Potassium Balances in Maintenance Hemodialysis: Role of Potassium Supplementation

Reviewed by:

Dr. Shriniwas Ambike
MBBS, MD Nephrology
Nephrologist and Transplant physician
Jehangir Hospital, Pune

Overview

Although the surfacing of hemodialysis has enabled nephrologists to enhance the quality-of-life of the individuals, potassium balance is one of the dangers that accompany end-stage renal disease (ESRD) cases along with an increase in mortality rates. The annual mortality rates of hemodialysis patients in India have been estimated to be 9-13%.[1,2] According to data available, evidence had shown significant adverse impact of dyskalemia on life expectancy in patients receiving hemodialysis; wherein both hypo- and hyperkalemia can cause potentially fatal cardiac arrhythmias and sudden death.[3] Kidney plays a vital role in maintaining potassium ([K]) homeostasis by excreting excess potassium; potassium excretion depends primarily on renal excretion (about 90%) and to a lesser extent (about 10%) on colonic excretion. However, it is the non-renal excretion of [K] and dialytic [K] removal, that plays a significant role in maintaining potassium balance in ESRD patients on hemodialysis because of markedly decreased renal excretion of potassium.[4] Hypokalemia and a low potassium level, defined as serum potassium levels of <3.5 mmol/L and <4.0 mmol/L, respectively, occurring in 2% and 13% of patients receiving hemodialysis, respectively is an independent prognostic factor of hemodialysis. Malnourishment, metabolic alkalosis, potassium binders, and low potassium dialysate are risk factors for hypokalemia.[3] Furthermore, hypokalemia is associated with increased risk of ventricular arrhythmias in patients with underlying cardiac diseases and a higher incidence of ventricular arrhythmias; the incidence increases from 9 to 40% during hemodialysis.[4]

Potassium Homeostasis: Pathophysiology of Hypokalemia

Maintenance of the total body potassium content and plasma potassium level within narrow limits in regards to wide variations in dietary potassium intake is denoted as potassium homeostasis. It involves two concurrent processes: external and internal; the former regulates renal potassium excretion to balance potassium intake, minus extrarenal potassium loss and correction for any potassium deficits. Internal potassium regulation controls the asymmetric distribution of total body potassium with the greater part (approximately 98%) intracellular and only a small fraction (approximately 2%) extracellular.[5]

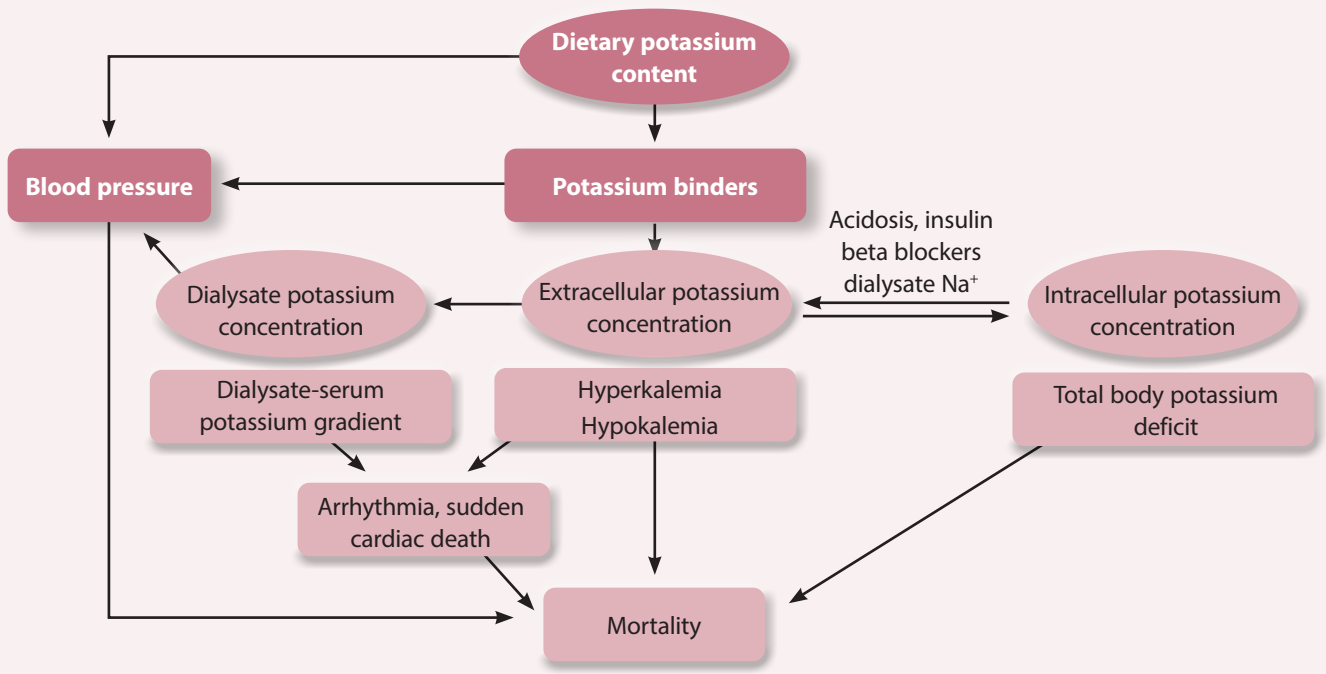
In hemodialysis patients, hypokalemia is induced by a range of factors affecting internal and external potassium balance that include diminished potassium uptake by cells because of uremia, acidosis, drugs, hormonal alterations, retarded renal excretion, lower dietary intake, and high stool fractional excretion of potassium. These factors affect the potassium movement and its redistribution between the intracellular and the extracellular compartments.[4,6] Moreover, serum potassium concentrations decrease rapidly in hemodialysis patients as they are dialyzed against a 1.0-2.0 mEq/L potassium bath. Thus, chronic hypokalemia may give rise to several long-term complications in patients undergoing hemodialysis.[7] Figure 1 shows potassium balance during hemodialysis and how it may affect mortality.[8]

Effects of Hypokalemia in Maintenance Hemodialysis Patients

It is the degree and duration of serum potassium decrease that determines the severity of clinical manifestations of hypokalemia; symptoms are not evident until serum potassium is <3.0 mEq/L, or the patient has a potentiating factor, such as the use of digitalis, in which patients have a predisposition to arrhythmias.[9]

Though majority of hypokalemic patients are asymptomatic, symptoms can range from mild muscle weakness to serious sudden cardiac death. Symptoms of hypokalemia are categorized according to the system affected and may include renal, neurological, gastrointestinal, endocrine, respiratory and cardiovascular manifestations (Table 1).[2,9,10] These effects of hypokalemia have been linked with increased mortality in hemodialysis patients.[11]

Figure 1: Potassium balance during hemodialysis and its association with mortality[8]



Consequences of hypokalemia may lead to alterations in the resting membrane potential of cardiac and neuromuscular cells. Disturbance in cardiac rhythm leading to cardiac arrest is the most serious and potentially fatal effect of hypokalemia. Patients with underlying cardiac disease or patients taking digitalis are more prone to develop this effect. Furthermore, in patients with cardiovascular disease, hypokalemia is associated with arrhythmia and increased mortality. Moreover, it has been contemplated that hypokalemia is associated with higher mortality rates due to malnutrition; which can be related to hypokalemic effect on smooth muscles of the gastrointestinal tract, leading to decreased appetite and even paralytic ileus, which is possibly related to malnutrition.[11]

Evidence has also shown that there is an increased post-dialysis mortality in patients undergoing maintenance hemodialysis.[12] Also, chronic hypokalemia in patients with renal impairment may contribute to renal cyst formation, parenchymal fibrosis, CKD progression and increased risk of developing ESRD over time, thereby indicating the importance of early detection and prudent management of the condition.[13]

Management of Hypokalemia in Hemodialysis Patients

The cornerstone treatment strategy for hypokalemia in maintenance hemodialysis patients is to balance the levels of potassium and also to ameliorate the risk of associated comorbidities. Potassium supplementation is the key to the therapy and is usually achieved with the oral administration of potassium preparations. The four vital goals in managing hypokalemia include:

- To minimize the potassium losses
- To replenish the potassium stores
- To evaluate potential toxicities
- To determine the underlying cause to prevent recurrences.

Furthermore, prevention of cardiac rhythm disturbances and serious neuromuscular weaknesses are aimed while treating hypokalemia in maintenance hemodialysis patients.[4] Supplementation of potassium is the mainstay of treatment for managing hypokalemia in patients on maintenance hemodialysis and is usually achieved with the oral administration of potassium preparations, available as: potassium chloride, potassium phosphate, potassium bicarbonate and potassium citrate (Figure 2).[4,10] Based on the severity of the disease, route of administration is determined. Oral route is the preferred route of administration, except in severe hypokalemia cases which is associated with respiratory or cardiac instability, and hence IV route is preferred route.[6,9]

Potassium chloride

For the treatment of mild and moderate hypokalemia, oral potassium chloride at 20-80 mEq/day in divided doses is preferred.[6] Potassium chloride has been used preferably in hypokalemic patients, especially in those with accompanying chloride responsive metabolic alkalosis as its administration is associated with chloride reabsorption in distal nephron in exchange for bicarbonate secretion,

Table 1: Clinical manifestations of hypokalemia[2,9,10]	
Cardiovascular System	• **ECG changes:** Prominent U wave, flattened or inverted T waves, ST segment depression, T and U wave fusion giving appearance of QT interval prolongation with severe hypokalemia • **Arrhythmias:** Atrial tachycardia with or without block, premature ventricular contraction, ventricular tachycardia and/or fibrillation, torsades de pointes • Worsening hypertension • Sudden death
Kidney	• Polyuria due to decreased concentrating ability • Hypokalemic nephropathy • Chloride-depletion metabolic alkalosis • Increased risk of nephrolithiasis
Neuromuscular	• Cramp • Myalgia • Rhabdomyolysis • Weakness • Paralysis • Paresthesia
Gastrointestinal tract	• Altered gastrointestinal motility (nausea, vomiting, constipation, paralytic ileus) • Worsening of hepatic encephalopathy
Genitourinary tract	• Hypotonic bladder
Respiratory System	• Respiratory acidosis secondary to respiratory muscle weakness
Endocrine System	• Insulin resistance and impairment in insulin release

thus correcting the metabolic alkalosis. As metabolic alkalosis is associated with enhanced renal potassium clearance, correction of the metabolic alkalosis with potassium chloride can help in replenishing serum potassium concentration to normal. Therefore, correction of serum potassium concentration is generally faster with potassium chloride than with other salts.[10]

A multicenter, open-label, prospective, randomized controlled trial[14] was done in 167 adult hypokalemic patients on dialysis. Patients were randomized to receive either titrable dose of oral potassium chloride to maintain serum potassium of 4-5 mEq/L (intervention group) or conventional potassium supplementation (reactive supplementation when serum potassium is <3.5 mEq/L) for 52 weeks. Findings of the study were:

- There was an increase in serum potassium levels in the intervention group (increased to 4.36 ± 0.70 mEq/L) as compared with 3.57 ± 0.65 mEq/L in the group treated conventionally
- Median time to first peritonitis episode was significantly longer in the intervention group as compared to conventional treatment group (223 vs 133 days)
- Lower hazard of peritonitis was seen in intervention group

In conclusion, protocol-based oral potassium treatment appears to be safe and may reduce the risk of peritonitis in hypokalemic dialysis patients.

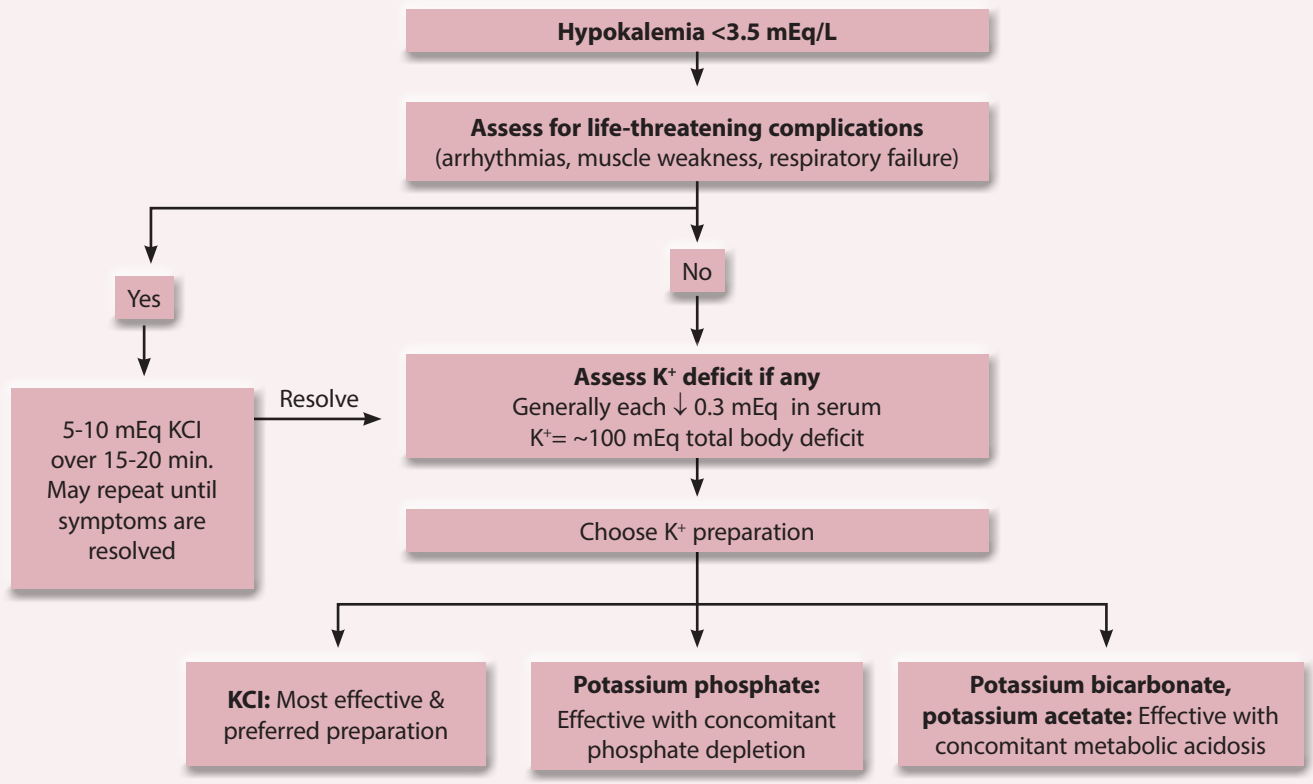
Potassium citrate

Potassium citrate is preferred in patients with hypokalemia and metabolic acidosis.[11] Potassium citrate, while being an effective urinary alkalinizer, also displays an acceptable tolerability profile as well.[15,16] It neither neutralizes the gastric juice nor alters the digestion.[17] Other advantages of potassium citrate include high palatability, pleasant taste, and tolerable even on prolonged use, which makes it suitable to be considered as a first line urine alkalizing agent.[18] Further, it is preferred over sodium containing salts, such as sodium bicarbonate or sodium citrate, as the latter may result in excessive sodium load and thus has to be carefully used in patients with hypertension, heart failure, edema, renal impairment, eclampsia, or hyperaldosteronism.[6,18]

Conclusion

Although the surfacing of hemodialysis has enabled nephrologists to enhance the quality of life of the individuals, potassium balance is one of the dangers that accompany end-stage renal disease cases along with

Figure 2: Managing principles for hypokalemia[10]



an increase in mortality rates. Hypokalemia and a low potassium level, defined as serum potassium levels of <3.5 mmol/L and <4.0 mmol/L, respectively, occurring in 2% and 13% of patients receiving hemodialysis, respectively is an independent prognostic factor of hemodialysis. The cornerstone treatment strategy for hypokalemia in maintenance hemodialysis patients is to balance the levels of potassium and also to ameliorate the risk of associated comorbidities. Supplementation of potassium is the mainstay of treatment for managing hypokalemia in patients on maintenance hemodialysis and is usually achieved with the oral administration of potassium preparations. Potassium chloride and potassium citrate are among the most valuable as well as well-tolerated agents which significantly normalize the potassium levels.

References

1. Prabha DR, Prasad G. Predictors of mortality among patients on maintenance hemodialysis. *J NTR Univ Health Sci.* 2016;5:255-60.
2. Sanghavi S, Whiting S, Uribarri J. Potassium balance in dialysis patients. *Semin Dial*. 2013;26(5):597-603.
3. de Rooij ENM, Dekker FW, Le Cessie S, Hoorn EJ, de Fijter JW, Hoogeveen EK; Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD) Study Group. Serum Potassium and Mortality Risk in Hemodialysis Patients: A Cohort Study. *Kidney Med.* 2021;4(1):100379.
4. Choi HY, Ha SK. Potassium balances in maintenance hemodialysis. *Electrolyte Blood Press*. 2013;11(1):9-16.
5. Gumz ML, Rabinowitz L, Wingo CS. An Integrated View of Potassium Homeostasis. *N Engl J Med.* 2015;373(1):60-72.
6. Kim HW, Chang JH, Park SY, Moon SJ, Kim DK, Lee JE, Han SH, Kim BS, Kang SW, Choi KH, Lee HY, Han DS. Factors associated with Hypokalemia in Continuous Ambulatory Peritoneal Dialysis Patients. *Electrolyte Blood Press*. 2007;5(2):102-10.
7. Hwang JC, Wang CT, Chen CA, Chen HC. Hypokalemia is associated with increased mortality rate in chronic hemodialysis patients. *Blood Purif.* 2011;32(4):254-61.
8. Wouda RD, Vogt L, Hoorn EJ. Personalizing potassium management in patients on haemodialysis. *Nephrology Dialysis Transplantation.* 2021;36(1):13–18.
9. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect.* 2018;7(4):R135-R146.
10. Asmar A, Mohandas R, Wingo CS. A physiologic-based approach to the treatment of a patient with hypokalemia. *Am J Kidney Dis.* 2012;60(3):492-7.
11. Lee S, Kang E, Yoo KD, Choi Y, Kim DK, Joo KW, Yang SH, Kim YL, Kang SW, Yang CW, Kim NH, Kim YS, Lee H. Lower serum potassium associated with increased mortality in dialysis patients: A nationwide prospective observational cohort study in Korea. *PLoS One.* 2017;12(3):e0171842.
12. Tsuyoshi O, Miho K, Shingo F, Tadao A, Shunichi F. Postdialysis Hypokalemia and All-Cause Mortality in Patients Undergoing Maintenance Hemodialysis. *CJASN.* 2019; 14(6):873-881.
13. Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. *Kidney Dis (Basel).* 2017;3(4):136-148.
14. Pichitporn W, Kanjanabuch T, Phannajit J, Puapatanakul P, Chuengsaman P, Parapiboon W, Treamtrakanpon W, Boonyakrai C, Matayart S, Katavetin P, Perl J, Praditpornilpa K, Eiam-Ong S, Tungsanga K, Johnson DW. Efficacy of Potassium Supplementation in Hypokalemic Patients Receiving Peritoneal Dialysis: A Randomized Controlled Trial. *Am J Kidney Dis.* 2022;80(5):580-588.e1.
15. Zuckerman JM, Assimos DG. Hypocitraturia: Pathophysiology and Medical Management. *Rev Urol.* 2009;11(3):134-144.
16. Whitmore KE. Complementary and Alternative Therapies as Treatment Approaches for Interstitial Cystitis. *Rev Urol.* 2002;4(Suppl 1):S28-S35.
17. Sweetman S. Martindale: The Complete Drug Reference. Edition 37;London:pharmaceutical press; 2011.
18. Sakhaee K, Nicar M, Hill K, Pak CY. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stoneforming salts. *Kidney International*. 1983;24:348-352.