Potassium homeostasis is generally well maintained in patients with advanced CKD until the GFR falls below 10–15 ml/min. Loss of nephron mass is counterbalanced by an adaptive increase in the secretory rate of K⁺ in remaining nephrons, such that fractional excretion of K⁺ is increased. In a study of normokalemic patients with stage 4 CKD, the fractional excretion of K⁺ was 126% compared with 26% in normal controls (1). Intravenous administration of amiloride decreased the fractional excretion by 87% in CKD patients compared with a fall of only 19.5% in controls, suggesting amiloride-sensitive renal K⁺ secretion is an important adaptive mechanism in the maintenance of normal K⁺ homeostasis in these patients.

This adaptive response is influenced by the same factors that determine K⁺ excretion in the setting of normal renal function and include adequate distal delivery of Na⁺, normal mineralocorticoid levels, and an intact cortical collecting duct (2). However, limits of adaptation render the CKD patient susceptible to hyperkalemia with even minor perturbations in these factors. Such is the case in patients with diabetes, where decreased mineralocorticoid activity is often an early finding caused by hyporeninemic hypoaldosteronism, or in patients with renal injury primarily directed toward the tubule, as in tubulointerstitial renal disease. In these settings, hyperkalemia often develops with only mild or moderate reductions in the GFR.

In this issue of CJASN, Sarafidis et al. (3) identifies all of the factors known to interfere in K⁺ homeostasis simultaneously present during a single clinic visit in a population of CKD patients. These patients were receiving regular follow-up in a clinic specifically designed and structured to optimize the care of advanced CKD (low-clearance clinic). Despite the focus of the clinic, the mean serum K⁺ concentration was increased at 5.1 mEq/L in 54.2% of patients. In further analysis, hyperkalemia was defined as ≥5.5 mEq/L, a value present in 31.5% of patients. While the average estimated GFR (eGFR) of the entire study population was 14.4 ml/min per 1.73 m², those with hyperkalemia had a significantly lower eGFR compared with those without (14.8 versus 13.5 ml/min per 1.73 m²). Although this difference is quite small in magnitude, presumably at this level of renal function, an inflection point is reached whereby small incremental losses of renal function are accompanied by progressively steeper rises in the steady-state serum K⁺ concentration required to maintain total body K⁺ balance. Similarly, the impact of factors known to adversely affect K⁺ homeostasis are likely to be much greater in magnitude once this level of renal function is reached.

In addition to worse renal function, hyperkalemic subjects had significantly lower serum bicarbonate concentrations (22.5 versus 24.1 mEq/L) and higher urea concentrations (26.3 versus 23.2 mmol/L). These values may be a reflection of the expected biochemical changes accompanying a lower eGFR. Alternatively, a greater degree of acidosis, azotemia, and hyperkalemia could be the result of a slightly higher protein intake. The lower serum bicarbonate concentration may also be explained by the known effect of hyperkalemia to decrease the amount of ammonia availability to act as a urinary buffer, thus impairing renal acidification. In this regard, use of sodium bicarbonate therapy was significantly greater in the hyperkalemic patients, suggesting in prior follow-up that this group had more severe acidosis. Equally as likely, administration of sodium bicarbonate may have been part of an ongoing treatment for hyperkalemia previously noted and still present at the time of analysis. Nevertheless, as the authors emphasize, given the cross-sectional design of the study, cause and effect relationships between these issues cannot be delineated.

Data generated for analysis were taken from clinic visits occurring between mid-March and mid-September. Several seasonal factors may have played an exacerbating role in the high prevalence of hyperkalemia. High ambient temperatures during the peak of summer predispose patients to subtle degrees of both volume depletion and dehydration, potentially decreasing distal Na⁺ and water delivery and thus impairing renal K⁺ secretion. In fact, there was a trend toward lower systolic pressure in the hyperkalemic subjects, perhaps suggesting a subtle degree of volume depletion. Consumption of fresh fruit and vegetables that are enriched in K⁺ are increased during the summer months compared with the winter months (4). It would be of interest to know if the prevalence of hyperkalemia would be lower with a similar analysis conducted during the winter months.

Seasonality also impacts pseudohyperkalemia. The incidence of pseudohyperkalemia increases during the winter when samples are likely to be exposed to lower ambient temperatures during transport, whereas higher ambient temperatures decrease the frequency of this complication (5). The description of specimen handling in the low-clearance clinic suggests a great
deal of attention was focused on minimizing known factors associated with pseudohyperkalemia such as fist clenching during the phlebotomy procedure, application of tourniquets, use of small-bore needles, and transport of specimens by way of a pneumatic tube transport system.

The older age of the study population is another factor likely contributing to the high prevalence of hyperkalemia. Although there was no statistical difference in age between the two groups, the average age of the entire cohort was 66 years. Otherwise healthy elderly subjects excrete K⁺ loads less well compared with young adults, in part because of age-related declines in plasma renin activity and aldosterone, as well as aldosterone resistance at the level of the renal tubule (6). For these reasons, elderly subjects are vulnerable to hyperkalemia when prescribed drugs that further suppress the renin-angiotensin-aldosterone axis or interfere with distal tubular K⁺ secretion, particularly in the setting of CKD.

There was no significant difference in use of antagonists of the renin-angiotensin-aldosterone system (RAAS) between the two groups of patients. Although one would have anticipated greater use in those with hyperkalemia, patients in this group are likely to have been tried and subsequently discontinued on these drugs because of worsening hyperkalemia, thus lessening any potential association at the time of analysis. Despite the advanced nature of CKD, more than one half of the patients in each group were receiving an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker either alone or in combination. It is worth emphasizing that in patients with CKD, the level of renal function should not be the sole determinant of whether these drugs should be initiated or continued. In fact, the very factors that enhance the likelihood of hyperkalemia with RAAS antagonists also identify the subgroup of patients with the highest cardiovascular risk and therefore the greatest opportunity to derive benefit from drug treatment. In a randomized, double-blind study of 224 patients with a serum creatinine concentration of 3.1–5.0 mg/dl, the administration of 20 mg/d of benazepril reduced the composite end point of doubling of the serum creatinine concentration, ESRD, or death compared with placebo (7).

To be sure, successful use of RAAS blockers in patients at increased risk for hyperkalemia requires the type of surveillance and follow-up described in the low-clearance clinic. In this setting, particular attention can be given to measures designed to limit drug toxicity such as reducing dietary K⁺ intake, eliminating K⁺ supplements (including those found in herbal medications), discontinuing prescribed or over-the-counter drugs known to interfere in renal K⁺ excretion (nonsteroidal anti-inflammatory drugs), ensuring effective diuretic therapy, correcting metabolic acidosis, and individualizing drug dosing (8).

In less specialized settings, the frequency with which clinicians monitor patients for development of hyperkalemia is often less than optimal (9). In addition, the discovery of hyperkalemia during laboratory testing does not guarantee appropriate follow-up. In a retrospective observational cohort study of a large primary care practice, 109 instances of hyperkalemia (defined as K⁺ >5.8 mEq/L) were identified in 86 patients (10). Although more than one half of the patients were recalled to the clinic for retesting, 25% of the cases had no repeat testing until they were seen on routine follow-up visits or when they came to the clinic for unrelated issues. Even in the setting of an emergency department, there is often a delay from the time of hyperkalemia discovery until appropriate therapy is instituted (11).

While adaptive mechanisms in the CKD patient may attenuate cardiac toxicity from hyperkalemia, lack of appropriate follow-up remains of particular concern because hyperkalemic events are still associated with an increased risk of death in this population (12). The electrocardiogram in a hyperkalemic subject can progress from normal to ventricular tachycardia and asystole in a precipitous manner (13). Although the study by Sarafidis et al. was not designed to examine the association of hyperkalemia with subsequent morbidity and mortality, the frequency of hyperkalemia in the low-clearance clinic makes a strong argument for early referral and management of these patients in a clinic environment focused on the management of this common electrolyte disorder.

Disclosures

None.

References


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See related article, “Prevalence and Factors Associated with Hyperkalemia in Predialysis Patients Followed in a Low-Clearance Clinic,” on pages 1234–1241.