Kaliuresis and intracellular uptake of potassium with potassium citrate and potassium chloride supplements: a randomized controlled trial

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Kaliuresis and Intracellular Uptake of Potassium with Potassium Citrate and Potassium Chloride Supplements

A Randomized Controlled Trial

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Abstract

Background A potassium replete diet is associated with lower cardiovascular risk but may increase the risk of hyperkalemia, particularly in people using renin-angiotensin-aldosterone system inhibitors. We investigated whether intracellular uptake and potassium excretion after an acute oral potassium load depend on the accompanying anion and/or aldosterone and whether this results in altered plasma potassium change.

Methods In this placebo-controlled interventional cross-over trial including 18 healthy individuals, we studied the acute effects of one oral load of potassium citrate (40 mmol), potassium chloride (40 mmol), and placebo in random order after overnight fasting. Supplements were administered after a 6-week period with and without lisinopril pretreatment. Linear mixed effect models were used to compare blood and urine values before and after supplementation and between the interventions. Univariable linear regression was used to determine the association between baseline variables and change in blood and urine values after supplementation.

Results During the 4-hour follow-up, the rise in plasma potassium was similar for all interventions. After potassium citrate, both red blood cell potassium—as measure of the intracellular potassium—and transtubular potassium gradient (TTKG)—reflecting potassium secretory capacity—were higher than after potassium chloride or potassium citrate with lisinopril pretreatment. Baseline aldosterone was significantly associated with TTKG after potassium citrate, but not after potassium chloride or potassium citrate with lisinopril pretreatment. The observed TTKG change after potassium citrate was significantly associated with urine pH change during this intervention ($R=0.60$, $P < 0.001$).

Conclusions With similar plasma potassium increase, red blood cell potassium uptake and kaliuresis were higher after an acute load of potassium citrate as compared with potassium chloride alone or pretreatment with lisinopril.

Clinical Trial registry name and registration number: Potassium supplementation in patients with chronic kidney disease and healthy subjects: effects on potassium and sodium balance, NL7618.

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Introduction

Epidemiological studies and a large-scale interventional study demonstrated that both a potassium replete diet and substitution of table salt with potassium chloride are associated with a lower BP and lower risk of cardiovascular disease.[1–7] These studies, however, did not address the role of the accompanying anion. Although potassium chloride is often used as a salt substitute, potassium in food is mostly accompanied by nonchloride organic acids, such as citrate.[8] A crucial difference is that citrate, unlike chloride, is an alkalizing agent, which may influence kaliuresis. In a previous study in healthy volunteers, treatment with fludrocortisone and sodium bicarbonate resulted in higher levels of urinary potassium excretion than treatment with fludrocortisone alone.[9]

Under normal circumstances, when a potassium load is combined with a carbohydrate-rich meal, potassium is shifted from the blood into the cells to prevent hyperkalemia.[10] To keep the total amount of potassium in the intracellular compartment constant, the kidneys will match potassium load by excretion. Potassium is freely filtered in the glomerulus, almost completely reabsorbed in the proximal tubule, and mainly secreted in the distal segment of the distal convoluted tubule and the early segment of the connecting tubule.[11–13] These segments are often

referred to as the aldosterone-sensitive distal nephron; however, in some segments (late distal convoluted tubule), the mineralocorticoid receptor is activated in the absence of aldosterone.[14] Transporters responsible for potassium secretion in the distal convoluted tubule and connecting tubule include the renal outer medullary potassium channels and the calcium and voltage-activated potassium (BK) channels.[15] The Na^+-Cl^- cotransporter and epithelial Na^+ channel play a key role in this process by regulating distal sodium delivery and reabsorption, thereby creating a favorable electrochemical gradient for potassium secretion. Basolateral Na^+-K^+-ATPase activity indirectly promotes potassium secretion through increasing intracellular uptake of potassium in the distal convoluted tubule and connecting tubule.[16] In addition, particularly during potassium restriction, potassium is actively reabsorbed *via* H^+-K^+-ATPases in type A intercalated cells of the collecting duct.[17,18] Specifically, some of the transporters may respond differently to a potassium chloride or potassium citrate load.[19–21]

Data on the acute effects of potassium citrate and potassium chloride on plasma and intracellular potassium and kaliuresis are however scarce. We hypothesize that intracellular uptake of potassium and kaliuresis is higher after potassium citrate than after potassium chloride supplementation. Therefore, the objective of this study was to investigate whether there is a difference in plasma and red blood cell (RBC) potassium and kaliuresis in response to an acute oral load of potassium chloride and potassium citrate in healthy individuals. Moreover, because renin-angiotensin-aldosterone system inhibitors reduce aldosterone-mediated potassium secretion, we explored whether potential differences in kaliuresis were the same after pretreatment with lisinopril.

Methods

Study Design and Participants

We conducted a single-blind randomized interventional cross-over study in the Amsterdam University Medical Center (Amsterdam, The Netherlands) between April 2019 and July 2021. Healthy adult men and women were recruited through local advertisement. After informed consent was obtained, a screening visit took place during which general information on health was collected, blood was drawn, and a 24-hour urine sample was handed in. The exclusion criteria are presented in Supplemental Table 1. This study was approved by the local Medical Ethics Committee (METC; No. 2018_103) and was registered at the Dutch Trial Register (https://clinicaltrialregister.nl; NL7618). Adjustments to the protocol are described in the Supplemental Material.

Study Procedures

This study consisted of two study periods (Supplemental Figure 1): a 7-week study period with lisinopril 10 mg (TEVA Pharmaceuticals, HU) once daily and an 8-week study period without lisinopril. One healthy participant developed a dry cough after initiation of lisinopril and was prescribed an equipotent dose of losartan 50 mg (Pharmachemie B.V., NL) once daily. The washout period between the two study periods was 6 weeks. In total, five study visits were scheduled: three during the study period without lisinopril, including the visit during which participants received placebo, and two during the study period with lisinopril. The interval between the visits within one study period was 4–7 days. The order of the study periods, as well as the interventions, was determined by block randomization *via* sealed envelopes by the study investigators. Each block contained 24 allocations. Participants were blinded for the intervention sequence.

The day preceding each study visit, participants collected a 24-hour urine sample. At the day of the study visit, participants visited the research facility after an overnight fast. After baseline hemodynamic measurements and blood and urine sampling, participants received the oral load of 40-mmol (1.56 g) potassium and 13.3-mmol (2.56 g) citrate, 40-mmol (1.56 g) potassium, and 40-mmol (1.42 g) chloride or matching placebo (Lab Medisan, NL). Although the combination of lisinopril and a 40-mmol oral load of potassium may cause hyperkaliemia, the expected risk of hyperkaliemia in healthy participants is low.[10,22,23] Six capsules of potassium citrate, potassium chloride, or placebo were administered with 140 ml of tap water. During the course of this study, the potassium chloride capsules were substituted by potassium chloride oral solution because of heavy gastrointestinal symptoms after ingestion of the potassium chloride capsules (Supplemental Material).

During a 4-hour follow-up after the oral load of either potassium or placebo, venous blood was sampled and urine was collected. Laboratory analyses, calculation of the transtubular potassium gradient (TTKG), and determination of RBC potassium are described in the Supplemental Material.

Study Outcomes

The primary study outcome was plasma potassium. Secondary outcomes included RBC potassium, urine potassium, plasma sodium, urine sodium, and plasma aldosterone. Other outcomes included venous pH, urine pH, plasma chloride, and urine chloride.

Statistical Analysis

A detailed description of the statistics is provided in the Supplemental Material. In brief, linear mixed effect models were used to compare blood and urine values before and after supplementation and between the interventions. To assess correlation between variables, we used Pearson correlation. Fisher Z transformation was applied to pool correlation coefficients of the different interventions and time points.[24] Univariable linear regression was used to determine the association between baseline variables and change in blood and urine values after supplementation.

Results

Study Population

Twenty-six healthy individuals were screened, of whom 18 completed the study (Supplemental Figure 2). The median (interquartile range) age of the 18 healthy participants included in this analysis was 28 (23–54) years. All participants had a normal BP and kidney function at the

Table 1. Baseline characteristics at screening

Baseline Characteristics	Healthy Participants (n=18)
General characteristics	
Age, yr[a]	28 (23–54)
Sex, female, n (%)	7 (39)
BMI, kg/m^2	23.9±4.4
Office BP[b]	
Systolic BP, mm Hg	124±9
Diastolic BP, mm Hg	78±8
Blood	
Hb, g/dl	14.4±1.3
Ht, L/L	0.44±0.04
Plasma sodium, mmol/L	141±2
Plasma potassium, mmol/L	4.0±0.3
Plasma creatinine, mg/dl	0.90±0.15
eGFR CKD-EPI, ml/min per 1.73 m^2	100±20
24-h urine	
Volume, L/24 h	1.8±0.7
Osmolality, mOsm/kg	531±220
Urinary sodium excretion, mmol/24 h	127±52
Urinary potassium excretion, mmol/24 h	78±27
Creatinine, mg/24 h	1576±417
Creatinine clearance, ml/min	122±25

Continuous values are mean±SD and proportional values are n (percentage). BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; IQR, interquartile range.
[a]Median±IQR.
[b]Office BP (mean of three measurements).

screening visit (Table 1). No significant differences were observed in baseline hemodynamics, blood, and urine results preceding the interventions, except for a lower diastolic BP and higher plasma renin level after treatment with lisinopril (Supplemental Table 2).

Potassium Chloride and Potassium Citrate Lead to Similar Rises in Plasma Potassium and Aldosterone

After 40 mmol of potassium citrate and potassium chloride, plasma potassium increased and reached the highest concentration 60 minutes after administration. The maximum increase in plasma potassium was +0.7±0.3 mmol/L after potassium citrate and +0.6±0.2 mmol/L after potassium chloride ($P < 0.001$ compared with baseline for both). Four hours after supplementation, plasma potassium returned to baseline levels. After supplementation of placebo, plasma potassium remained stable (Figure 1A). Pretreatment with lisinopril did not increase maximal plasma potassium concentrations after potassium citrate and potassium chloride (Figure 1B). Although the peak plasma potassium concentration seems to be reached earlier after potassium citrate than after potassium chloride, the linear mixed model showed no significant differences in plasma potassium during follow-up between potassium citrate and potassium chloride (Table 2).

Plasma chloride during follow-up was higher after potassium chloride than after potassium citrate, while plasma bicarbonate during follow-up was higher after potassium citrate than after potassium chloride. Plasma sodium did not change after both supplements (Table 2).

Plasma aldosterone significantly increased after supplementation of potassium citrate and potassium chloride (Table 2). Compared with baseline, the largest difference in plasma aldosterone was observed 60 minutes after potassium supplementation (potassium citrate: 103 [59–233] ng/L; potassium chloride: 106 [37–142] ng/L, $P < 0.001$ for both). No difference in plasma aldosterone was observed between potassium citrate and potassium chloride. After pretreatment with lisinopril, the increase in plasma aldosterone at this time point was attenuated, however not significantly different (Figure 1, C and D).

Lisinopril Mitigates the Rise in Venous pH after Potassium Citrate

During both study periods, venous pH differed significantly between the potassium citrate and potassium chloride interventions (Table 2). Without lisinopril pretreatment, venous pH increased after supplementation of potassium citrate with a maximum increase at 60 minutes after supplementation (+0.03±0.03, $P < 0.001$ compared with baseline). After supplementation of potassium chloride and placebo, no change in venous pH was observed (Figure 1E). Conversely, after treatment with lisinopril, no significant increase in venous pH was observed in response to potassium citrate, but venous pH significantly decreased after potassium chloride with a maximal decrease at 240 minutes after supplementation (Figure 1F). No correlation was present between change in venous pH and change in plasma potassium after supplementation of placebo, potassium citrate, and potassium chloride (without lisinopril pretreatment: R_{pooled}=−0.32, $P = 0.13$; with lisinopril pretreatment: R_{pooled}=−0.07, $P = 0.79$).

Potassium Citrate but Not Potassium Chloride or Potassium Citrate with Lisinopril Pretreatment Increases RBC Potassium

RBC potassium during follow-up was higher after potassium citrate than after potassium chloride ($P = 0.02$), with the largest difference between the supplements at 120 minutes (0.4×10^{-12} mmol, $P = 0.04$) (Table 2). Hematocrit and mean corpuscular volume remained stable. Moreover, after placebo, potassium citrate, and potassium chloride supplementation, a positive correlation was found between the change from baseline in venous pH and RBC potassium (R_{pooled}=0.40, $P = 0.04$, Figure 2A). No correlation was present between the change in venous pH and RBC potassium after pretreatment with lisinopril (R_{pooled}=−0.07, $P = 0.79$) (Figure 2B). In addition, no correlations were present between the change in plasma bicarbonate, plasma chloride, or plasma sodium and RBC potassium after placebo, potassium citrate, and potassium chloride supplementation (Supplemental Figure 3).

Univariable regression analysis showed a significant association between baseline venous pH and change from baseline in RBC potassium 120 minutes after potassium citrate (β=−15, $P = 0.01$). Baseline aldosterone was associated with change in RBC potassium 120 minutes after potassium chloride (β=−0.7, $P = 0.02$). No associations were present between baseline plasma aldosterone or venous pH and change in RBC potassium after potassium

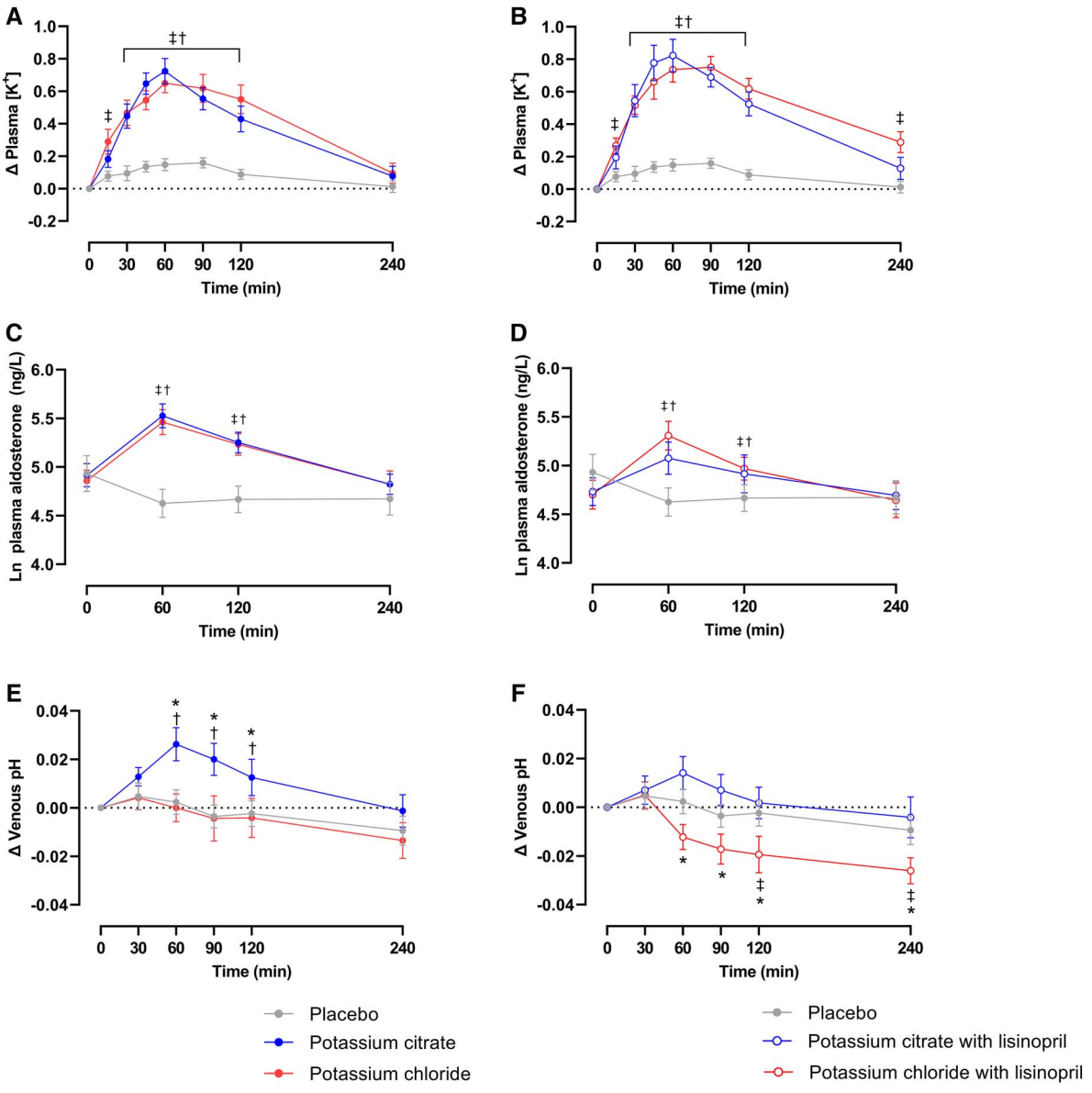

Figure 1. Change in plasma potassium, plasma aldosterone, and venous pH after a placebo, potassium citrate, and potassium chloride load. Change in plasma potassium after a placebo, potassium citrate, and potassium chloride load without lisinopril pretreatment (A) and with lisinopril pretreatment (B). Natural log-transformed plasma aldosterone after a potassium citrate and potassium chloride load without lisinopril pretreatment (C) and with lisinopril pretreatment (D). Change in venous pH after a placebo, potassium citrate, and potassium chloride load without lisinopril pretreatment (E) and with lisinopril pretreatment (F). Values are mean±SEM. †Potassium citrate versus placebo. ‡Potassium chloride versus placebo. *$P < 0.05$ potassium citrate versus potassium chloride. Figure 1 can be viewed in color online at www.cjasn.org.

chloride and potassium citrate with lisinopril pretreatment (Table 3).

Potassium Citrate Increases Urinary Potassium Excretion more than Potassium Chloride or Potassium Citrate with Lisinopril Pretreatment

Placebo-subtracted cumulative potassium excretion was 29±14 mmol after potassium citrate and 18±17 mmol after potassium chloride ($P = 0.002$). After lisinopril pretreatment, potassium excretion on potassium citrate administration was lower than without lisinopril and similar as potassium chloride (potassium citrate: 19±11 mmol and potassium chloride: 18±13 mmol, Figure 3). Urine volumes and urine osmolality were similar after the potassium supplements, both with and without lisinopril pretreatment (Table 2). TTKG was higher after potassium citrate than after potassium chloride, with the largest difference at 240 minutes (19±5 and 15±4 mmol, respectively, $P = 0.04$). After lisinopril pretreatment, no differences between potassium citrate and potassium chloride were present (Table 2). The results were similar for urine potassium-to-creatinine ratio (Supplemental Table 3).

Table 2. Blood and urine results at baseline and during follow-up

Blood and Urine Values		T0	T30	T60	T90	T120	T240	*P* Value versus Placebo	*P* Value versus KCl
Plasma [K^+] (mmol/L)	Placebo	4.0±0.2	4.1±0.3	4.2±0.4	4.1±0.3	4.0±0.2	4.0±0.2		
	K-cit	4.0±0.2	4.5±0.4[a]	4.7±0.4[a]	4.6±0.3[a]	4.5±0.4[a]	4.1±0.3	<0.001	0.76
	KCl	4.0±0.2	4.5±0.3[b]	4.7±0.3[b]	4.7±0.3[b]	4.6±0.4[b]	4.1±0.2	<0.001	
	K-cit+lis	4.0±0.3	4.7±0.5[a]	4.9±0.5[a]	4.8±0.4[a]	4.6±0.4[a]	4.2±0.3	<0.001	0.94
	KCl+lis	4.0±0.2	4.5±0.3[b]	4.7±0.4[b]	4.7±0.4[b]	4.6±0.3[b]	4.3±0.3[b]	<0.001	
Plasma [Na^+] (mmol/L)	Placebo	141±2	140±2	140±2	140±2	140±2	140±2		
	K-cit	140±2	139±2	139±2	140±2	140±3	140±2	0.89	0.96
	KCl	140±2	140±2	140±2	139±2	140±2	140±2	0.93	
	K-cit+lis	139±2	139±2	139±2	139±2	139±2	139±2	0.94	0.62
	KCl+lis	140±3	140±2	139±2	139±3	139±3	140±2	0.71	
Plasma [Cl^-] (mmol/L)	Placebo	104±2	104±2	104±3	103±2	104±3	103±3		
	K-cit	103±3	102±3	103±3	103±3	103±3	102±3	0.13	<0.001
	KCl	103±2	103±2[c]	104±2[b,c]	104±2	104±2[c]	103±2[c]	0.02	
	K-cit+lis	103±2	103±3	103±3	103±2	103±3	103±3	0.81	0.02
	KCl+lis	104±3	104±3	104±3	104±3[c]	104±3	104±3[c]	0.04	
Plasma [HCO_3^-] (mmol/L)	Placebo	27±3	27±2	27±2	28±2	27±2	28±2		
	K-cit	26±4	27±3	28±2	27±2	27±2	28±2	0.18	<0.001
	KCl	26±3	26±2	26±3[b,c]	26±2[b,c]	26±2[c]	26±2[b,c]	0.004	
	K-cit+lis	26±3	27±2	28±2[a]	28±2	27±2	28±2	0.02	<0.001
	KCl+lis	26±2	26±2[c]	27±2[c]	26±2[b,c]	26±2[c]	27±2[b,c]	0.01	
Venous pH	Placebo	7.37±0.02	7.38±0.02	7.38±0.02	7.37±0.02	7.37±0.03	7.36±0.02		
	K-cit	7.37±0.04	7.37±0.02	7.39±0.03[a,c]	7.39±0.02[a,c]	7.38±0.03[c]	7.37±0.02[c]	<0.001	<0.001
	KCl	7.37±0.03	7.37±0.02	7.37±0.03	7.36±0.02	7.36±0.02	7.35±0.02	0.10	
	K-cit+lis	7.37±0.03	7.38±0.02	7.39±0.03	7.38±0.03	7.38±0.02	7.37±0.02	0.06	<0.001
	KCl+lis	7.38±0.03	7.38±0.03	7.36±0.2[b,c]	7.36±0.2[b,c]	7.36±0.2[b,c]	7.35±0.02[b,c]	0.002	
Plasma aldosterone (ng/L)[d]	Placebo	171 (74–235)		85 (74–157)		99 (82–144)	98 (61–181)		
	K-cit	119 (98–187)		277 (167–360)[a]		191 (136–280)[a]	127 (84–189)	<0.001	0.99
	KCl	133 (91–169)		248 (194–322)[b]		188 (143–305)[b]	136 (85–182)	<0.001	
	K-cit+lis	93 (78–138)		175 (88–281)[a]		134 (80–302)	88 (69–160)	0.01	0.32
	KCl+lis	96 (73–173)		165 (139–322)[b]		120 (104–178)[b]	120 (74–157)	0.001	
RBC K^+ (mmol×10^{-12})	Placebo	8.5±0.7	8.8±0.7	8.6±0.7	8.8±0.7	8.4±0.5	8.4±0.5		
	K-cit	8.5±0.8	8.4±0.7	8.4±0.6	8.7±0.7[c]	8.7±0.7[c]	8.7±0.5	0.58	0.02
	KCl	8.4±0.5	8.5±0.8	8.5±0.8	8.4±0.5	8.4±0.7	8.5±0.8	0.08	
	K-cit+lis	8.6±0.7	8.5±0.8	8.5±0.6	8.4±0.6	8.4±0.7	8.3±0.4	0.07	0.64
	KCl+lis	8.4±0.8	8.4±0.6	8.7±0.7	8.5±0.7	8.4±0.5	8.2±0.4	0.17	
Urine volume (ml)	Placebo	63±45				203±163	104±64		
	K-cit	77±83				298±126[a]	103±50	0.02	0.31
	KCl	75±74				259±147	103±60	0.15	
	K-cit+lis	70±38				302±162[a]	105±55	0.05	0.45
	KCl+lis	62±35				235±89	118±73	0.21	
Urine osmolality (mOsm/kg)	Placebo	821±135				633±212	752±137		
	K-cit	810±168				596±144	789±138	0.88	0.43
	KCl	801±152				649±188	777±156	0.36	
	K-cit+lis	768±175				591±167	759±153	0.58	0.63
	KCl+lis	786±123				650±125	772±147	0.30	

Table 2. (Continued)

Blood and Urine Values		T0	T30	T60	T90	T120	T240	*P* Value versus Placebo	*P* Value versus KCl
Urine potassium (mmol)	Placebo	6±5				16±8	11±7		
	K-cit	7±8				36±11	20±7	<0.001	<0.001
	KCl	7±5				28±12	16±6	<0.001	
	K-cit+lis	6±3				29±12	16±5	<0.001	0.50
	KCl+lis	5±3				27±10	17±6	<0.001	
TTKG	Placebo	10±3				10±4	10±4		
	K-cit	10±4				14±4[a]	19±5[a,c]	<0.001	0.007
	KCl	9±3				12±3[b]	15±4[b]	<0.001	
	K-cit+lis	10±4				12±4[a]	16±4[a]	<0.001	0.47
	KCl+lis	8±3				12±3[b]	14±3[b]	<0.001	
Urine pH	Placebo	6.1±0.6				6.8±0.8	6.6±0.9		
	K-cit	6.2±0.7				7.7±0.3[a,c]	7.7±0.5[a,c]	<0.001	<0.001
	KCl	6.1±1.0				7.1±0.5	6.5±1.0	0.18	
	K-cit+lis	6.2±0.9				7.6±0.2[a]	7.3±0.6[a,c]	<0.001	<0.001
	KCl+lis	6.0±0.7				7.3±0.5[b]	6.6±0.8	0.02	

The last two columns on the right side show the *P* value for the global null hypothesis; no difference at any time. In case of a $P < 0.05$, pairwise comparisons were performed with least significant difference *post hoc* test. Values are mean±SD. KCl, potassium chloride; K-cit, potassium citrate; lis, with lisinopril pretreatment; RBC, red blood cell; TTKG, transtubular potassium gradient; IQR, interquartile range.

[a]$P < 0.05$ potassium citrate versus placebo.

[b]$P < 0.05$ potassium chloride versus placebo.

[c]$P < 0.05$ potassium citrate versus potassium chloride.

[d]Values are median±IQR.

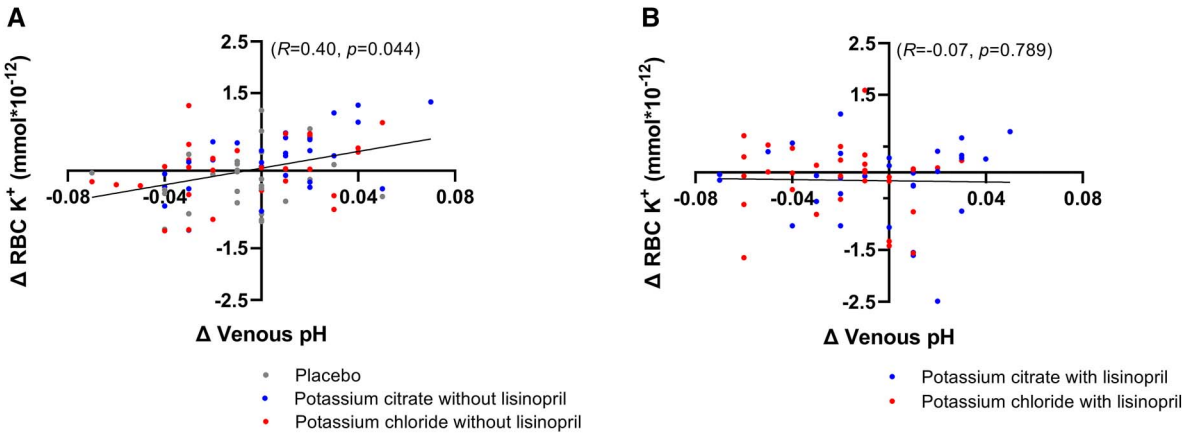

Figure 2. Correlation between change in venous pH and RBC K^+ after a placebo, potassium citrate, and potassium chloride load. Pooled correlation between change in venous pH and RBC K^+ 120 and 240 minutes after supplementation of placebo, potassium citrate, and potassium chloride without lisinopril pretreatment (A) and with lisinopril pretreatment (B). Pooled correlation coefficients were calculated with the Fisher Z transformation. The black line represents the linear regression line. RBC K^+, red blood cell potassium. Figure 2 can be viewed in color online at www.cjasn.org.

Univariable regression analysis showed that both venous pH (β=−52, P = 0.03) and baseline plasma aldosterone (β=5.2, P < 0.001) were significantly associated with change from baseline in TTKG 120 minutes after potassium citrate. However, after pretreatment with lisinopril, no association was present, except for an inverse association with age (β=−0.1, P = 0.04). In addition, no significant associations were present between baseline plasma aldosterone and venous pH and change from baseline in TTKG 120 minutes after potassium chloride with and without lisinopril pretreatment (Table 4).

Potassium Citrate Increases Urine pH more than Potassium Chloride Regardless of Lisinopril Pretreatment

After potassium citrate, urine pH was significantly higher than after potassium chloride (Table 2) with the

Table 3. Univariable regression analyses for the association of the change in red blood cell potassium after each intervention

Variables	Difference in Change (95% CI)	*P* Value	Difference in Change (95% CI)	*P* Value
	Potassium Citrate without Lisinopril		Potassium Chloride without Lisinopril	
		Δ RBC K^+ (mmol) T0–T120		
Age, yr	0.01 (−0.02 to 0.03)	0.54	0.01 (−0.1 to 0.03)	0.18
Sex, woman	−0.5 (−1.4 to 0.3)	0.18	0.3 (−0.4 to 0.9)	0.36
BMI, kg/m^2	−0.03 (−0.13 to 0.08)	0.61	0.07 (−0.01 to 0.16)	0.08
24-h potassium excretion, mmol	0.01 (−0.01 to 0.02)	0.30	−0.00 (−0.01 to 0.01)	0.49
Baseline eGFR, ml/min per 1.73 m^2	−0.01 (−0.03 to 0.01)	0.23	−0.01 (−0.03 to 0.01)	0.15
Baseline plasma potassium, mmol/L	0.4 (−2.2 to 3.1)	0.74	0.7 (−0.6 to 2.1)	0.26
Baseline venous pH	−15 (−24 to −4)	0.01	−2 (−12 to 9)	0.71
Baseline plasma bicarbonate, mmol/L	0.02 (−0.09 to 0.14)	0.67	0.02 (−0.11 to 0.15)	0.74
Baseline Ln plasma aldosterone, ng/L	−0.4 (−1.2 to 0.5)	0.38	−0.7 (−1.3 to −0.1)	0.02
Baseline Ln plasma renin, ng/L	−0.1 (−1.7 to 1.4)	0.87	−0.8 (−1.5 to 0.0)	0.06
	Potassium Citrate with Lisinopril		Potassium Chloride with Lisinopril	
		Δ RBC K^+ (mmol) T0–T120		
Age, yr	−0.01 (−0.04 to 0.02)	0.51	0.00 (−0.02 to 0.03)	0.87
Sex, woman	0.8 (−0.2 to 1.7)	0.10	0.1 (−0.8 to 0.9)	0.89
BMI, kg/m^2	−0.03 (−0.17 to 0.11)	0.69	0.01 (−0.09 to 0.11)	0.88
24-h potassium excretion, mmol	0.01 (−0.01 to 0.02)	0.27	0.00 (−0.01 to 0.01)	0.98
Baseline eGFR, ml/min per 1.73 m^2	0.02 (−0.01 to 0.05)	0.11	0.00 (−0.02 to 0.03)	0.70
Baseline plasma potassium, mmol/L	−1.4 (−3.0 to 0.3)	0.09	−0.5 (−2.7 to 1.8)	0.65
Baseline venous pH	−4 (−23 to 14)	0.62	−7 (−19 to 5)	0.26
Baseline plasma bicarbonate, mmol/L	−0.07 (−0.28 to 0.14)	0.50	0.08 (−0.09 to 0.25)	0.35
Baseline Ln plasma aldosterone, ng/L	−0.2 (−1.0 to 0.7)	0.68	0.01 (−0.63 to 0.65)	0.97
Baseline Ln plasma renin, ng/L	−0.5 (−1.1 to 0.1)	0.13	0.14 (−0.29 to 0.56)	0.50

CI, confidence interval; RBC K^+, red blood cell potassium; BMI, body mass index.

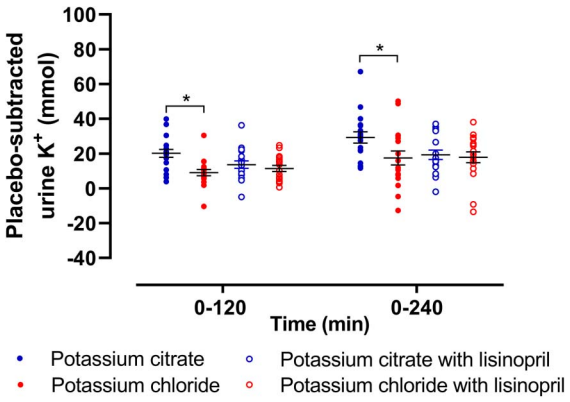

Figure 3. Placebo-subtracted cumulative excretion of potassium 120 and 240 minutes after an oral load of potassium citrate and potassium chloride load. Values are mean±SEM. *$P < 0.05$ potassium citrate versus potassium chloride. Figure 3 can be viewed in color online at www.cjasn.org.

largest difference at 240 minutes after supplementation ($P < 0.001$). After lisinopril pretreatment, the difference in urine pH became smaller but was still statistically significant at 240 minutes after supplementation (potassium citrate: 7.3±0.6 and potassium chloride: 6.6±0.8, $P < 0.001$). Moreover, after supplementation of placebo, potassium citrate, and potassium chloride, a positive correlation was present between change from baseline in urine pH and TTKG (R_{pooled}=0.60, $P < 0.001$) (Figure 4A). However, after lisinopril pretreatment, no correlation was present (R_{pooled}=0.28, $P = 0.20$) (Figure 4B).

Lisinopril Does Not Affect Potassium-Induced Natriuresis

Placebo-subtracted cumulative urinary excretions of sodium were similar for potassium citrate and potassium chloride, both with and without lisinopril pretreatment (Supplemental Figure 4). Placebo-subtracted cumulative chloride excretion was significantly higher after potassium chloride than after potassium citrate during both study periods (Supplemental Figure 5).

Discussion

In this randomized interventional cross-over study in healthy individuals, we demonstrate that the rise of plasma potassium was similar after an oral load of potassium citrate and potassium chloride. However, RBC potassium, total potassium excretion, and TTKG were higher after potassium citrate than after potassium chloride. This provides evidence that the accompanying anion affects kaliuresis and intracellular uptake of potassium after an acute oral potassium load. Moreover, a positive correlation was present between the change in venous pH and RBC potassium and change in urine pH and TTKG, suggesting that differences in uptake and excretion are mediated by changes in acid–base balance. In addition, differences in kaliuresis and intracellular uptake between

Table 4. Unadjusted regression analyses for the association of the change in transtubular potassium gradient after each intervention

Variables	Difference in Change (95% CI)	*P* Value	Difference in Change (95% CI)	*P* Value
	Potassium Citrate without Lisinopril		Potassium Chloride without Lisinopril	
			TTKG T0–T120	
Age, yr	−0.08 (−0.19 to 0.03)	0.16	−0.03 (−0.13 to 0.07)	0.58
Sex, woman	−0.9 (−4.7 to 3.0)	0.64	−0.2 (−3.6 to 3.2)	0.91
BMI, kg/m^2	−0.21 (−0.67 to 0.26)	0.36	−0.11 (−0.60 to 0.39)	0.66
24-h sodium excretion, mmol	−0.01 (−0.06 to 0.04)	0.69	−0.01 (−0.03 to 0.02)	0.56
24-h potassium excretion, mmol	0.00 (−0.05 to 0.06)	0.92	0.02 (−0.02 to 0.07)	0.24
Baseline eGFR, ml/min per 1.73 m^2	0.04 (−0.06 to 0.14)	0.39	−0.03 (−0.12 to 0.07)	0.60
Baseline plasma potassium, mmol/L	2.0 (−9.7 to 13.6)	0.72	−3.1 (−10.6 to 4.3)	0.38
Baseline venous pH	−52 (−96 to −7)	0.03	−37 (−79 to 4)	0.07
Baseline plasma bicarbonate, mmol/L	0.22 (−0.30 to 0.75)	0.38	0.41 (−0.16 to 0.98)	0.15
Baseline Ln plasma aldosterone, ng/L	5.2 (2.6 to 7.9)	<0.001	1.3 (−2.3 to 4.9)	0.46
Baseline Ln plasma renin, ng/L	0.5 (−6.8 to 7.8)	0.88	3.3 (−1.1 to 7.7)	0.13
	Potassium Citrate with Lisinopril		Potassium Chloride with Lisinopril	
			TTKG T0–T120	
Age, yr	−0.1 (−0.2 to −0.0)	0.04	−0.1 (−0.1 to 0.0)	0.30
Sex, woman	−3.1 (−6.1 to −0.0)	0.05	−2.5 (−5.5 to 0.6)	0.11
BMI, kg/m^2	−0.30 (−0.77 to 0.17)	0.20	−0.07 (−0.48 to 0.34)	0.74
24-h sodium excretion, mmol	0.01 (−0.01 to 0.04)	0.34	−0.01 (−0.04 to 0.02)	0.54
24-h potassium excretion, mmol	−0.02 (−0.07 to 0.03)	0.33	0.04 (−0.01 to 0.08)	0.11
Baseline eGFR, ml/min per 1.73 m^2	0.08 (−0.02 to 0.17)	0.10	0.03 (−0.05 to 0.12)	0.42
Baseline plasma potassium, mmol/L	−1.3 (−7.8 to 5.1)	0.66	−4.4 (−15.5 to 6.7)	0.41
Baseline venous pH	−18 (−99 to 64)	0.65	−31 (−80 to 18)	0.20
Baseline plasma bicarbonate, mmol/L	−0.11 (−1.08 to 0.86)	0.81	0.21 (−0.50 to 0.93)	0.54
Baseline Ln plasma aldosterone, ng/L	1.2 (−1.6 to 4.0)	0.38	1.0 (−1.7 to 3.7)	0.45
Baseline Ln plasma renin, ng/L	0.1 (−1.9 to 2.2)	0.89	1.3 (−0.4 to 3.0)	0.12

CI, confidence interval; TTKG, transtubular potassium gradient; BMI, body mass index.

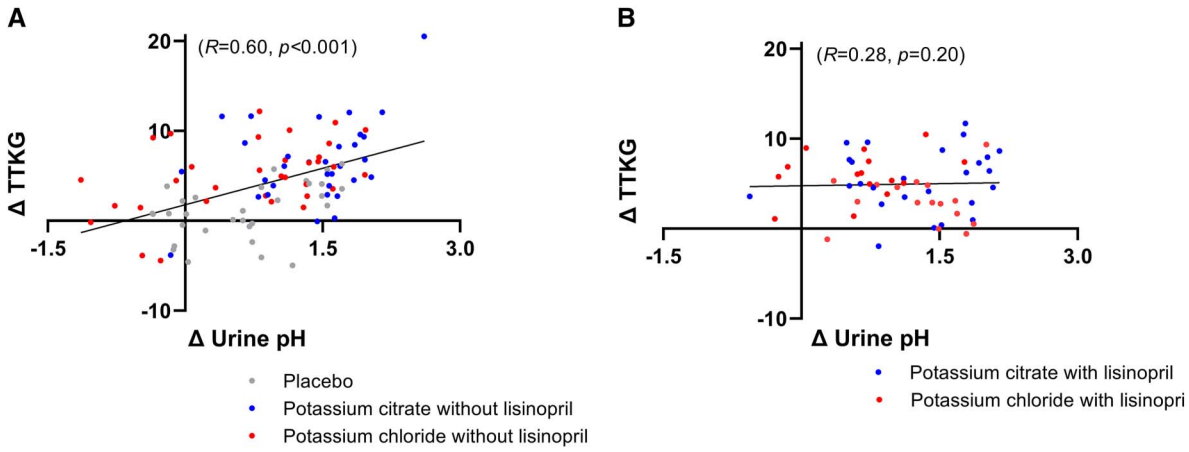

Figure 4. Correlation between change in urine pH and TTKG after a placebo, potassium citrate, and potassium chloride load. Pooled correlation between change in urine pH and TTKG 120 and 240 minutes after supplementation of placebo, potassium citrate, and potassium chloride without lisinopril pretreatment (A) and with lisinopril pretreatment (B). Pooled correlation coefficients were calculated with the Fisher Z transformation. The black line represents the linear regression line. TTKG, transtubular potassium gradient. Figure 4 can be viewed in color online at www.cjasn.org.

potassium citrate and potassium chloride disappeared with lisinopril, suggesting that both changes in acid–base balance and aldosterone contribute to the increased intracellular uptake and excretion of potassium after potassium citrate.

The differences in intracellular uptake of potassium between potassium citrate and potassium chloride are likely attributable to the alkalizing properties of potassium citrate. After potassium citrate, there was a small but significant rise in venous pH, which promotes intracellular uptake of potassium in exchange for hydrogen ions leaving the cell.[25] In agreement with our results, a previous study in potassium-depleted nephrectomized dogs showed that cellular uptake of potassium was higher after intravenous potassium bicarbonate supplementation than after intravenous potassium chloride supplementation.[26]

After supplementation of potassium citrate, total potassium excretion and TTKG were higher as compared with potassium chloride. Potassium secretion is mainly regulated by the distal convoluted tubule and connecting tubule. Major regulators of potassium secretion are plasma potassium, plasma aldosterone, sodium delivery, and luminal flow rate.[27,28] Because no significant differences were observed in plasma aldosterone, plasma potassium, natriuresis, and urinary flow rate between potassium citrate and potassium chloride, the increased kaliuresis after potassium citrate compared with potassium chloride was likely the result of the higher venous pH after potassium citrate.[29] Several mechanisms may contribute to increased potassium secretion during metabolic alkalosis. First, increased potassium secretion during alkalosis might be mediated by higher potassium uptake in the principal cells. In an experimental study, it was shown that the active uptake of ^{42}K, an isotope of potassium, in cells of the initial and cortical collecting duct, presumably principal cells, and secretion of ^{42}K into the lumen was higher after infusion of 5% sodium bicarbonate as compared with 3% mannitol in saline.[29,30] As described above, this is likely the result of the higher blood pH stimulating a shift of potassium into cells. Second, increased potassium secretion after potassium citrate compared with potassium chloride might be caused by a higher intracellular pH of the principal cells and subsequent increased activity of the pH-sensitive renal outer medullary potassium and BK channels.[19,20] A higher intracellular pH also stimulates the activity of the basolateral potassium channel (Kir4.1/5.1) in the distal convoluted tubule, resulting in increased potassium reabsorption.[31] However, because a high-potassium diet decreases the activity of Kir4.1/Kir5.1, these two opposing effects might cancel each other out.[32] Third, increased potassium secretion might be the consequence of decreased activity of H^+-K^+-ATPase in the collecting duct's type A intercalated cells in response to metabolic alkalosis.[33] Fourth, an alkali load might reduce the activity of the Na^+/H^+ exchanger in the proximal tubule and the thick ascending limb, leading to increased distal sodium delivery and enhanced sodium reabsorption through epithelial Na^+ channel, thereby creating favorable electrochemical gradient for potassium excretion.[34]

Conversely, pretreatment with lisinopril attenuated the differences in intracellular uptake and secretion of potassium between potassium citrate and potassium chloride. Although plasma aldosterone varied, concentrations tended to be lower after pretreatment with lisinopril. Moreover, the aldosterone-to-renin ratio was significantly lower after lisinopril pretreatment, indicating that lisinopril effectively inhibited angiotensin-converting enzyme activity. Aldosterone promotes the intracellular uptake of potassium through stimulation of Na^+-K^+-ATPase.[35] In rats, it was shown that after adrenalectomy, Na^+-K^+-ATPase activity decreased both in RBCs and various nephron segments,[36] which may result in diminished intracellular uptake of potassium. Regarding potassium secretion, a previous study has shown that aldosterone may increase the expression of BK channels.[37] Interestingly, we only found a significant association between baseline plasma aldosterone and change in TTKG after supplementation

of potassium citrate, but not after supplementation of potassium chloride, suggesting that the effects of aldosterone on potassium secretion are influenced by the anion accompanying potassium. In mice, a high-potassium alkaline diet (5.0% K with 5% of equal carbonate/citrate/Cl) increased apical BK-α in the cortical collecting duct, while a high-potassium acidic diet (5.0% K with 5.0% Cl) only increased cytoplasmic BK-α, suggesting that alkalosis promotes the apical localization of BK-α.[37] Moreover, when a high-potassium alkaline diet was combined with spironolactone apical expression of BK-α was lower.[37] The slightly lower plasma aldosterone concentrations after lisinopril pretreatment may explain, at least in part, the lower potassium secretion and TTKG after potassium citrate supplementation during the study period with lisinopril.

Although differences were observed in intracellular uptake and excretion of potassium, no differences were observed in plasma potassium concentration between potassium citrate and potassium chloride. A potential explanation is that participants received the potassium supplements after an overnight fast, and therefore, their insulin levels were low. Insulin promotes intracellular uptake of potassium by increasing Na^+-K^+-ATPase activity and thereby prevents increases in plasma potassium concentrations after potassium-rich meals.[38,39] In a previous study in healthy individuals, it was shown that plasma potassium increased after a single oral load of potassium chloride, but when potassium chloride was combined with a meal, no increase in plasma potassium was observed.[10] Thus, low levels of insulin may reduce intracellular uptake of potassium and mask the differences in plasma potassium between potassium citrate and potassium chloride.

Our study has several strengths and limitations. Strengths include the randomized cross-over design and serial blood and urine collections. In addition, we assessed intracellular shift of potassium by measuring RBC potassium. A potential limitation is that change in RBC potassium does not reflect change in other tissues that buffer potassium, including skeletal muscle and liver. However, in a previous study, a good correlation was present between RBC potassium and total body potassium.[40] Second, the potassium chloride capsules were substituted by potassium chloride oral solution halfway through the course of the study, which might have affected the gastrointestinal uptake of potassium. Yet, no differences in plasma potassium and potassium secretion were observed between participants who received the potassium chloride capsules and potassium chloride oral solution (Supplemental Table 4). Third, the use of the TTKG is debated because it does not account for distal tubular urea reabsorption, which may affect potassium excretion.[41] However, 24-hour excretion of urea preceding the study visit and cumulative excretion of urea during follow-up did not differ between the interventions (data not shown). In addition, similar to the TTKG, total potassium excretion and urine potassium-to-creatinine ratio were higher after an oral load of potassium citrate than after an oral load of potassium chloride during the study period without lisinopril. A fourth limitation is the single-blind study design. Yet, on the basis of 24-hour excretions of sodium, potassium, and urea, baseline values preceding each intervention were similar regardless of the study visit, that is, changes in diet did not contribute to differences between the interventions. Fifth, only the acute effects of a single potassium dose were studied, while results might be different during chronic potassium supplementation. Sixth, because of the sample size and exploratory objective of our study, only univariable regression analyses were performed to assess the association between baseline values and change from baseline in RBC potassium and TTKG. Finally, because we only included healthy individuals with a normal kidney function, further studies are needed to assess whether differences between potassium citrate and potassium chloride are also present in patients with reduced kidney function. These patients have a high risk of hyperkalemia and metabolic acidosis but may also benefit from a potassium replete diet. Therefore, a potassium replete alkaline diet might be preferable.[42]

In conclusion, we demonstrated that in healthy individuals, RBC uptake and urinary excretion of potassium after an acute oral load of potassium citrate were higher than after an acute oral load of potassium chloride, while plasma potassium was similar. Because changes in venous pH and RBC potassium were correlated with changes in urine pH and TTKG, differences in RBC uptake and excretion of potassium are likely the result of changes in acid–base status caused by the accompanying anion. These results support current recommendations to administer potassium chloride instead of potassium citrate in patients with hypokalemia.[43] Conversely, after pretreatment with lisinopril, no differences were observed between potassium citrate and potassium chloride, suggesting that aldosterone also plays a key role in the increased intracellular uptake and excretion of potassium after potassium citrate. Because differences in intracellular uptake and excretion of potassium may have implications for hyperkaliemia development in the long term, future studies should focus on the chronic effects of potassium citrate and potassium chloride supplementation, especially when combined with a meal or renin-angiotensin-aldosterone system inhibitors.

Disclosures

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Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B785.

Supplemental Methods.

Supplemental Table 1. Exclusion criteria.

Supplemental Table 2. Baseline characteristics preceding all interventions.

Supplemental Table 3. Urine potassium-to-creatinine ratio during follow-up.

Supplemental Table 4. Change in plasma potassium and potassium excretion in participants receiving potassium chloride capsules and potassium chloride oral solution.

Supplemental Figure 1. Study design.

Supplemental Figure 2. Flow chart of inclusion of participants.

Supplemental Figure 3. Correlation between change in plasma [HCO_3^-], plasma [Cl^-], and plasma [Na^+] and change in RBC K^+ after a placebo, potassium citrate, and potassium chloride load.

Supplemental Figure 4. Placebo-subtracted cumulative excretion of sodium 120 and 240 minutes after an oral load of potassium citrate and potassium chloride load.

Supplemental Figure 5. Placebo-subtracted cumulative excretion of chloride 120 and 240 minutes after an oral load of potassium citrate and potassium chloride load.

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