and 5.5 mEq/l were 54% and 40%, respectively.[4] Another study that examined 1277 male veterans with a mean eGFR of 37 ml/min/1.73 m^2 reported serum potassium levels of >5.3 mEq/l in 7.7% of patients at baseline. However, when considering serial measurements of serum potassium, 42% of patients had at least 1 episode of hyperkalemia during a median follow-up of 2.7 years,[5] highlighting the fleeting nature of hyperkalemia. Patients undergoing maintenance dialysis are perhaps the population with the highest incidence of hyperkalemia, due to their frequent complete anuria. In a study of 74,219 maintenance hemodialysis patients, 12.5% had a 3-month averaged serum potassium level of >5.5 mEq/l, suggesting an even higher incidence of single elevations in serum potassium.[6] In

addition to patients with CKD and end-stage renal disease, hyperkalemia is also commonly observed in kidney transplant recipients, with a reported incidence of 44% to 73% in patients maintained on calcineurin inhibitors.[7]

Predictors of hyperkalemia

The principal predictors of higher serum potassium levels in cohort studies were the presence of diabetes mellitus, higher protein intake, lower serum bicarbonate, white race, and, most importantly, lower eGFR,[5,6] and patients at highest risk are those in whom there is clustering of several risk factors.[8,9] In concordance with these findings, a large study performed in 245,808 hospitalized US veterans identified CKD as the most important risk factor of hyperkalemia, along with the use of renin-angiotensin-aldosterone system inhibitors (RAASi). In this study the adjusted incidence rates of hyperkalemia in CKD patients with and without RAASi therapy were 8.22 and 1.77 per 100 patient-months, respectively.[2] Interestingly, RAASis seem to induce hyperkalemia even in patients receiving maintenance dialysis,[10] most likely due to their effect on gastrointestinal potassium secretion.

The importance of RAASis as risk factors of hyperkalemia can be gleaned perhaps more accurately from the results of clinical trials using these agents, in patients both with and without CKD. There are a large number of clinical trials assessing RAASi therapy, and a detailed assessment of these is beyond the scope of this brief review. In general, hyperkalemia tends to be more common in studies that enrolled patients with CKD, especially patients with more advanced stages of CKD, and in patients who received double RAAS blockade versus single blockade. The incidence of hyperkalemia can also vary according to the definition used, with higher incidences reported when using a lower threshold to define hyperkalemia. Considering all these factors, it is not surprising that the incidence of hyperkalemia associated with RAAS blockade varies substantially from clinical trial to clinical trial, ranging from 1.9% to 38.4% in trials conducted among patients with CKD (Table 1).[11–21]

The pivotal role of RAASis in engendering hyperkalemia was summarized by the findings of 2 meta-analyses that examined clinical trials of single versus dual RAAS blockade. One of these identified 33 randomized controlled trials with 68,405 patients, and reported that dual RAAS blockade was associated, among other factors, with a 55% increase in the relative risk of hyperkalemia.[22] The second meta-analysis examined studies conducted in patients with CKD, identifying 59 randomized controlled trials with a total of 4975 participants. This analysis reported that dual RAAS blockade resulted in an increase in serum potassium concentrations and a 3.4% increase in the absolute rate of hyperkalemia.[23]

Compared to observational studies, clinical trials offer several advantages when evaluating the incidence and the risk factors of hyperkalemia: typically, they have few missed measurements of serum potassium, and the protocol-driven nature of serum potassium monitoring lessens bias by indication when detecting hyperkalemia. Furthermore, in clinical trials assessing the effects of RAASis there is a concerted effort to maintain patients on the study intervention, and hence discontinuation rates caused by milder hyperkalemia events (which are probably substantially affecting observational studies) are less common. Due to these considerations, information from clinical trials is more likely to provide an unbiased assessment of the likelihood of hyperkalemia in patients receiving RAASis. However, the select nature of the clinical trial populations may lessen the generalizability of these findings; thus the reported incidence of hyperkalemia, and the RAASi discontinuation rates caused by hyperkalemia, tend to be significantly higher in everyday clinical practice.[24,25]

Table 1 | Hyperkalemia associated with RAASi use in select clinical trials of patients with CKD

Study	Patients on RAASis	Definition of hyperkalemia	Incidence	Discontinuations due to hyperkalemia
RENAAL[13] 2011	675 patients with diabetic nephropathy SCr 1.3–3 mg/dl	>5.0 and >5.5 mEq/l	38.4% (>5.0) and 10.8% (>5.5)	Not reported
IDNT[15] 2001	579 patients with diabetic nephropathy SCr 1–3 mg/dl	>6.0 mEq/l	18.6%	2.1% vs. 0.4% (irbesartan vs. placebo)
J-LIGHT[12] 2004	58 Japanese patients, SCr 2.04 ± 0.48	>5.1 mEq/l	5.2%	Not reported
Benazepril in advanced CKD[20] 2006	226 Chinese patients with advanced CKD, eGFR 37.1 ± 6.3 (group 1) and 26.3 ± 5.3 (group 2)	≥6 mEq/l	1.9% (group 1) and 5.3% (group 2)	3 patients (1.3%) from group 2 (unclear from which treatment arm)
AASK[11] 2009	417 African American patients, eGFR 46.3 ± 13.5	>5.5 mEq/l	7.2%	Not reported
NEPHRON-D[14] 2013	1448 US veterans (99% males) with diabetic nephropathy, eGFR 30–90	>6 mEq/l, or need for emergency room visit, hospitalization, or dialysis	4.4% (losartan + placebo) and 9.9% (losartan + lisinopril)	Not reported

AASK, African American Study of Kidney Disease and Hypertension; CKD, chronic kidney disease; IDNT, Irbesartan Diabetic Nephropathy Trial; J-LIGHT, Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients; NEPHRON-D, Veterans Affairs Nephropathy in Diabetes; RAASi, renin–angiotensin–aldosterone system inhibitor; RENAAL, Reduction of Endpoints in NIDDM (non–insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan; SCr, serum creatinine. Adapted by permission from Macmillan Publishers Ltd: Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. *Nat Rev Nephrol.* 2014;10:653–662.[8]

Outcomes associated with hyperkalemia

Hyperkalemia has been associated with increased mortality in patients with normal kidney function and in patients along the entire spectrum of CKD severity. In a large cohort of patients hospitalized with acute myocardial infarction, serum potassium levels showed a U-shaped association with adverse outcomes, with incrementally higher mortality observed with serum potassium levels above 4.0 mEq/l, and with higher risk of ventricular fibrillation associated with serum potassium levels >5.0 mEq/l.[26] Similar U-shaped associations between serum potassium and long-term mortality were present in patients with non–dialysis-dependent CKD[5,27,28] and in patients receiving chronic hemodialysis.[6,29,30] In the latter studies the lowest mortality was seen in patients with serum potassium levels of approximately 4.0 to 5.0 mEq/l.[5,6,28] In patients receiving peritoneal dialysis, hyperkalemia and serum potassium variability were associated with higher 1-year mortality but not longer-term mortality.[31] The presence of short-term adverse effects associated with hyperkalemia was also described in a study of 245,808 hospitalized US veterans, in whom serum potassium levels >5.5 mEq/l were associated with a significant increase in 1-day mortality,[2] corroborating the hypothesis that the higher mortality associated with hyperkalemia may be caused by malignant arrhythmias.[32,33] This study also compared the relative risk of 1-day mortality associated with hyperkalemia in patients with and without CKD. Interestingly, the risk associated with similar levels of hyperkalemia was much higher in patients with normal kidney function and gradually decreased in those with increasingly severe CKD (odds ratios of 1-day mortality associated with serum potassium >6.0 vs. <5.5 mEq/l in patients with normal eGFR and in those with CKD stages 3, 4, and 5 were 31.64, 19.52, 11.56, and 8.02, respectively). These findings suggest that patients with more frequent episodes of hyperkalemia may have better adaptive mechanisms against its deleterious effects, and also underscore the serious nature of hyperkalemia in patients with normal kidney function, in spite of its rare occurrence in this group.

In addition to general concerns about the association of hyperkalemia with malignant arrhythmias and mortality, special consideration should be given to patients receiving intermittent hemodialysis. Due to the lack of kidney function and the intermittent nature of the renal replacement therapy in these patients, large fluctuations in serum potassium levels occur frequently and are often accompanied by other arrhythmogenic electrolyte and acid–base abnormalities such as hypocalcemia, hypomagnesemia, and metabolic alkalosis.[34,35] All of these changes occur on a background of preexisting cardiovascular disease and left ventricular hypertrophy in a large proportion of dialysis patients,[36] potentially resulting in a high-risk environment for malignant arrhythmias.[37,38] Large-scale, detailed epidemiologic studies linking dynamic intradialytic changes with arrhythmias are lacking, although available observational studies suggest that predialysis hyperkalemia,[6] hypocalcemia,[39] and hypomagnesemia[40] are all individually associated with higher mortality, and low-potassium dialysates are associated with higher risk of sudden cardiac death.[41,42]

In conclusion, hyperkalemia is relatively rare in patients with normal kidney function but much more common among patients with CKD, especially in those exposed to exacerbating factors. Of the factors causing hyperkalemia, lower GFR and treatment with RAASis are perhaps the most significant. Hyperkalemia is associated with higher short-term mortality, and with higher incidence of ventricular fibrillation. Prevention of hyperkalemia in patients who are most prone to its development could thus be beneficial, not only by preventing malignant arrhythmias but also by reaping additional benefits from a more liberal utilization of RAASis in vulnerable patient populations, such as those with CKD.

DISCLOSURE

Publication of this article was supported by Relypsa, Inc. CPK served as a consultant to Relypsa, Inc., Sanofi-Aventis U.S. LLC, and ZS Pharma Inc.; has received research support from AbbVie, Amgen, Janssen Pharmaceutical Companies of Johnson & Johnson, OPKO Health Inc., and Shire; and is the recipient of honoraria from Abbott Nutrition, Relypsa, Inc., Sanofi-Aventis U.S. LLC, and ZS Pharma Inc.

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