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ORIGINAL ARTICLE

Diminished antiproteinuric effect of the angiotensin receptor blocker losartan during high potassium intake in patients with CKD

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ABSTRACT

Background. Angiotensin II type 1 receptor blockers (ARBs) lower blood pressure (BP) and proteinuria and reduce renal disease progression in many—but not all—patients. Reduction of dietary sodium intake improves these effects of ARBs. Dietary potassium intake affects BP and proteinuria. We set out to address the effect of potassium intake on BP and proteinuria response to losartan in non-diabetic proteinuric chronic kidney disease (CKD) patients.

Methods. We performed a *post hoc* analysis of a placebo-controlled interventional cross-over study in 33 non-diabetic proteinuric patients (baseline mean arterial pressure and proteinuria: 105 mmHg and 3.8 g/day, respectively). Patients were treated for 6 weeks with placebo, losartan and losartan/hydrochlorothiazide (HCT), combined with a habitual (∼200 mmol/day) and low-sodium (LS) diet (<100 mmol/day), in randomized order. To analyse the effects of potassium intake, we categorized patients based on median split of 24-h urinary potassium excretion, reflecting potassium intake.

Results. Mean potassium intake was stable during all six treatment periods. Losartan and losartan/HCT lowered BP and proteinuria in all treatment groups. Patients with high potassium intake showed no difference in the BP effects compared with patients with low potassium intake. The antiproteinuric response to losartan monotherapy and losartan combined with HCT during the habitual sodium diet was significantly diminished in patients with high potassium intake (20% versus 41%, P = 0.011; and 48% versus 64%, P = 0.036). These differences in antiproteinuric response abolished when shifting to the LS diet.

Conclusions. In proteinuric CKD patients, the proteinuria, but not BP-lowering response to losartan during a habitual high-sodium diet was hampered during high potassium intake. Differences disappeared after sodium status change by LS diet.

Keywords: blood pressure, chronic kidney disease, potassium intake, proteinuria, RAAS inhibition

INTRODUCTION

Renin–angiotensin–aldosterone system (RAAS) inhibitors are regarded as the pharmacological cornerstone of renoprotective therapy in chronic kidney disease (CKD), because of their blood pressure (BP) lowering and antiproteinuric effects [1–3]. Although RAAS inhibitors are effective in reducing BP and proteinuria in most patients, large individual differences in treatment effects exist [4, 5]. Many strategies have been studied to optimize the renoprotective action of RAAS inhibitors, including additional treatment with diuretics and dietary measures. It has been shown by several studies that the efficacy of single RAAS inhibitor, either an angiotensin-converting enzyme inhibitor or an angiotensin II type 1 receptor blocker (ARB), can be increased by adding a diuretic or restriction of the dietary sodium intake [6–8]. Although differences in sodium status may explain part of the variation in therapeutic response, it does not explain all inter-individual variation. Moreover, patients with CKD still progress to end-stage renal disease while using these agents. Therefore, to improve therapy, additional factors that affect therapeutic response need to be identified.

Another dietary component that may interfere with RAAS inhibitor therapy is potassium. Recent insights in the epidemiology of cardiovascular disease (CVD) have outlined a protective role of a potassium-rich diet. Large cohort studies have shown that high urinary potassium excretion—as proxy for dietary potassium intake—is associated with a lower BP [9, 10] and reduced proteinuria [11, 12]. Whether a high dietary potassium intake improves the BP and proteinuria-lowering efficacy of single RAAS inhibitor therapy in patients with CKD is unknown. It also remains to be determined whether high potassium intake will interfere with the added proteinuria-lowering effect of dietary sodium restriction on top of single RAAS inhibition. In this *post hoc* analysis of a randomized-placebo controlled crossover study, comparing the efficacy of losartan during a habitual high-sodium (HS) and low-sodium (LS) diet with and without addition of hydrochlorothiazide (HCT), we set out to address the effect of potassium intake on BP and proteinuria response to the ARB losartan in patients with non-diabetic proteinuric CKD.

MATERIALS AND METHODS

Patients and study design

We performed a *post hoc* analysis of a placebo-controlled interventional cross-over study conducted in the University Medical Centre Groningen [6]. The study was conducted in accordance with the declaration of Helsinki and approved by the local Medical Ethics Committee. All subjects signed informed consent. Patients were selected from the outpatient renal clinic between March 2004 and June 2006. All enrolled patients had non-diabetic CKD and were aged between 18 and 70 years. The underlying causes of glomerular disease are presented in the supporting document (Supplementary data, Figure S1). All patients had stable creatinine clearance (>30 mL/min and <6 mL/min/year decline) and stable proteinuria (>2 and <10 g/day). Patients were excluded if they had diabetes, uncontrolled hypertension [mean arterial pressure (MAP) >100 mmHg], hyperkalaemia (serum potassium >5.5 mmol/L), any CVD or cardiovascular event within the last 6 months or a contraindication for ARBs and/or diuretics. The use of antihypertensive medication other than RAAS inhibitors and diuretics was allowed, provided that the use of this medication did not change during the study.

After inclusion patients were treated with placebo, losartan 100 mg [Cozaar (Merck & Co. Inc., Whitehouse Station, NJ, USA)], and losartan/HCT 100 mg/25 mg [Fortzaar (Merck & Co. Inc.)], respectively. To allow washout each treatment period lasted for 6 weeks. Patients underwent the three interventions during both an HS diet (∼200 mmol/day) and an LS diet (<100 mmol/day); therefore, each patient had 18 weeks of HS and 18 weeks of LS for a total study period of 36 weeks (Figure 1). The order of the drug intervention as well as the sodium intervention was determined by randomization. To improve adherence to both sodium diets participants were counselled by a dietician. During the LS diet, patients were instructed to resemble their normal diet as much as possible, but to replace sodium-rich products with LS products from the same product group to keep protein, carbohydrate and fat intake as stable as possible. Vice versa, during the HS diet, patients with a low 24-h urine sodium excretion were instructed to replace LS products with sodium-rich products. Additionally, to assess dietary adherence 24-h urine samples were collected every 2 weeks during the course of the study. For this analysis, we used 24-h urine collections of the day preceding each 6-week study visit.

Study measurements

At the end of each 6-week period, a study visit was planned. After an overnight fast, patients visited the research department for blood sampling and BP measurements. Twenty four-hour urine was collected for analysis of proteinuria and electrolyte concentrations. Proteinuria was measured using the pyrogallol red-molybdate method. Serum and urine electrolyte concentrations were measured using an automated
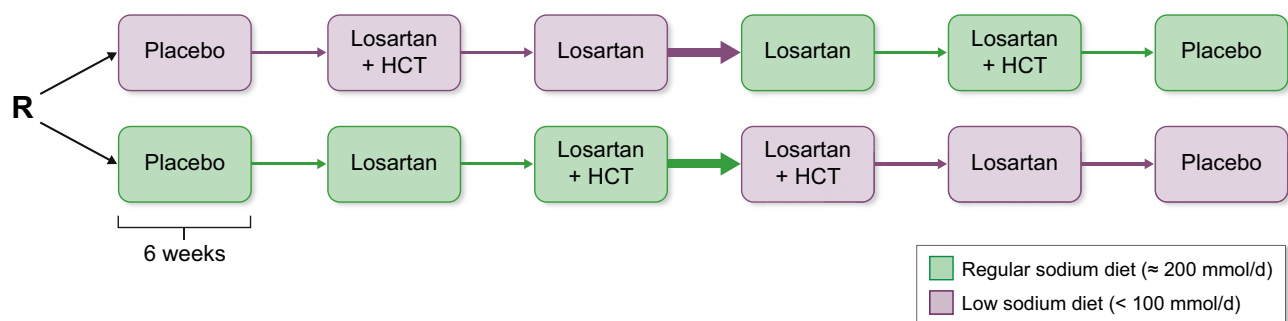

FIGURE 1: Study design. After inclusion patients were treated for 6 weeks with placebo, losartan (100 mg/day) and losartan plus HCT (losartan 100 mg/day plus HCT 25 mg/day). Patients underwent the three interventions during both an HS diet (∼200 mmol/day) and an LS diet (<100 mmol/day). The order of the drug intervention, as well as the sodium diet, was determined by randomization. R, randomization.

multi-analyser (SMA-C; Technicon, Tarrytown, NY, USA). Radioimmunoassay (RIA kit, Diagnostic Products Corp., Los Angeles, CA, USA) was used to determine plasma aldosterone and plasma renin activity (PRA). Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were measured with an electrochemiluminescent sandwich immunoassay (ElecsysProBNP, Roche Diagnostics, Mannheim, Germany). BP was measured in semisupine position using a semi-automatic device (Dinamap, GE Medical Systems, Milwaukee, WI, USA) over a period of 15 min with an interval of 1 min. The mean of the last four measurements was used for statistical analysis.

To monitor unanticipated changes in intake of other nutrients than sodium during the dietary sodium intervention, both potassium intake and protein intake, respectively, were calculated by the use of 24-h urine potassium excretion (in mmol/day multiplied by the correction factor of 1.3 to estimate potassium intake[13, 14]) and protein equivalent of total nitrogen appearance normalized to body weight (nPNA) based on 24-h urea excretion, using the following equation: $nPNA_{(g/kg \text{ per day})} = (15.7 + 0.209 \text{ urea appearance}_{(mmol/day)})/\text{body weight}_{(kg)}$ [15].

Statistical analysis

Continuous data are expressed as mean and standard error (SE). Data that followed skewed distribution are shown as median and interquartile range (IQR). Multiple imputation was used to replace missing values of 24-h potassium excretion (8 out of 198 values missing). The visit after 6 weeks placebo on HS diet was considered as baseline visit. To analyse whether 24-h urinary potassium excretion changed during the course of the study, we used a general linear model for repeated measures. Based on the median 24-h urinary potassium excretion of the six 24-h urine collections, patients were categorized into high and low potassium intake. High potassium intake was defined as equal to or above median value, while low potassium intake was defined as below the median. Differences between patients with a high and low potassium intake at baseline were assessed using unpaired t-tests or—in case of non-normal distributed variables—Mann–Whitney U test. We then used a mixed-effects model with least significant difference (LSD)*post hoc* test to point out differences in laboratory and haemodynamic parameters between high and low potassium intake during the interventions. Skewed variables were natural-log transformed before analysing. To predict the antiproteinuric and antihypertensive response to treatment, we performed a multiple regression analysis. Antiproteinuric and antihypertensive response to treatment was defined as percent reduction from baseline. Next to patient characteristics [age, sex and body mass index (BMI)], other known clinical relevant variables were entered in the model, including potassium intake, 24-h sodium excretion, PRA, plasma aldosterone concentrations and serum NT-proBNP levels [16]. In the model of the antiproteinuric response, baseline MAP and estimated protein intake were added as well. We used backward elimination to yield the most appropriate regression equation. Multicollinearity was assessed by examining tolerance and the variance inflation factor. Significant differences were assumed to be at $P < 0.05$ (SPSS, version 24.0, Inc., Chicago, IL, USA, GraphPad Prism version 8.0.2).

RESULTS

Patient characteristics

Thirty-four patients with non-diabetic CKD were included in the study, because one patient could not fulfil the complete study protocol, 33 patients (24 males and 9 females) were included in this analysis. Age ranged from 23 to 68 years, with a mean of 50 years. Subjects were slightly overweight with a mean BMI of $27.5 \pm 0.8 \text{ kg/m}^2$. At baseline, all patients had a stable creatinine clearance [estimated glomerular filtration rate (eGFR) $60 \pm 4 \text{ mL/min/1.73 m}^2$] and proteinuria ($3.8 \pm 0.4$ g/day). Mean 24-h urine sodium excretion during the HS diet was 196 ± 9 mmol versus 92 ± 8 mmol during the LS diet. Median 24-h potassium excretion was 77 ± 29 mmol, reflecting an estimated potassium intake of 100 ± 38 mmol/day. After separating patients into two groups based on median split of potassium intake, no significant differences in sex, age, BMI, plasma potassium, BP, eGFR and proteinuria between subjects with a low and high potassium intake were observed at baseline, except for PRA and 24-h urine creatinine excretion. Potassium intake was stable during all six treatment periods. Estimated protein intake, however, varied during the course of the study with a lower median protein intake in the low potassium intake group (Table 1).

The effect of potassium intake on the antihypertensive and antiproteinuric response to treatment

BP and proteinuria were significantly reduced by all interventions (losartan, losartan/HCT on both LS and HS, and placebo—LS) (overall reduction of MAP and proteinuria: $-9 \pm 2\%$ and $-47 \pm 9\%$, $P < 0.001$ for both MAP and proteinuria). Patients with a high potassium intake (above median) had similar BP reductions across all interventions as compared with low potassium intake (below median), whereas overall reduction of proteinuria was less in patients with a high potassium intake (low potassium: $-55 \pm 7\%$ and high potassium: $-39 \pm 10\%$, $P = 0.01$). To further specify the difference in reduction of proteinuria between high and low potassium intake, groups were compared within each intervention. The difference in antiproteinuric response was significant during losartan monotherapy ($20 \pm 6\%$ versus $41 \pm 6\%$, $P = 0.01$) (Figure 2A) and became smaller after adding HCT to losartan ($48 \pm 6\%$ versus $64 \pm 4\%$, $P = 0.04$) (Figure 2B).

Also, after introduction of a LS diet alone there was a significant difference in reduction of proteinuria from baseline between patients with high and low potassium intake ($11 \pm 8\%$ versus $35 \pm 7\%$, $P = 0.03$) (Figure 2C). However, when adding an LS diet to losartan therapy, the differences abolished (losartan—LS: low potassium: $-61 \pm 5\%$ and high potassium: $-50 \pm 7\%$, $P = 0.18$; losartan/HCT—LS: low potassium: $-74 \pm 5\%$ high potassium: $-66 \pm 6\%$, $P = 0.30$) (Supplementary data, Figure S2).

Determinants of the BP response

We observed no difference in BP response to therapy between patients with a high potassium intake as compared with patients with a low potassium intake. Multiple regression analysis pointed out that baseline PRA ($\beta = 6.1 \pm 2.4$, $P = 0.018$) was a significant predictor of the antihypertensive response to losartan monotherapy. The antihypertensive response to losartan combined with HCT was determined 24-h sodium excretion during the HS diet ($\beta = -0.07 \pm 0.03$, $P = 0.015$). Lastly, during an LS diet alone baseline PRA ($\beta = -3.4 \pm 1.6$, $P = 0.047$) was a significant predictor of the BP response.

Table 1. Patient characteristics low versus high potassium intake at baseline (the visit after 6 weeks placebo on HS diet)

Characteristic	Low potassium intake (<100 mmol/day)[a] $n = 16$	High potassium intake (≥100 mmol/day)[a] $n = 17$	P-value
Sex (male), n/N	11/16	13/17	0.63
Age (years)	49 ± 3	52 ± 3	0.54
BMI (kg/m^2)	27 ± 1	28 ± 1	0.80
BP			
Systolic BP (mmHg)	140 ± 6	145 ± 6	0.60
Diastolic BP (mmHg)	87 ± 4	86 ± 2	0.68
MAP (mmHg)	105 ± 5	106 ± 3	0.91
Blood			
Serum potassium (mmol/L)	4.3 ± 0.1	4.2 ± 0.1	0.51
Serum sodium (mmol/L)	139 ± 1	139 ± 1	0.93
Serum creatinine (μmol/L)	133 ± 15	117 ± 6	0.31
Creatinine clearance (mL/min)	79 ± 7	97 ± 6	0.06
eGFR (mL/min/1.73 m^2)	60 ± 6	60 ± 4	0.92
Serum urea (mmol/L)	7.4 ± 0.9	6.7 ± 0.4	0.45
Haemoglobin (mmol/L)	8.9 ± 0.2	9.4 ± 0.2	0.11
Haematocrit (L/L)	0.43 ± 0.01	0.45 ± 0.01	0.15
Plasma aldosterone (pg/mL)[c]	99 ± 130	60 ± 64	0.20[b]
PRA (ng/mL)[c]	4.6 ± 3.5	3.5 ± 2.3	0.04[b]
Serum NT-proBNP (pg/mL)[c]	121 ± 256	61 ± 177	0.36[b]
24-h urine			
Volume (L)	2.1 ± 0.2	2.2 ± 0.2	0.82
Potassium (mmol/day)	70 ± 4	94 ± 6	0.002
Sodium (mmol/day)	186 ± 15	213 ± 13	0.18
Creatinine (mmol/day)	13 ± 1	16 ± 1	0.03
Urea (mmol/day)	346 ± 20	432 ± 20	0.005
Proteinuria (g/day)[c]	4.2 ± 2.7	2.3 ± 4.1	0.60[b]
Protein intake (nPNA) (g/kg/day)[c,d]	1.0 ± 0.3	1.2 ± 0.4	0.13[b]

All data are presented as mean ± SEM by independent sample test, unless indicated otherwise.[a]Estimated potassium intake based on six 24-h urine collections.[b]Mann–Whitney U test.[c]Median ± IQR.
[d]Although no significant difference in protein intake between the high and low potassium intake group was observed at baseline, median protein intake during the total study period of 36 weeks was lower in patients with a low potassium intake (low potassium intake group: 1.0 ± 0.3; high potassium intake group 1.2 ± 0.3, P = 0.01).
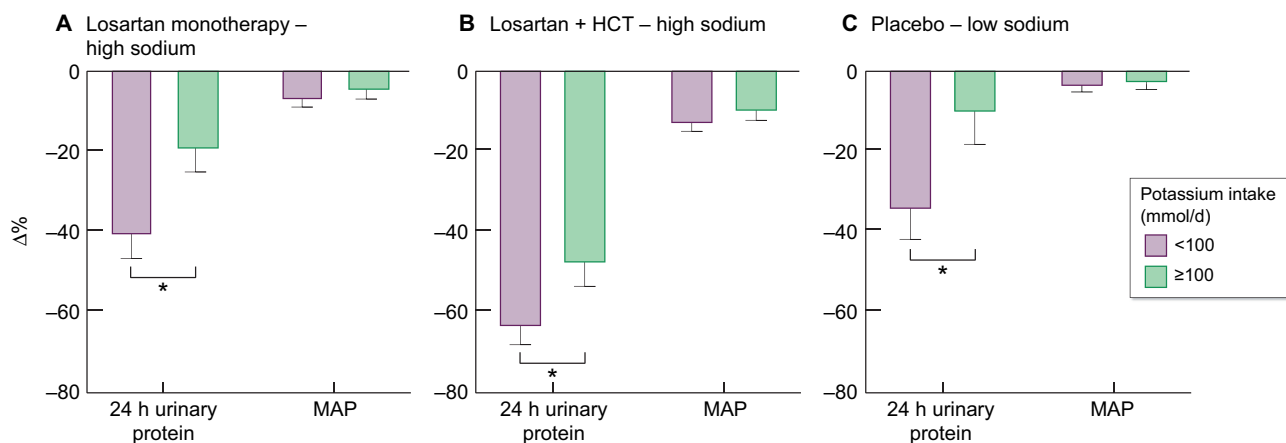

FIGURE 2: The relative antiproteinuric and BP response to losartan with and without HCT during a HS diet and placebo during LS diet. (A) The antiproteinuric response to losartan monotherapy was significantly higher in patients with a low potassium intake compared with patients with a high potassium intake (P = 0.011). (B) This difference became smaller, but was still significant after adding HCT (P = 0.036). (C) Also, the antiproteinuric response to placebo during an LS diet was significantly higher in patients with a low potassium intake compared with patients with a high potassium intake (P = 0.032). No significant differences in BP response were observed between a high and low potassium intake. Values are mean ± SEM.

Determinants of the antiproteinuric response

To predict the antiproteinuric response to losartan a multiple regression analysis was performed. Results indicated that potassium intake ($\beta = -0.4 \pm 0.2$, P = 0.036) and baseline protein intake ($\beta = 47.1 \pm 18.8$, P = 0.019) were significant independent predictors of the antiproteinuric response to losartan monotherapy. Following from these results, every 1 mmol increase in daily potassium intake decreases the antiproteinuric effect of

Table 2. Results of multiple linear regression analysis with backward elimination for the prediction of the antiproteinuric effect of losartan

Independent variable	β	SE	T	P-value
Ln baseline protein intake (nPNA)(g/kg/day)	47.1	18.8	2.5	0.019
Potassium intake (mmol/day)	−0.4	0.2	−2.2	0.036
Ln baseline plasma aldosterone (pg/mL)	9.1	4.5	2.0	0.052
Age (years)	−0.6	0.3	−1.7	0.094

Variables entered: sex, age, BMI, 24-h potassium and sodium excretion, ln baseline protein intake, ln baseline aldosterone, ln baseline PRA, ln baseline NT-proBNP and baseline MAP. After backward elimination of covariates the R-squared for this model was 0.38 (P = 0.012).
Ln, natural logarithm.

Table 3. Results of multiple linear regression analysis with backward elimination for the prediction of the antiproteinuric effect of losartan combined with HCT

Independent variable	β	SE	T	P-value
Baseline MAP (mmHg)	0.5	0.2	2.2	0.038
24-h sodium excretion (mmol/day)[a]	−0.1	0.1	−1.9	0.065
Ln baseline protein intake (nPNA)(g/kg/day)	26.5	15.3	1.7	0.095

Variables entered: sex, age, BMI, 24-h potassium and 24-h sodium excretion, ln baseline protein intake, ln baseline aldosterone, ln baseline PRA, ln NT-proBNP and baseline MAP. After backward elimination of covariates the R-squared for this model was 0.27 (P = 0.042).
[a]Mean of three visits during habitual sodium diet.
Ln, natural logarithm.

Table 4. Results of multiple linear regression analysis with backward elimination for the prediction of the antiproteinuric response to an LS diet alone (i.e. during placebo)

Independent variable	β	SE	T	P-value
24-h sodium excretion (mmol/day)[a]	−0.3	0.1	−2.2	0.034
24-h potassium excretion (mmol/day)	−0.4	0.2	−2.0	0.057

Variables entered: sex, age, BMI, 24-h potassium and sodium excretion, ln baseline nPNA, ln baseline aldosterone, ln baseline PRA, lnnt-proBNP and baseline MAP. After backward elimination of covariates the R-squared for this model was 0.28 (P = 0.013).
[a]Mean of three visits during LS diet.
Ln, natural logarithm.

losartan with 0.4%. Baseline aldosterone concentration showed a trend towards association ($\beta = 9.1 \pm 4.5$, P = 0.052) (Table 2).

After correction for covariates baseline MAP ($\beta = 0.5 \pm 0.2$, P = 0.038) was the only significant predictor of the antiproteinuric effect of losartan with HCT (Table 3).

Finally, the antiproteinuric response to an LS diet alone (i.e. during placebo) was determined by 24-h sodium excretion during the LS diet ($\beta = -0.3 \pm 0.1$, P = 0.03). Potassium intake showed a trend towards association ($\beta = -0.4 \pm 0.2$, P = 0.057) (Table 4).

DISCUSSION

This study shows that in patients with proteinuric CKD on a habitual sodium diet, the proteinuria, but not BP-lowering response to losartan, was hampered in patients with a high potassium intake. Differences became smaller after addition of HCT. The antiproteinuric response to an LS diet during placebo was reduced in patients with a high potassium intake as well. During both single losartan and losartan plus HCT, differences disappeared when an LS diet was added to both treatments. Results from multiple linear regression analysis also showed that potassium intake, independent of baseline protein intake and plasma aldosterone concentration, represented a significant predictor of the antiproteinuric response during losartan monotherapy. During losartan combined with HCT, potassium intake was no longer a predictor of the antiproteinuric response. In this analysis, baseline MAP was a significant predictor of the antiproteinuric response during the losartan and HCT combination. Response in BP during losartan monotherapy was determined by baseline PRA, but not potassium intake.

We hypothesized that a potassium-rich diet would increase the efficacy of losartan (either with or without HCT) and an LS diet. Surprisingly, the opposite effect was observed with regard to the antiproteinuric effect. A potential explanation for this phenomenon could be that a high potassium diet mimics the effects of an LS diet and losartan, due to its natriuretic effects [17], reducing the net effect of these interventions. Since the effect of potassium intake seems to be independent of baseline aldosterone, a possible point of action could be the type-1 angiotensin receptor (AT1R). Losartan is an ARB that competes with angiotensin II for binding to the AT1R, the antagonizing effect of losartan results in reduced sodium and water retention and diminished sympathetic activation and vasoconstriction [18]. The effects of potassium on the AT1R are less well known, but have been previously studied in experimental studies. An *in vitro* study demonstrated that high concentrations of potassium induce downregulation of the AT1R expression in human H295R adrenocortical cells in a dose-dependent way. After 24-h treatment of these cells with high levels of potassium (14 mmol/L), receptor binding of labelled angiotensin II was reduced to a minimum of 60% [19]. Additionally, a study in rats showed that rats fed a high potassium diet (2.5% and 10%) for 7 days had a 50% and 75% lower expression of AT1R in the kidney, respectively, compared with rats fed a normal potassium diet (1%) [20]. Likewise, rats and mice subjected to a low potassium diet (0.1%) for 7 days showed an increase in the expression of AT1R in the kidney of 110% (rats) and 95% (mice) compared with rats and mice fed with a normal potassium diet (1%) [21]. Finally, in rabbits fed with a potassium-deficient diet for 14 days, the expression of the AT1R in the kidney was increased, but the AT1R expression in the liver was not [22]. The above animal data, together with our finding that efficacy in terms of BP reduction was not influenced by potassium intake, suggest that potassium intake specifically affects the renal AT1R. Since losartan is a selective AT1R antagonist, our data suggest that the antiproteinuric efficacy of losartan might be reduced in patients with a lower renal expression of this receptor as a result of a high potassium intake.

Next to the effects of a high potassium diet on the AT1R, several studies have shown that an LS diet decreases the expression of the AT1R in aortas and heart tissue of rodents [23, 24]. Similarly, in spontaneously hypertensive rats an HS diet (6% NaCl) led to an increase of the AT1R density in the renal cortex of 41% [25]. Since both a high potassium intake, as well as

an LS intake cause downregulation of the AT1R, the antiproteinuric effect of an LS diet may be less pronounced in patients with a high potassium intake. Differences in antiproteinuric effect between high and low potassium intake disappeared during losartan treatment combined with an LS diet. After adding an LS diet on top of losartan plus HCT, proteinuria was reduced even more. We hypothesize that these interventions combined may overshadow the potential effects of a high potassium diet, resulting in an equal antiproteinuric response between both groups.

In contrast to what one would expect based on cohort studies and dietary intervention studies in non-renal subjects [10, 26, 27], we found no differences in BP between a high and low potassium intake. Also, the BP response to the interventions of our study did not differ. This could be explained by the fact that the effect of a high potassium intake on the AT1R is kidney specific, as was shown in the animal studies. Binding of angiotensin II to the AT1R in the kidney leads to vasoconstriction of the efferent arterioles in the kidney, resulting in an increased glomerular pressure and subsequently ultrafiltration of plasma proteins [28]. Next to that, angiotensin II may also directly contribute to kidney damage because of its pro-inflammatory properties [29]. These kidney-specific effects may explain why we found a difference in the antiproteinuric response, but not in the BP response, between patients with a high potassium intake.

A potential limitation of this study is that there was a difference in PRA at baseline. The inverse relation between potassium intake and PRA was described in earlier animal and human studies [30–32]. In normal and hypertensive subjects administration of potassium reduced PRA, independently of changes in plasma aldosterone and sodium balance [30]. Although there was a difference in PRA at baseline our multiple regression model showed that PRA was not a significant predictor of the antiproteinuric effect of losartan, indicating that it is unlikely that the differences in antiproteinuric response to losartan are caused by a difference in PRA. Second, a higher protein intake was observed in the high potassium intake group. These differences may explain the diminished antiproteinuric effect in patients with a high potassium intake [33]. However, in the multivariate analysis, potassium intake was a significant predictor of the antiproteinuric response to losartan, independent of protein intake. Therefore, the difference in baseline protein intake may not explain the hampered antiproteinuric response during losartan-based therapy. Third, the sample size of this study is small, particularly given the associative nature of this analysis. Nevertheless, this is the first study assessing the influence of dietary potassium intake on the efficacy of losartan-based therapy. Fourthly, because we did not do an actual intervention on the potassium intake, differences in potassium intake between the high and low potassium intake group were rather small. Also, 24-h potassium excretion in our study was relatively high as compared with other large-cohort studies in patients with CKD [34, 35]. This may explain why we did not observe differences in BP and proteinuria at baseline. Finally, yet importantly, the diminished antiproteinuric response to losartan may not be exclusively attributed to a higher potassium intake, as a higher potassium intake may reflect a better diet quality and nutritional status. To confirm these observations a randomized intervention study on potassium supplementation is needed. Currently, a long-term randomized placebo-controlled trial studying the effects of potassium supplementation in patients with CKD using single RAAS inhibition on renal outcomes, including BP and proteinuria, is conducted [36].

In conclusion, our data show that in patients with proteinuric CKD the antiproteinuric effect, but not antihypertensive effect, to losartan was blunted in patients with a high potassium intake. This difference disappeared after sodium status change by LS diet.

SUPPLEMENTARY DATA

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AUTHORS' CONTRIBUTIONS

The original trial was designed by L.V., G.N. and D.Z. L.V. and F.W. carried out the experiments. This *post hoc* analysis was performed by R.D.W. and supervision was provided by L.V. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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