95905_Revision_Auto_Edited.docx

WORD COUNT 4435
TIME SUBMITTED 07-JUN-2024 10:17AM
PAPER ID 109486426

Name of Journal: *World Journal of Transplantation*

Manuscript NO: 95905

Manuscript Type: MINIREVIEWS

Disorders of Potassium Homeostasis after Kidney Transplantation

Abstract

Disturbances of potassium balance are often encountered when managing kidney transplant recipients (KTR). Both hyperkalemia and hypokalemia may present either as medical emergencies or chronic outpatient abnormalities. Despite the high incidence of hyperkalemia and its potential life-threatening implications, consensus on its management in KTR is lacking. Hypokalemia in KTR is also well-described, although it is given less attention by clinicians compared to hyperkalemia. This article discusses the etiology, pathophysiology and management of both types of potassium disorders in KTR. Once any emergent situation has been corrected, treatment approaches include correcting insulin deficiency if present, adjusting non-immunosuppressive and immunosuppressive medications, eliminating or supplementing potassium as needed, and dietary counselling. Although commonly of multifactorial etiology, ascertaining the specific cause in a particular patient will help guide successful management. Monitoring KTR through regular laboratory testing is essential to detect serious disturbances in potassium balance since patients are often asymptomatic.

Key Words: Balance; Dialysis; Hyperkalemia; Hypokalemia; Kidney; Metabolism; Potassium

Core Tip: Both hyperkalemia and hypokalemia are usually asymptomatic in kidney transplant recipients but can lead to serious morbidity, so regular monitoring is needed. Since medications are a common cause, dose adjustments or medication changes are often required.

INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for end-stage kidney disease (ESKD)[1]. Successful KT improves quality of life and survival for many ESKD patients compared to long-term dialysis[2]. Among the complications faced by kidney transplant recipients (KTR), an increased susceptibility to hyperkalemia occurs compared to non-

KTR with similar kidney function[3]. Hyperkalemia increases patient morbidity and possibly cardiovascular mortality, and also adds to healthcare expenses by delaying discharge from hospital whether it occurs during the first or subsequent admissions. The prevalence of hyperkalemia in KTR is estimated to be between 25% and 44%[4]. Hyperkalemia can occur at any time in the post-transplant period. Many clinicians intervene when plasma or serum potassium levels exceed 5.5 mmol/L[5]. Despite the high incidence of hyperkalemia and its potential life-threatening implications, consensus on its management in KTR is lacking. Hypokalemia in KTR is also well-described, although it is given less attention by clinicians compared to hyperkalemia. This article discusses the pathophysiology and management of both types of potassium disorders in KTR. Hyperkalemia is defined here as a plasma potassium ion (K+) concentration exceeding 5 mmol/L and hypokalemia as K+ less than 3.5 mmol/L.

For this narrative review, we surveyed the published English literature using PubMed and MEDLINE (1965-2024) using the search terms *potassium, hyperkalemia, hypokalemia,* and *transplantation* to identify the most relevant articles for inclusion. Criteria for selection included relevance to kidney pathophysiology and clinical practice.

HYPERKALEMIA

Etiology

The major causes of post-transplant hyperkalemia are summarized in Table 1. Frequently prescribed post-transplant medications, including calcineurin inhibitors (CNI), sulfa antibiotics, and antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), and beta blockers are common etiologic culprits for post-transplant hyperkalemia even in KTR with a well-functioning graft. Simultaneous kidney-pancreas transplant recipients with bladder drainage may have an incidence of up to 73%[4]. Hyperkalemia may be more frequent in KTR with delayed graft function. Dietary non-adherence when present along with other

risk factors[5], transcellular K+ shifts from uncontrolled diabetes or intraoperative mannitol use, and metabolic acidosis are other common causes[6].

Pathophysiology

Potassium Homeostasis: Potassium is the predominant intracellular cation, with a concentration of 140–150 mmol/L intracellularly and 3.5–5 mmol/L extracellularly. Serum K+ is slightly elevated compared to plasma K+ due to K+ release from clotted red blood cells. A high intracellular K+ concentration maintained by Na/K-ATPase establishes the resting membrane potential essential for cellular excitability and contraction. K+ enters the body through diet, and kaliuresis results in K+ leaving the body, with a lesser amount leaving *via* the colon. Since the ratio of intracellular to extracellular K+ concentration substantially impacts the resting membrane potential, a stable plasma K+ concentration is essential to optimal cellular function[7].

Mannitol: Acute hyperkalemia in the early post-transplant phase is not uncommon. Mannitol is often used during the KT operative procedure as an osmotic diuretic to improve renal blood flow and reduce warm ischemia related injury[8], although its use is controversial[9]. Mannitol can cause intraoperative hyperkalemia[10], even leading to cardiac arrest[11]. Possible mechanisms include hemolysis from its hypertonicity, acidosis from dilution of bicarbonate as a consequence to the desired temporary intravascular volume expansion, and solvent drag[11]. Hypertonic mannitol also decreases sodium reabsorption if significant native kidney function is present, and there may be dilution of plasma proteins, decreased blood viscosity, release of prostaglandins and atrial natriuretic factor, and renin-angiotensin system inhibition[12]. Mannitol through solvent drag moves water and K+ out of cells, and this movement is exacerbated by concomitant hyperglycemia. Mannitol use remains popular however due to a reduced incidence of delayed graft function and acute kidney injury [13].

Insulin Deficiency: Dietary K+ is normally absorbed by the gastrointestinal tract, then rapidly taken up by muscle and liver cells, facilitated by insulin and beta-2 adrenergic receptors. Most K+ load is excreted renally, being tightly regulated predominantly in

the connecting tubule and cortical collecting duct. Aldosterone, along with adequate distal water and sodium delivery are crucial determinants to renal K+ secretion. Dietary K+ is not a significant determinant of plasma K+ unless renal function is impaired[14]. Sodium reabsorption *via* the epithelial sodium channel (ENaC) establishes the electrical gradient required for K+ secretion. Hyperkalemia can thereby result from insulin deficiency, inorganic metabolic acidosis, diminished glomerular filtration rate (GFR), and reduced distal sodium delivery. In KTR, hyperkalemia can however result from type 4 renal tubular acidosis (RTA) from calcineurin inhibitors (CNI), even in the absence of any of these other risk factors[15]. Insulin deficiency or resistance can hinder the translocation of K+ to the intracellular compartment, resulting in post-transplant hyperkalemia along with hyperglycemia, especially in KTR with diabetes[16].

Non-Immunosuppressive Medications: Medications contribute significantly to hyperkalemia even in KTR with well-functioning grafts. Trimethoprim in trimethoprim/sulfamethoxazole (TMP/SMX) being structurally similar to amiloride and triamterene, competitively blocks ENaC, diminishing the lumen-negative voltage in the cortical distal nephron (CDN) critical to K+ secretion[17]. This mechanism holds true for pentamidine, also used for prophylaxis against Pneumocystis jirovecii pneumonia (PJP)[18]. Depressed GFR, hyporeninemic hypoaldosteronism, and a low flow rate in the CDN from intravascular volume depletion combine to affect the luminal fluid's osmole content and potentially increase trimethoprim concentration in the CDN, enhancing further its ability to block ENaC. ACE inhibitors and ARB are popular drugs for KTR[19], but increase plasma K+ due to impaired K+ secretion[20]. Heparin is commonly administered to hospitalized patients. KTR with poor mobility may receive subcutaneous heparin, and complications such as deep vein thrombosis and pulmonary embolism often require intravenous (IV) heparin. Although not specifically described in KTR, both unfractionated and low-molecular-weight heparin selectively reduce aldosterone synthesis, and decrease the number and affinity of adrenal angiotensin II receptors[21,22]. Severe hyperkalemia is more likely when kidney function is impaired or when ACE inhibitors, ARB, or potassium-sparing diuretics are used concomitantly.

Beta-blockers are also associated with hyperkalemia due to plasma K+ shifts[23] although the evidence for persistent or severe hyperkalemia is low[6].

Calcineurin Inhibitors: CNI (tacrolimus and cyclosporine) are a mainstay of post kidney-transplant immunosuppression, often being prescribed for the life of the allograft. CNI are a well-described cause of hyperkalemia, with up to 32% of KTR receiving cyclosporine experiencing hyperkalemia[24]. Tacrolimus may portend a greater risk than cyclosporine[25]. The sodium chloride cotransporter (NCC)-regulatory kinase (with no lysine) WNK4 is increased[26]. WNK kinases exert their effect on NCC by phosphorylating members of the sterile (STE)-20 superfamily of serine/threonine kinases, specifically the STE20-related proline-alanine-rich-kinase (SPAK) and the oxidative stress response kinase type 1 (OSR1), and they in turn phosphorylate and activate the NCC. WNK4 is the major regulatory kinase of SPAK/OSR1-NCC pathway. CNI increase phosphorylation of the NCC in the first part of the DCT (DCT1), thereby maintaining its active state[26]. WNK4 in turn is degraded by binding to Kelch-like 3 (KLHL3)[27] and Cullin 3 (CUL3) proteins as part of a E3 ubiquitin ligase complex. The proper functioning of this ubiquitin ligase complex requires the dephosphorylation of KLHL3, a process mediated by protein phosphatase 3 (PP3 or calcineurin). CNI maintain KLHL3 in its phosphorylated, inactive state, consequently reducing the degradation of WNK kinases. Increased NaCl reabsorption by NCC leads to volume expansion to suppress renin and aldosterone release, reducing the number of open ENaC units in the luminal membranes of principal cells in the aldosterone-sensitive distal nephron. Atrial natriuretic peptide (ANP) released in response to volume expansion suppresses renin release and inhibits hyperkalemia-induced aldosterone secretion. Diminished NaCl delivery to the aldosterone sensitive distal nephron (ASDN) decreases the ability to generate a lumen negative voltage. These kinases also cause ROMK endocytosis from the luminal membrane of principal cells. Mineralocorticoid resistance[28,29] combined with metabolic acidosis leads to impaired K+ secretion and hyperkalemic type 4 RTA. CNI also induce afferent renal arteriolar vasoconstriction and exacerbate AKI[30], reducing K+ elimination further. Chronic

downregulation of nuclear factor of activated T cells (NFAT) from long-term CNI use leads to renal vasculature hyalinosis, tubular atrophy, interstitial fibrosis, and glomerular thickening[26], all of which associate with worsened renal allograft function[31].

Obstructive Uropathy: A type 4 RTA may also occur in patients with obstructive uropathy, a condition to which KTR are prone. In this situation, Type 4 RTA results from a defect in H+ and K+ secretion in the distal nephron, similar to chronic interstitial nephritis, rather than from aldosterone deficiency[32]. Reduced renal blood flow causes ischemia, and T lymphocytes as well as macrophages enter the interstitium. These cells produce transforming growth factor β, leading to progressive fibrosis and reduced glomerular filtration if the obstruction is left unchecked. Patients with type 4 RTA including KTR are often asymptomatic with a normal urine output, but the associated hyperkalemia can still be severe.

Clinical Manifestations

Although hyperkalemia often presents asymptomatically, untreated hyperkalemia can quickly cause ascending muscle weakness, parasthesias, decreased reflexes, and ultimately cardiac arrhythmias and fatality[6]. The specific consequences of untreated hyperkalemia to KTR have not been well described. Nonetheless, insights from CKD populations underscore the importance of maintaining normal serum K+ concentrations[33]. Most post-transplant programs perform regular blood testing as part of their routine monitoring, resulting in a greater likelihood of detecting hyperkalemia compared to other CKD patients as a result of ascertainment bias. However, KTR may present to transplant clinics or emergency departments in the context of acute illness, at which time hyperkalemia may be detected as part of their admission screening. All new KTR should be admitted to either an intensive care or step-down unit with available continuous cardiac rhythm monitoring in the immediate post-operative period, due to the risk for hyperkalemia.

The detection of hyperkalemia warrants urgent assessment, even though symptomatic manifestations directly attributable to the hyperkalemia are rare. After excluding pseudohyperkalemia from sample hemolysis[34], which is typically commented in the laboratory report but is not uncommon in KTR who are subject to poor vascular access. It is important to assess if an emergency situation is present through electrocardiogram (ECG) changes, such as peaked T-waves, widened QRS complexes, prolonged QT-interval, and hidden p-waves[35,36]. Considerable variability exists regarding the plasma K+ concentration required to induce cardiac toxicity. Increased K+ conductance shortens the action potential duration leading to sinus arrest, sinus bradycardia, ventricular fibrillation, and asystole[36].

Management

Cardiac Membrane Stabilization: An ECG can often be quickly obtained in the hospital immediately post-transplant or even in the outpatient setting, although some outpatient clinics may prefer to send their patients immediately to an emergency department. Successfully handling hyperkalemia revolves around safeguarding against arrhythmias. Intravenous calcium gluconate is commonly used if ECG changes consistent with hyperkalemia are present. Even mild ECG changes can rapidly progress to dangerous arrhythmias. Emergency treatment can be considered even when ECG changes are absent, usually when the K+ is around 6.5 mmol/L, and especially when hypocalcemia, acidemia, and/or hyponatremia are also present. For unclear reasons, patients on chronic hemodialysis may tolerate serious hyperkalemia without adverse effects[37], but it is unclear if this benefit exists in KTR despite their long-standing CKD. Calcium directly antagonizes the adverse myocardial effects that hyperkalemia induces, reducing the threshold potential of cardiac myocytes and thereby stabilizing the membrane potential. This beneficial effect does not depend on a change in serum K+. A typical dose of calcium gluconate is 1,000 mg (or 10 mL of a 10% solution) infused over 2 to 3 minutes under cardiac monitoring. If EKG changes persist, the dose can be repeated after 5 minutes.

Shifting Potassium into Cells: If the serum K+ exceeds 7.0 mmol/L, shifting K+ into cells can proceed simultaneously, but shifting K+ is usually the second step in managing emergent situations. IV short-acting insulin promotes K+ shift into the intracellular space. Due to a fear of hypoglycemia, IV glucose is often administered prior to IV insulin, but great care must be taken to stabilize the cardiac cell membrane first when IV glucose is given prior to administering insulin, since the transient hyperglycemia can shift more K+ out of cells and cause a potentially fatal arrhythmia. Some authors suggest using 5 units or 0.1 units/kg with 50g dextrose as a bolus, or administering dextrose as an infusion[38]. Patients should be monitored closely for hypoglycemia for at least 4 h. Sufficient evidence from randomized trials of therapy are lacking[39]. Pre-transplant hyperkalemia predicts post-transplant hyperkalemia[40], so the plasma K+ should be kept under 5.5 mmol/L before transplant surgery, if necessary through an extra session of dialysis. Maximizing the K+ gradient through a lower dialysate K+ content and increasing the dialysis blood flow rate[41] may enhance K+ clearance.

Beta-2 adrenergic receptor agonists enhance activation of Na-K ATPase pumps, shifting K+ intracellularly. Nebulized salbutamol is easily available, effective and dose-dependent, acting within 30 minutes and peaking at 60 minutes. Salbutamol at a dose of 10 or 20 mg can reduce plasma K+ by about 1 mmol/L for 2 h, and is considered effective therapy[42]. Although data specific to KTR are lacking, side effects include tremor, tachycardia, and headaches, which may confound tacrolimus-related side effects. Another measure to consider is administering sodium bicarbonate. Elevating extracellular bicarbonate levels increases cellular K+ uptake, although bicarbonate infusion is generally considered ineffective[43,44] especially in isolation, and risks sodium overload and pulmonary edema. Oral sodium bicarbonate (3-5g/day) in non-emergent situations may be considered adjunctive when concurrent with metabolic acidosis, but there is sparse evidence for this maneuver in KTR.

Potassium Elimination: Once the cardiac cell membrane is stable and K+ has shifted intracellularly, focus can then shift to eliminating excess K+ from the body. Dialysis is

efficient therapy for hyperkalemia[39], so the availability of dialysis support at the time of transplant surgery must be ensured. Vascular access for dialysis may not be immediately available in KTR transplanted preemptively, and for KTR on peritoneal dialysis (PD), inadvertent nicking of the peritoneal membrane may cause leaking of dialysate and necessitate placing a hemodialysis catheter, rather than continuing PD. At the other end of the transplant life spectrum, patients with failing renal allografts may also require urgent dialysis for hyperkalemia in the absence of viable access, such as from a clotted or immature fistula or graft. Removing K+ *via* the transplanted kidney by a loop diuretic such as furosemide or bumetanide is often employed, even in the early post-transplant setting. Some evidence of existing or establishing kidney function such as measurable urine output is required however, as well as an adequate blood pressure. Loop diuretics may be used in chronic hyperkalemia in normovolemic or hypervolemic patients, in addition to adding other drugs such as thiazides[45].

Fludrocortisone promotes potassium secretion and can help lower plasma K+ concentration[46]. Evidence for efficacy in KTR is limited primarily to case reports. At a dose of 0.1 mg/day, both acute and chronic hyperkalemia can be effectively managed[47]. Fludrocortisone may address tacrolimus-induced aldosterone resistance, with normokalemia achievable quickly[48]. Since fludrocortisone causes fluid retention, it may be most useful in early post-transplant patients who are also intravascularly volume depleted.

The gastrointestinal tract can also be a useful route for K+ removal. Commonly used agents in the current era include patiromer and sodium zirconium cyclosilicate (ZS-9), with the use of sodium polystyrene sulfonate (SPS) largely abandoned despite its efficacy with sorbitol, due to concerns over the possibility of intestinal ischemia and thrombosis, leading to bowel necrosis[49]. Patiromer is being used with increasing comfort in KTR based on published clinical experiences[50]. Patiromer is an organic potassium-binding polymer employing calcium as the exchange ion especially in the colon, and so is not particularly helpful in the acute setting. Gastrointestinal side effects are usually limited, but patiromer can cause hypomagnesemia and affect the

bioavailability of other drugs[6]. However, there is no clear evidence to-date of interference with immunosuppressive medications. ZS-9 facilitates exchange of H+ and Na+ for K+ and NH4+ throughout the gastrointestinal tract, acting one hour after ingestion, and so may be more useful in the acute setting both for KTR[51] and hospitalized patients more generally[52]. There is no appreciable impact on tacrolimus pharmacokinetics[53]. However, cost remains a concern for using both patiromer and ZS-9.

Adjusting Medications: Besides administering new therapies such as those outlined above, adjusting existing medications through discontinuation, switch, or dose reduction is also an important part of hyperkalemia management. Trimethoprim and antihypertensive agents are often the first targets of change for clinicians. While trimethoprim/sulfamethoxazole (TMP/SMX) remains the standard for PJP prevention, alternative agents such as dapsone or atovaquone are equally effective. Hyperkalemia is not necessarily dependent on the dose of trimethoprim[54]. Thrice weekly TMP/SMX in the first post-transplant year is a safe and an effective regimen to prevent PJP[55]. Antihypertensives affecting the renin–angiotensin–aldosterone system are typically avoided early post-transplant but may be warranted later for patients with cardiovascular comorbidities. Beta blockers are not typically discontinued early post-transplant unlike ACEi or ARB. Adding patiromer or ZS-9 might facilitate continuing these medications over the long term. In cases of mild to moderate hyperkalemia, such medication adjustment can help normalize serum K+ levels without the need for total discontinuation.

Changes in immunosuppressive medication are rarely pursued in response to hyperkalemia given the effectiveness of all the preceding measures, since immunosuppressive medication changes might increase risks for new side effects or even acute rejection. Similarly, the risk of hyperkalemia is typically not considered when selecting de-novo immunosuppressive regimens. Nonetheless, some studies report a lower incidence of hyperkalemia with drugs such as sirolimus[56,57],

everolimus[58], and belatacept[59,60], so switches made for this indication are at theoretically feasible.

Dietary Modification: Dietary modification can be a very useful adjunct in managing post-transplant hyperkalemia. All KTR with a measured plasma or serum K+ greater than 5.0 mmol/L should receive dedicated dietician counseling, customized to their ethnic and sociocultural background, and be given appropriate dietary information sheets. Repeated consultations might be required if hyperkalemia persists. Such counseling may help prevent visits to the emergency department for severe hyperkalemia.

HYPOKALEMIA

Hypokalemia is characterized by a plasma K+ concentration below 3.5 mmol/L, and can be life-threatening when below <2.5 mEq/L. In an outpatient population undergoing laboratory testing, nearly 14% exhibit mild hypokalemia. The incidence of hypokalemia is less than that of hypomagnesemia in stable outpatient KTR[61]. Additionally, about 20% of hospitalized patients generally are found to have hypokalemia, but only a small fraction of these instances is clinically significant.

Etiology and Pathogenesis

Hypokalemia can be experimentally induced[62], but is rarely seen in healthy subjects. The kidney can minimize potassium excretion to 5 to 25 mmol per day in the presence of total body potassium depletion[62]. Reducing potassium intake to 20 mmol per day therefore seldom results in significant hypokalemia. Enhanced insulin availability promotes K+ entry into skeletal muscle and hepatic cells by increased Na-K-ATPase pump activity, such as when exogenous insulin is administered in severely hyperglycemic states even when there is initial normokalemia or hyperkalemia. However, hypokalemia arising from insulin overdose is rare. Furthermore, endogenous insulin release in response to carbohydrate intake, as observed in refeeding syndrome or administration of dextrose may contribute to hypokalemia. IV potassium is therefore

administered using a saline solution rather than dextrose[63-65]. Elevated beta-adrenergic activity and exercise-induced catecholamine surges are some other causes[66,67], though these events are not specific to KTR. Hypokalemia is more severe in patients with pre-existing hypokalemia receiving diuretic therapy[68], and is dose-dependent. Increased gastrointestinal losses due to vomiting, diarrhea, laxatives, or nasogastric tube drainage lead to metabolic alkalosis and substantial urinary potassium losses. Diarrhea from any cause as well as secretions from villous adenomas can be associated with relatively high K+ concentrations due to hyperchloremic metabolic acidosis.

Urinary K+ excretion, mainly regulated by principal cells in the connecting tubule and cortical collecting tubule, is a key determinant of K+ balance. Increased mineralocorticoid activity creates an electronegative lumen that facilitates passive K+ secretion into the tubular lumen through potassium channels such as ROMK. Hypokalemia may result from polyuria when intravascular volume depletion enhances aldosterone secretion. Reduced activity of K+ secretory channels potentially mediated by increased angiotensin II activity may explain the inconsistent occurrence of hypokalemia in primary aldosteronism[69].

The use of both sirolimus[69,70] and everolimus[71] has been associated with hypokalemia. Hypokalemic nephropathy can occur, with tubular vacuolization, reversible with sirolimus discontinuation[72]. Mammalian target of rapamycin (MTOR), which sirolimus inhibits, plays a role in tubular epithelial cell integrity and regeneration[72]. Although an incidence of up to 50% has been reported with everolimus in antitumour regimens[73], the incidence is likely in the 5-10% range in KTR[70]. Hypokalemia can occur in KTR due to native renal artery stenosis[74]. Primary aldosteronism may be unmasked by KT[75]. The incidence of hypokalemia in KTR receiving thiazide diuretics can approach 30%[45]. Patients receiving hemodialysis against a low K+ bath, those on peritoneal dialysis prior to receiving their transplant, and those requiring plasmapheresis, for example as part of treatment for antibody-mediated rejection, may be at greater risk for hypokalemia. Low dietary potassium

intake from failure to unlearn dialysis restrictions post-transplant may lead to hypokalemia, usually when combined with factors.

Clinical Manifestations

Hypokalemia-induced ECG alterations include ST segment depression, diminished T wave amplitude, and increased U wave amplitude, particularly in lateral precordial leads V4 to V6, and QT interval prolongation. Skeletal muscle weakness and atrial fibrillation are sometimes noted. Prolonged hypokalemia impairs urine concentrating ability, and can lead to hypokalemic nephropathy and elevations in blood pressure, as well as decreased phosphate reabsorption. Hypokalemia also reduces insulin secretion and can contribute to glucose intolerance and thiazide-associated diabetes, although whether hypokalemia contributes to the incidence of post-transplant diabetes (PTDM) is unknown.

Management

Immediate Measures: Use of balanced solutions rather than normal saline as replacement fluids can be considered preventative in the early post-transplant period since concerns regarding hyperkalemia are minimal[76,77]. The cause for hypokalemia often evident from factors like vomiting, diarrhea, or diuretic therapy. If serum K+ is below 2.5 mEq/L and there is severe muscle weakness or ECG changes, then prompt treatment is indicated. Continuous cardiac monitoring is recommended if there are ECG changes linked to hypokalemia, or underlying cardiac conditions that increase arrhythmia risk in the context of hypokalemia[78,79]. Treating the underlying cause of gastrointestinal losses, reducing or discontinuing diuretics, and supplementing dietary potassium intake are some basic measures to be undertaken. Hospital units will typically strictly guide the constitution of IV K+ formulations and their permissible rate of administration.

Potassium Replacement: Continued replacement over days is required to address the marked total body potassium deficit, taking care to prevent transient hyperkalemia

during repletion. Serum K+ should be quickly raised to a safe level, followed by slower deficit replacement. Although there are no guidelines specific to KTR, the replacement rate should account for the patient's GFR. For patients with uncontrolled PTDM and hyperkalemia, insulin therapy and fluid replacement should lower serum K+ towards the deficit-appropriate level, and potassium supplementation can begin when the serum K+ is 4.5 mEq/L or lower. For patients presenting with hypokalemia, insulin therapy is delayed until potassium is above 3.3 mEq/L[80,81].

Long-Term Supplementation: For long-term management, a variety of oral potassium supplements in different dosage strengths are available, with the choice depending upon the presence of metabolic acidosis or hypophosphatemia[81]. Slow-release tablets have better tolerance but carry a low risk of gastrointestinal intolerance especially with microencapsulated preparations[82]. Other options include replacing loop or thiazide diuretics with potassium-sparing diuretics such as amiloride or triamterene, and adding aldosterone antagonists such as spironolactone or eplerenone if renal K+ wasting is present, although careful monitoring is required. Magnesium deficiency is frequently associated with hypokalemia, and if unrecognized can result in refractory hypokalemia. Reduced intracellular magnesium prevents inhibition of ROMK channels, increasing potassium secretion[83]. While magnesium deficiency alone is insufficient to cause hypokalemia, IV or oral supplementation can be considered if hypomagnesemia is noted. Not all transplant programs routinely monitor post-transplant serum magnesium concentrations, but they should be measured if hypokalemia is noted.

Dietary Modification: Dietary intervention for hypokalemia may be less effective due to the predominantly potassium phosphate or potassium citrate form in dietary potassium[84]. Increased fruit intake may have limited impact as well since a large consumption would be required[85]. However, providing dietary advice can still be considered as a part of the overall nutrition plan (Table 3), since hypokalemic patients are often undernourished as well. Food literacy and social support are particularly relevant[86]. Unfortunately there have been no clinical trials of dietary intervention in the context of electrolyte management in KTR.

All KTR should undergo regular laboratory testing that includes serum electrolyte measurement. On example of such a monitoring strategy includes daily testing until hospital discharge, twice weekly to the end of month three, weekly to the end of month six, every two weeks to the end of month nine, monthly to the end of year two, and then once every three months thereafter, with added testing performed as necessary. Some transplant programs monitor patients remotely, so a clear action plan for incidentally detected emergencies should be developed in advance. A brief summary of some common preventative and management strategies for disorders of K+ homeostasis in KTR is provided in Table 4.

CONCLUSION

Both hyperkalemia and hypokalemia are important electrolyte disturbances encountered when managing KTR, and can present either as medical emergencies or chronic outpatient abnormalities. Experience from the general population and patients with CKD in native kidneys is typically extrapolated to pathophysiology in the transplant kidney and thereby to KTR. Although commonly of multifactorial etiology, ascertaining the specific cause in a particular patient will help guide successful management. Regular monitoring through laboratory testing is essential to detect serious disturbances in K+ metabolism since patients are often asymptomatic. Transcellular shifting, potassium removal or supplementation, and longer-term measures including adjusting immunosuppressive and non-immunosuppressive medications as well as dietary counseling all play a role in ensuring optimal post-transplant patient outcomes.

95905_Revision_Auto_Edited.docx

ORIGINALITY REPORT

5%
SIMILARITY INDEX

PRIMARY SOURCES

1	d197for5662m48.cloudfront.net Internet	47 words — 1%
2	daneshyari.com Internet	47 words — 1%
3	Vaishnavi Pochineni, Helbert Rondon-Berrios. "Electrolyte and Acid-Base Disorders in the Renal Transplant Recipient", Frontiers in Medicine, 2018 Crossref	30 words — 1%
4	G. V. Ramesh Prasad, Manisha Sahay, Jack Kit-Chung Ng. "The Role of Registries in Kidney Transplantation Across International Boundaries", Seminars in Nephrology, 2022 Crossref	16 words — < 1%
5	id.scribd.com Internet	16 words — < 1%
6	pdfs.semanticscholar.org Internet	14 words — < 1%
7	www.science.gov Internet	14 words — < 1%
8	www.coursehero.com Internet	13 words — < 1%

9	Kamel S. Kamel, Mitchell L. Halperin. "Hyperkalemia", Elsevier BV, 2017 Crossref	12 words — < 1%
10	ec.bioscientifica.com Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS