
بسم الله الرحمن الرحيم

POTASSIUM DISTURBANCES IN KIDNEY TRANSPLANT PATIENT

ارائه‌دهنده:
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Hyperkalemia

INTRODUCTION

Hyperkalemia is a common and potentially life-threatening complication following kidney transplantation that can be caused by a composite of factors such as:

- Delayed graft function
- Increased potassium intake
- Comorbidities (diabetes , …)
- Medications

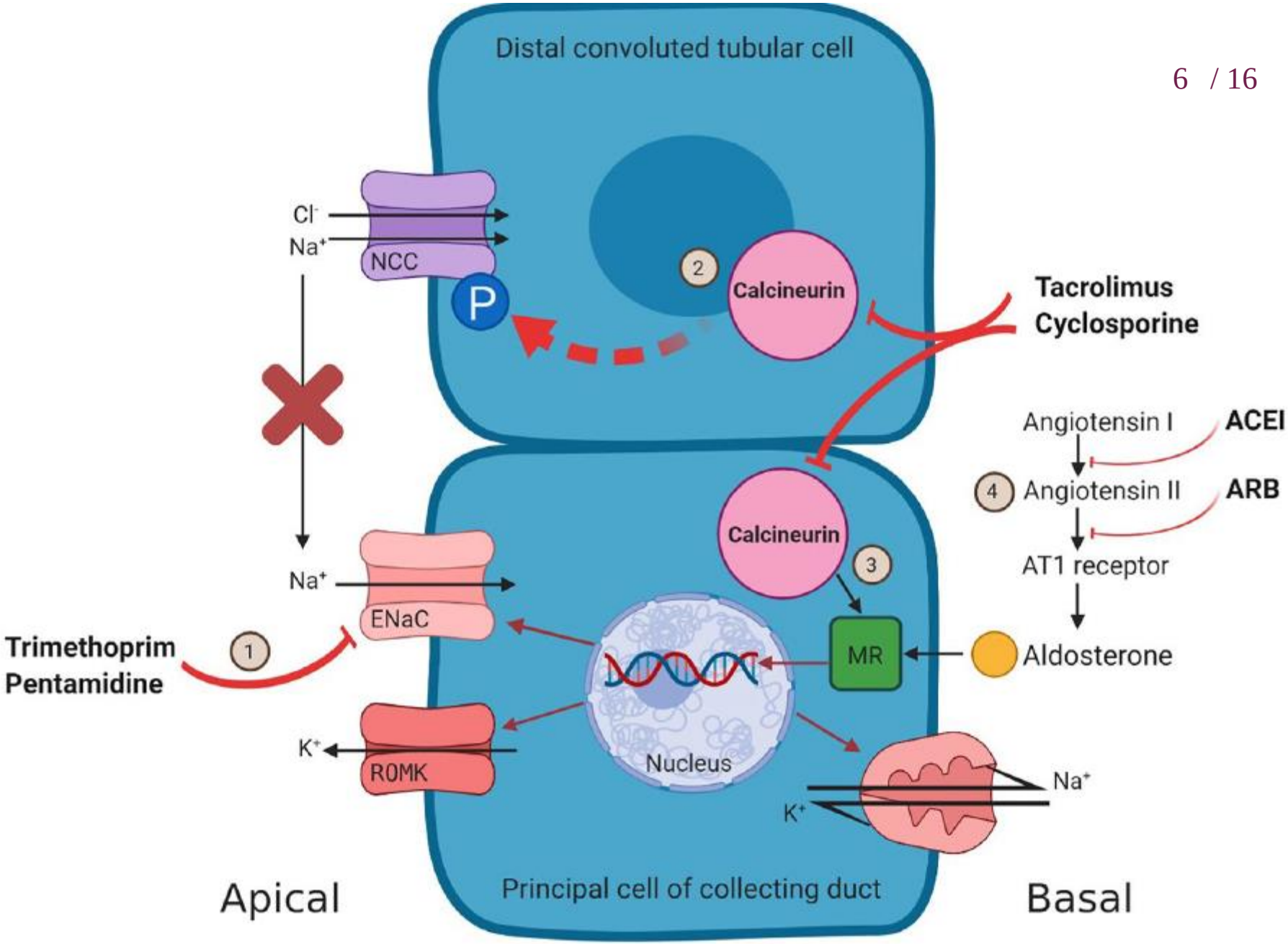
Medications	Utility in kidney transplantation
ACEI and ARB	Hypertension
Beta-blockers (non-selective and beta 2-selective)	Hypertension
Potassium-sparing diuretics (amiloride, triamterene, spironolactone)	Hypertension
Trimethoprim, pentamidine	PCP prophylaxis
Heparin	Prevent clot formation during transplant procedure
Succinylcholine	Used in transplant recipients in need for rapid sequence intubation and rapid airway control
Calcineurin inhibitors (cyclosporine, tacrolimus)	Immunosuppressive agents
NSAIDs	Headache or pain

CALCINEURIN INHIBITOR

- induce the down-regulation of mineralocorticoid receptor expression (aldosterone resistance that manifests as hyperkalemia and metabolic acidosis, also referred to as Type 4 renal tubular acidosis
- activate the sodium-chloride cotransporter in the distal convoluted tubule through unopposed phosphorylation of the cotransporter
- inhibiting renal outer medullary K+ channels, also known as ROMK, and Na–K ATPase in the distal tubules.
- nephrotoxic and have been increasingly recognized as the main cause of CKD in transplant patients.
- Tubular injury
- have a secondary and additive effect on potassium elevation in patients concomitantly receiving a beta blocker by a mechanism that is not understood

TRIMETHOPRIM/SULFAMETHOXAZOLE (TMP/SMX)

- inhibiting the apical epithelial sodium channels (ENaC) in the distal nephron
- reduces the amount of potassium transported from the cell into the tubular lumen and thus into the urine
- accumulation of potassium in the serum


Distal convoluted tubular cell
Cl⁻
Na⁺
NCC
P
2
Calcineurin
Tacrolimus
Cyclosporine
Angiotensin I
ACEI
4
Angiotensin II
ARB
AT1 receptor
Aldosterone
Calcineurin
3
MR
Na⁺
ENaC
Trimethoprim
Pentamidine
1
K⁺
ROMK
Nucleus
Na⁺
K⁺
Apical
Principal cell of collecting duct
Basal

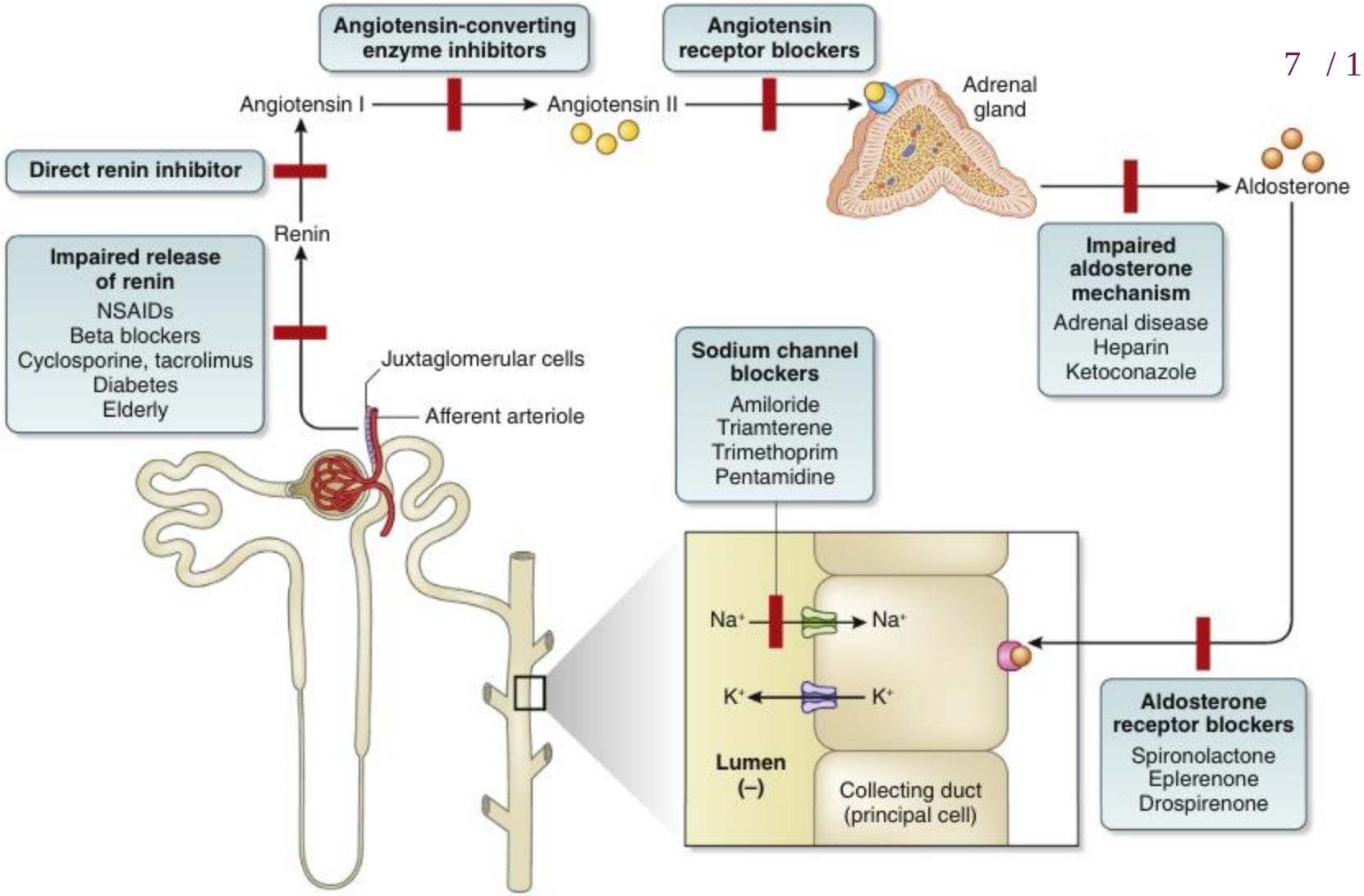


Figure 2 | The renin-angiotensin-aldosterone system and regulation of renal K^+ excretion. Disease states or drugs that interfere at any point along this system can impair renal K^+ secretion and increase the risk of hyperkalemia. In many patients this risk is magnified as a result of disturbances at multiple sites along this system. NSAIDs, nonsteroidal antiinflammatory drugs. Adapted from *The New England Journal of Medicine*, Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system, volume 351, pages 585–592. Copyright © 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[51]

Management of hyperkalemia

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Mechanisms and management of drug-induced hyperkalemia in kidney transplant patients

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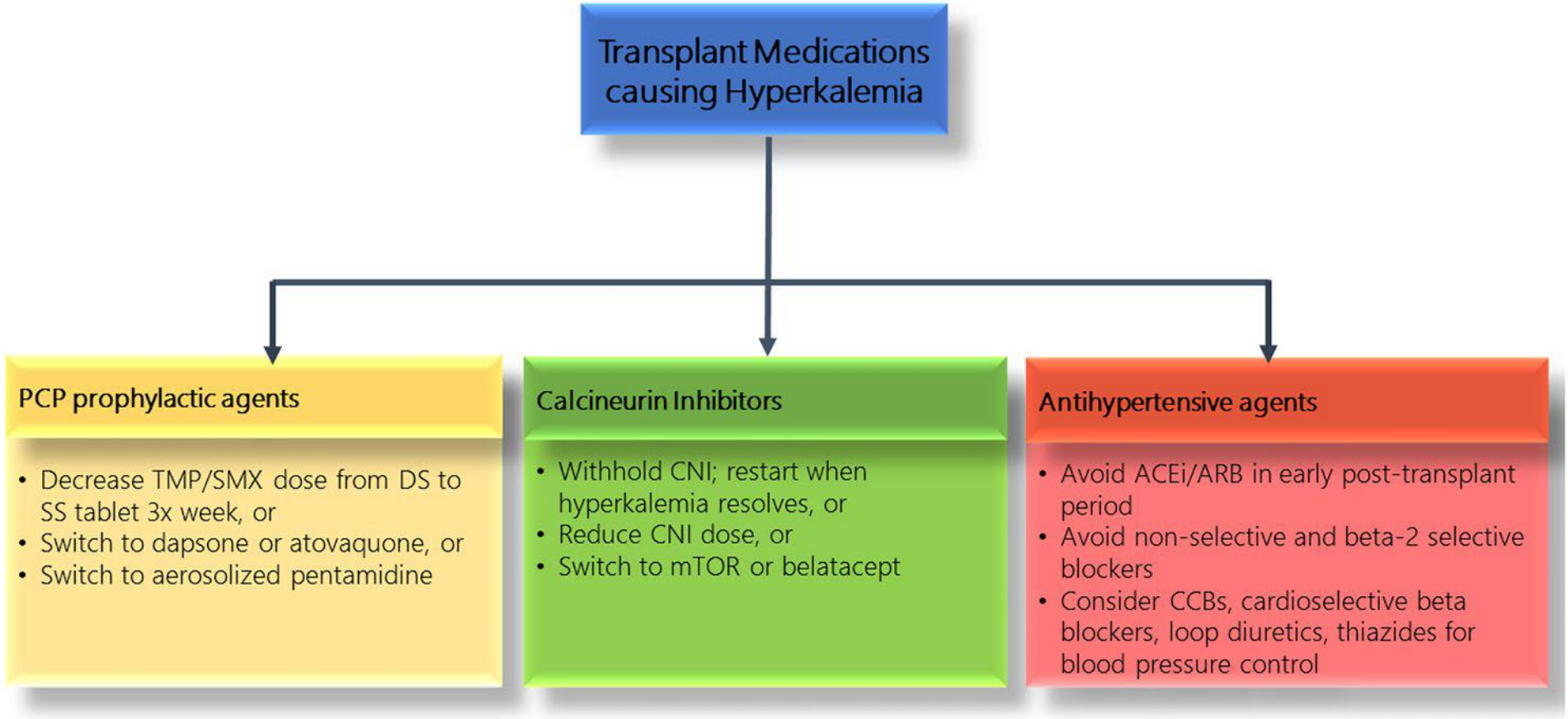
Abstract

Hyperkalemia is a common and potentially life-threatening complication following kidney transplantation that can be caused by a composite of factors such as medications, delayed graft function, and possibly potassium intake. Managing hyperkalemia after kidney transplantation is associated with increased morbidity and healthcare costs, and can be a cause of multiple hospital admissions and barriers to patient discharge. Medications used routinely after kidney transplantation are considered the most frequent culprit for post-transplant hyperkalemia in recipients with a well-functioning graft. These include calcineurin inhibitors (CNIs), pneumocystis pneumonia (PCP) prophylactic agents, and antihypertensives (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers). CNIs can cause hyperkalemic renal tubular acidosis. When hyperkalemia develops following transplantation, the potential offending medication may be discontinued, switched to another agent, or dose-reduced. Belatacept and mTOR inhibitors offer an alternative to calcineurin inhibitors in the event of hyperkalemia, however should be prescribed in the appropriate patient. While trimethoprim/sulfamethoxazole (TMP/SMX) remains the gold standard for prevention of PCP, alternative agents (e.g. dapsone, atovaquone) have been studied and can be recommend in place of TMP/SMX. Antihypertensives that act on the Renin–Angiotensin–Aldosterone System are generally avoided early after transplant but may be indicated later in the transplant course for patients with comorbidities. In cases of mild to moderate hyperkalemia, medical management can be used to normalize serum potassium levels and allow the transplant team additional time to evaluate the function of the graft. In the immediate post-operative setting following kidney transplantation, a rapidly rising potassium refractory to medical therapy can be an indication for dialysis. Patiromer and sodium zirconium cyclosilicate (ZS-9) may play an important role in the management of chronic hyperkalemia in kidney transplant patients, although additional long-term studies are necessary to confirm these effects.

Keywords Hyperkalemia · Potassium · Electrolyte Imbalance · Organ Transplant · Immunosuppression · PCP Prophylaxis · Antihypertensives

MANAGING HYPERKALEMIA



MANAGING HYPERKALEMIA

CNIs:

- post-transplant hyperkalemia should be managed despite keeping patients on these medications.
- routine monitoring of tacrolimus trough concentrations is required especially during first three months after transplant when CNI levels have to be higher.
- In addition, foods high in potassium, herbal supplements, potassium-enriched salt substitutes, and drugs that contain potassium (e.g. penicillin G potassium, phosphorus replacement products containing potassium, IV solutions with potassium) should be restricted
- Conversion from a CNI to other agents such as an mTOR inhibitor or belatacept can decrease the incidence of hyperkalemia, but require increased immune monitoring and may not be appropriate for all patients

Treatment of hyperkalemia

Drug	Dosing	Monitoring
Calcium	• Calcium gluconate is 1000 mg infused over 2 to 3 min • Repeat in 5 to 10 min if EKG changes persist	• Hypotension and arrhythmias
Insulin-glucose	• Intravenous insulin 5–10 units along with dextrose 25 g	• Hypoglycemia
Beta-2 agonists (e.g. albuterol)	• Albuterol 10 to 20 mg via nebulization over 10 min	• Tremor, tachycardia, and headache
Sodium bicarbonate	• Intravenous 50 mEq over 5 min	• Volume
Sodium polystyrene sulfonate (kayexalate)	• Oral 15 g 1 to 4 times daily • Rectal 30 to 50 g every 6 h	• Acute bowel necrosis, diarrhea, and gastrointestinal intolerance
Patiromer (Veltassa)	• Oral: Initial: 8.4 g once daily; adjust dose at ≥1-week intervals in increments of 8.4 g • Maximum dose: 25.2 g/day	• Constipation and hypomagnesemia
Sodium zirconium cyclosilicate (Lokelma)	• Oral: Initial: 10 g 3 times daily for up to 48 h; maintenance: 10 g once daily (range: 5 g every other day to 15 g once daily) • Maximum maintenance dose: 15 g/day	• Hypokalemia and edema

Hypokalemia

COMMON CAUSE

- Diuretic use
- Overzealous dietary restriction
- Hypomagnesemia
- mTor inhibitor use
- Previously adrenal adenoma

Urinary potassium excretion, renal ammoniagenesis, and risk of graft failure and mortality in renal transplant recipients[1–3]

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ABSTRACT

Background: Renal transplant recipients (RTRs) have commonly been urged to limit their potassium intake during renal insufficiency and may adhere to this principle after transplantation. Importantly, in experimental animal models, low dietary potassium intake induces kidney injury through stimulation of ammoniagenesis. In humans, low potassium intake is an established risk factor for high blood pressure.

Objective: We hypothesized that low 24-h urinary potassium excretion [UKV; urinary potassium concentration × volume], the gold standard for assessment of dietary potassium intake, represents a risk factor for graft failure and mortality in RTRs. In secondary analyses, we aimed to investigate whether these associations could be explained by ammoniagenesis, plasma potassium, or blood pressure.

Design: In a prospective cohort of 705 RTRs, we assessed dietary potassium intake by a single 24-h UKV and food-frequency questionnaires. Cox regression analyses were used to investigate prospective associations with outcome.

Results: We included 705 stable RTRs (mean ± SD age: 53 ± 13 y; 57% men) at 5.4 y (IQR: 1.9–12.0 y) after transplantation and 253 kidney donors. Mean ± SD UKV was 73 ± 24 mmol/24 h in RTRs compared with 85 ± 25 mmol/24 h in kidney donors. During follow-up for 3.1 y (IQR: 2.7–3.9 y), 45 RTRs developed graft failure and 83 died. RTRs in the lowest sex-specific tertile of UKV (women, <55 mmol/24 h; men, <65 mmol/24 h) had an increased risk of graft failure (HR: 3.70; 95% CI: 1.64, 8.34) and risk of mortality (HR; 2.66; 95% CI: 1.53, 4.61), independent of potential confounders. In causal path analyses, 24-h urinary ammonia excretion, plasma potassium, and blood pressure did not affect these associations.

Conclusions: Our results indicate that low UKV is associated with a higher risk of graft failure and mortality in RTRs. Specific attention for adequate potassium intake after transplantation seems warranted. This trial was registered at clinicaltrials.gov as NCT02811835. *Am J Clin Nutr* 2016;104:1703–11.

Keywords: graft failure, kidney transplantation, mortality, urinary potassium excretion, ammoniagenesis, dietary potassium intake

INTRODUCTION

Survival rates of renal transplant recipients (RTRs)[8] have markedly increased over the last decades (1). Advances in immunosuppressant medications have led to clinically relevant reductions in the incidence of acute rejection and early posttransplant mortality. However, long-term outcomes are still poor with approximately half of all cadaveric renal allografts lost in a period of 10–12 y after transplantation (2).

Before transplantation, patients with chronic kidney disease (CKD) are generally advised to limit potassium intake (e.g., fruit and vegetables) because of the risk of hyperkalemia. After transplantation, there is usually no clear incentive to increase potassium intake. It is therefore likely that RTRs maintain their habitual dietary potassium restrictions after transplantation.

Importantly, in the 1980s, Tolins et al. (3) and Nath et al. (4) showed in experimental animal models that chronic potassium deficiency induces kidney injury. It may therefore be hypothesized that a continued low potassium intake after transplantation is detrimental for the graft function in the long term.

One of the potential mechanisms by which the detrimental effect of low potassium intake has been suggested to ensue is through stimulation of ammoniagenesis, which may induce progressive, tubulointerstitial damage (3, 4). It is unclear whether low potassium intake needs to be associated with hypokalemia to render this mechanism operational (5).

An alternative mechanism in the causal path by which low potassium intake could lead to increased risk of graft failure and mortality would be through induction of high blood pressure (6). A meta-analysis of short-term, randomized controlled trials

[1] Parts of this study were presented in abstract form at the American Society of Nephrology Kidney Week 2014, Philadelphia, PA, 11–16 November 2014.

[2] Generation of the TransplantLines Food and Nutrition Biobank and Cohort Study (TxL-FN) was funded by the Top Institute Food and Nutrition.

[3] Supplemental Material, Supplemental Figures 1–3, and Supplemental Table 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: BSA, body surface area; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FFQ, food-frequency questionnaire; RTR, renal transplant recipient; UKV, urinary potassium excretion.

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