Renal Potassium Metabolism and Management in Patients with Chronic Kidney Disease

Reviewed by:

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Overview

Chronic kidney disease (CKD) is an important public health challenge and the prevalence of CKD is estimated to be 10 to 14% in the general population;[1,2] these rates are expected to increase modestly over the next 20 years.[3] African Americans, American Indians, Hispanics, and South Asians, specifically, people from developing nations like Pakistan, Sri Lanka, Bangladesh, and India, are at increased risk of having CKD.[4] CKD is chiefly defined as presence of kidney damage or estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 persisting for 3 months or more, regardless of the cause and it is classified into stages according to the level of GFR (Table 1).[2,5]

Table 1: Different stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73m²)
G1	Kidney damage with normal or ↑GFR	≥90
G2	Kidney damage with mild ↓GFR	60-89
G3a	Moderate ↓GFR	45-59
G3b	Moderate ↓GFR	30-44
G4	Severe ↓GFR	15-29
G5	Kidney failure	<15 (or dialysis)

Abbreviation: GFR, glomerular filtration rate.

Adapted from: 1. Vaidya SR, Aeddula NR. Chronic Renal Failure. [Updated 2021 Oct 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535404/. Accessed on 23/05/2022. **2.** Fabjan TH, Hojs R. Stroke and renal dysfunction. *Eur J Intern Med*. 2014;25(1):18-24

CKD is associated with increased risk of renal failure, cardiovascular disease (CVD), and all-cause mortality.[1] Cardiovascular mortality is about twice as high in patients with stage 3 CKD and three times higher at stage 4 compared to individuals with normal kidney functions. Surprisingly, in patients with mild to moderate CKD, the rate of mortality is much higher due to cardiovascular causes than due to ESRD.[6-8]

Usually, majority of patients with CKD require replacement treatments including hemodialysis, peritoneal dialysis, and kidney transplantation, among which hemodialysis are the most common replacement modalities.[4] Besides, various international guidelines for management of CKD recommend lifestyle modification, such as dietary sodium reduction. Nonetheless, the rationale for sodium reduction among patients with CKD is predicated on the antihypertensive-effect of a low sodium diet rather than a direct association between high sodium diet and the development of CKD.[1]

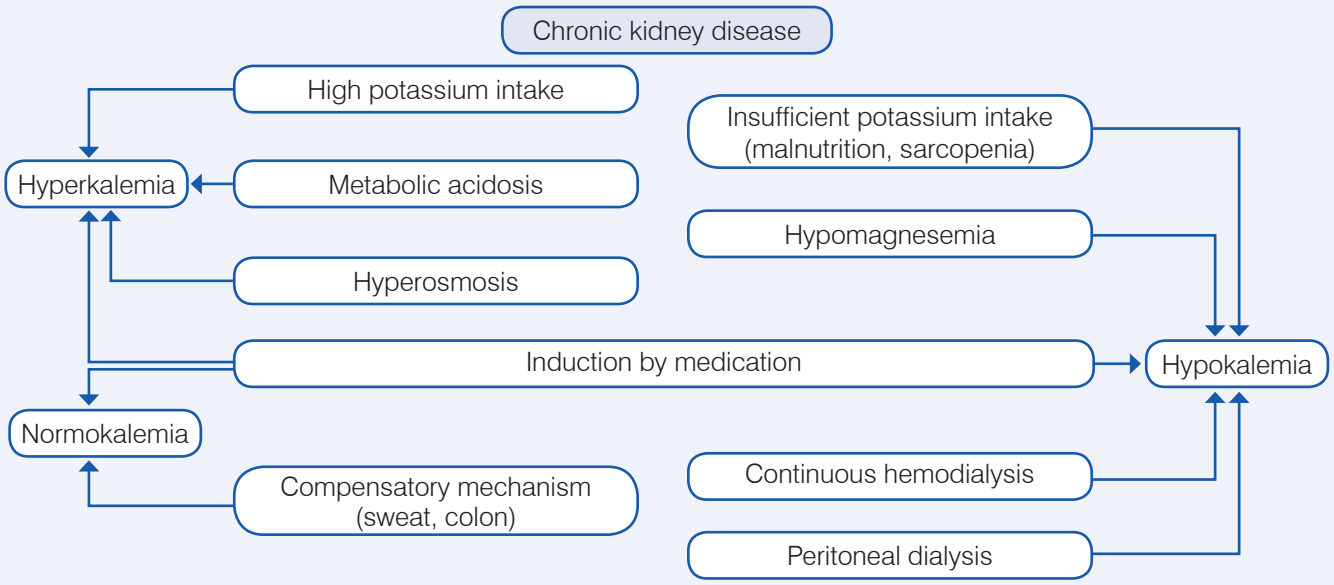
Since hypertension is a major risk factor for CKD, dietary risk factors for elevated blood pressure (BP), such as high sodium and low potassium intakes, may also act as risk factors for the development of CKD. Therefore, prevention and treatment of hypertension may be considered among the key targets in the prevention and reduction of CKD progression.[1,9]

Potassium Metabolism in Renal Disease

Patients with CKD often present with serum potassium abnormalities, likely induced by a variety of factors.[10,11] However, since potassium metabolism is regulated largely by the kidneys, most cases of hyper- and hypokalemia are attributed to renal mechanisms (Figure 1).[11]

Earlier evidences have reported hypokalemia to be a less frequent event in CKD patients undergoing hemodialysis.[12] Furthermore, hyperkalemia is more well-recognized as a complication in patients with CKD as compared to hypokalemia. However, recent data has shown that the prevalence rates of both hypokalemia and hyperkalemia are comparable (14-20% and 12-18%, respectively). Both hyperkalemia and hypokalemia are associated with similarly increased risks of death, CVD, and hospitalization. Moreover, some evidence suggests an association between hypokalemia and progression of CKD. Findings of a study revealed that patients with a serum potassium <4 mEq/L

Figure 1: Factors affecting potassium metabolism in chronic kidney disease



Adapted from: Yamada S, Inaba M. Potassium Metabolism and Management in Patients with CKD. *Nutrients*. 2021;13(6):1751.

had a 69% higher ESRD risk compared with those with normokalemia, whereas ESRD risk was not higher for those with potassium ≥5.5 mEq/L.[10]

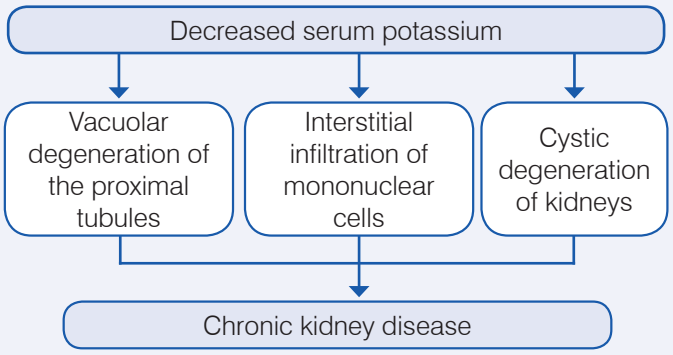
Hypokalemia and Chronic Kidney Disease

Hypokalemia is one of the most common electrolyte disturbances in daily clinical practice and it refers to serum potassium concentrations <3.5 mEq/L. It usually arises from an overall potassium deficiency in the body or when serum potassium shifts into the intracellular compartment.[13]

Although hypokalemia occurs infrequently in patients with end-stage renal failure due to reduced potassium excretion, it can occur in individuals with reduced dietary intake because the concentration of potassium in standard hemodialysis fluid is set at 2–2.5 mEq/L and standard peritoneal dialysis fluid does not contain potassium. In patients with CKD, a serum potassium level below 3.5–4.0 mEq/L is considered a significant risk factor for total mortality, with emerging reports of sudden cardiac death of hemodialysis patients due to hypokalemia.[11]

The causes of hypokalemia can be broadly classified into increased intracellular transport, decreased potassium uptake, and potassium loss (renal and extrarenal), with renal loss being the most frequent. As for extrarenal potassium loss, that can be caused by prolonged poor dietary intake, severe vomiting, and diarrhea. Hypokalemia also leads to a variety of tubulointerstitial pathologic and functional changes. As for pathologic changes, those include vacuolar degeneration of the proximal tubules, interstitial infiltration of mononuclear cells, and renal cysts. Chronic hypokalemia due to an eating disorder is a risk factor leading to end-stage renal failure (Figure 2).[11]

Figure 2: Effect of decreased serum potassium on CKD pathogenesis



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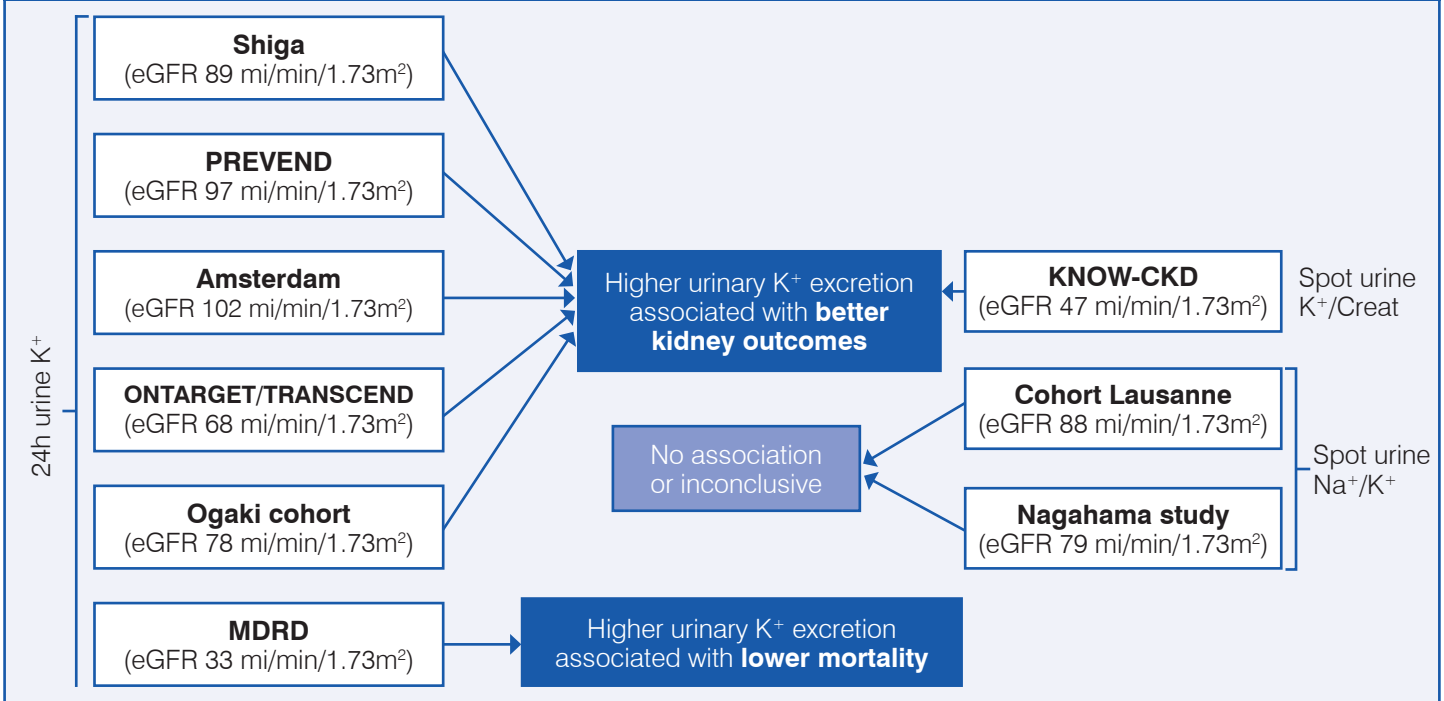
Potassium Supplementation and Chronic Kidney Disease

Accumulating evidence suggests that dietary potassium may be beneficial for patients with CKD. Epidemiological studies have shown that a higher urinary potassium excretion (as proxy for higher dietary potassium intake) is associated with lower BP and lower cardiovascular risk, as well as better kidney outcomes. Majority of these studies have shown that diets rich in potassium were associated with better kidney outcomes in the overall population or patients with early-stage CKD (Figure 3).[14]

Figure 3: Summary of cohort studies analyzing the association between urinary potassium or urine sodium/potassium (as proxy for dietary intake) and renal outcomes

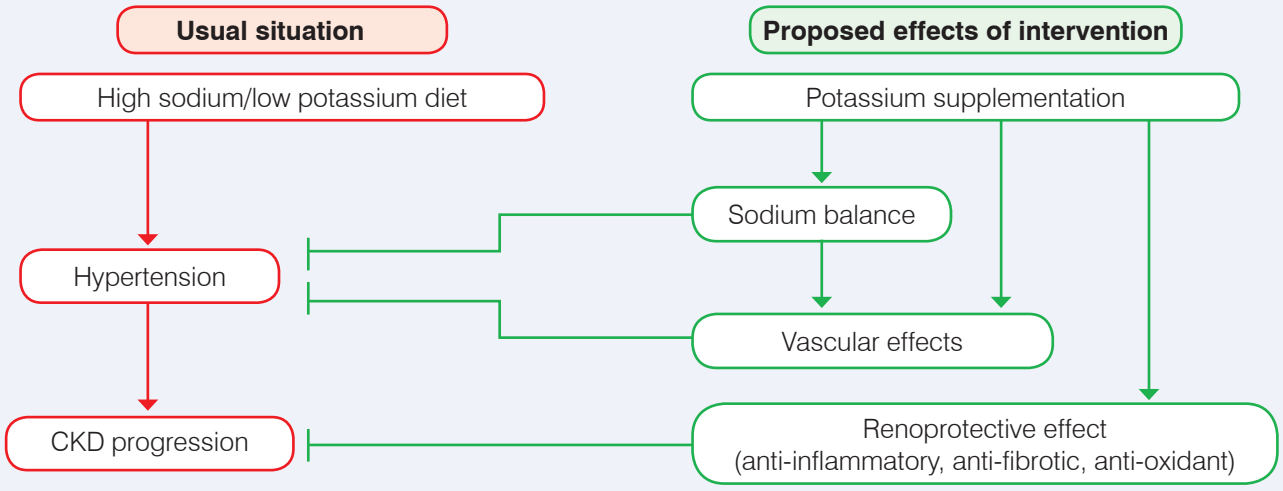


Adapted from: Wei KY, Gritter M, Vogt L, *et al*. Dietary potassium and the kidney: lifesaving physiology. *Clin Kidney J*. 2020;13(6):952-968

Elevated serum potassium has protective effects on the kidneys by promoting salt excretion and reducing renal function by acidosis due to suppression of NH3 production.[11] Besides lowering the BP, increasing dietary potassium intake can exert BP-independent effects on the kidney by relieving the deleterious effects of a low potassium diet (inflammation, oxidative stress and fibrosis) (Figure 4).[14,15]

As mentioned earlier, hemodialysis is one of the most common replacement approaches in patients with CKD.[4] Supplementation of oral potassium preparations is preferred for correcting the hypokalemia in patients undergoing hemodialysis. Management strategies usually depend on the severity of the disorder; however, mild-to-moderate cases are usually treated with oral supplements. Oral potassium

Figure 4: Proposed pathways for the beneficial effects of potassium supplementation in CKD



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supplementation is the preferred treatment modality in maintenance hemodialysis patients unless there is severe hypokalemia associated with respiratory or cardiac instability; in such cases, intravenous potassium administration may be required. Among the oral supplements, potassium chloride is the most commonly used agent for replacement therapy. Other preparations such as potassium citrate may be administered in patients with coexisting metabolic acidosis.[16] The rationale for the use of potassium chloride as the preferred agent for correcting low serum potassium levels is that most cases of hypokalemia are accompanied by metabolic alkalosis and require chloride repletion. Administration of potassium chloride causes distal nephron chloride reabsorption in exchange for bicarbonate secretion, thus correcting the metabolic alkalosis. As metabolic alkalosis is associated with enhanced renal potassium clearance, its correction with potassium chloride can further help in restoring normal serum potassium levels. These mechanisms contribute to the fact that correction of serum potassium concentration occurs faster with potassium chloride as compared to other preparations. Careful monitoring of serum potassium levels during potassium replacement is necessary to prevent hyperkalemia in patients undergoing maintenance hemodialysis.[16,17]

Potassium Chloride Replacement Therapy

A serum potassium concentration in the range of 4-5 mEq/L is associated with the lowest risk of major adverse clinical outcomes in patients with CKD. Therefore, strategies that maintain serum potassium concentration in this range might contribute to improved clinical outcomes.[10]

Potassium chloride is the preferred salt for replacement therapy in hypokalemia. This is because majority of the cases of hypokalemia present with concomitant chloride depletion and have a need for chloride repletion. A dosage of 40 mmol of potassium chloride given every 3 to 4 hours for 3 doses is considered favorable. Usually, 20 mEq/h of potassium chloride has been found to increase serum potassium concentration by an average of 0.25 mEq/h. In addition to the treatment of hypokalemia, oral potassium chloride can also aid in prevention of hypokalemia.[17-19]

Conclusion

Potassium is an electrolyte crucial for maintenance of body functions; however, a narrow range of optimal concentration makes it extremely vulnerable to metabolic abnormalities, particularly in cases of renal function impairment. Therefore, managing potassium levels in patients with CKD entails accurate determination and careful monitoring on an individual basis. Hypokalemia is a major complication in patients with hemodialysis as it is associated with potential cardiovascular side-effects and faster loss of kidney function. In patients with CKD, a serum potassium concentration in the range of 4-5 mEq/L is associated with the lowest risk of major adverse clinical outcomes. Therefore, strategies that maintain serum potassium concentration in this range might contribute to improved clinical outcomes. Oral potassium supplementation is the preferred treatment modality for correction of low potassium levels. Among the oral supplements, potassium chloride is the most commonly used agent for replacement therapy since correction of serum potassium concentration occurs faster with potassium chloride as compared to other preparations.

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