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Influence of potassium intake on the renoprotective response to sodium restriction and hydrochlorothiazide in patients with diabetic nephropathy

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Background and Aims: Both salt restriction and hydrochlorothiazide (HCT) potentiate the antihypertensive and antiproteinuric effects of renin-angiotensin-aldosterone-system inhibitors (RAASi) in chronic kidney disease (CKD). Potassium intake is another dietary component that influences blood pressure (BP) and albuminuria. The influence of potassium intake on the response to sodium restriction during RAASi treatment in diabetic nephropathy is unknown.

Method: We performed a post-hoc analysis of a randomised, double blind, placebo-controlled cross-over trial (n = 43) investigating the combined and separate effects of low sodium (LS; aim 50 mmol Na+/d) and HCT (50 mg/d) on BP and albuminuria during background ACE inhibition (ACEi; lisinopril 40 mg/d) in patients with diabetic nephropathy. Each treatment (normal sodium (NS), LS, NS+HCT, LS+HCT) period consisted of six weeks.

Participants were categorised as above or below median 24-hour urinary potassium excretion (UKV) at baseline, stratified by sex. Effects on BP and albuminuria were defined as % reduction from baseline systolic BP (SBP) and urinary albumin-creatinine ratio (ACR). Changes over time within both UKV subgroups were compared to baseline using repeated measures ANOVA (SBP) or paired Wilcoxon rank sum analysis (log-transformed ACR). Post-hoc between-group comparison was performed using Bonferroni testing.

Results: 43 patients (6 female; mean age 64.9±1.4 yrs) had UKV data available and were included in analysis. 33 patients had complete ACR data. Mean estimated glomerular filtration rate (eGFR) was 65.2 (±3.9), mean SBP was 146.6±2.4 mmHg and median albuminuria 648.6 [251.2 - 1883.0] mg/24 h. Median UKV in the high and low potassium groups was 64 [IQR 49-71] and 94 [90 – 111] mmol/24 u, respectively ($p<0.0001$). Mean baseline sodium excretion was higher in the high potassium group (191 vs. 260 mmol/d; $P = .002$), but percentual reduction in sodium excretion at SR was comparable between the two groups. There were no significant differences in baseline SBP, ACR, age and estimated glomerular filtration rate between the groups.

LS led to a significant reduction of ACR in the high potassium group ($P = .011$), whereas in the low potassium group the ACR reduction was not significant ($P = .058$; Fig. 1). Similarly, addition of HCT to background ACEi therapy without salt restriction reduced ACR compared to ACEi monotherapy in the high potassium group ($P < .0001$), not the low potassium group ($P = .211$). LS+HCT combined led to a reduction in ACR in both high ($P < .0001$) and low potassium ($P = .034$) groups. A post-hoc between-group analysis showed a significantly larger ACR reduction for the high potassium group ($P = .01$) upon HCT therapy, and a trend towards larger reduction for HCT+LS ($P = .05$). The effect of LS alone was similar between high and low potassium groups ($P = .485$).

During LS, within-group analysis showed a significant reduction in SBP compared to baseline for the low potassium group ($P = .003$), but not for the high potassium group ($P = .208$). In all further conditions, SBP was significantly reduced from baseline in both groups. Post-hoc analysis showed no significant differences in SBP reduction between high and low potassium groups, although there was a trend towards larger SBP reduction in the low potassium group during LS ($P = .07$).

Conclusion: Higher baseline potassium excretion is associated with stronger albuminuria lowering effects of salt restriction and HCT in patients with diabetic nephropathy on background ACEi therapy. These effects were not driven by similar effects on BP.

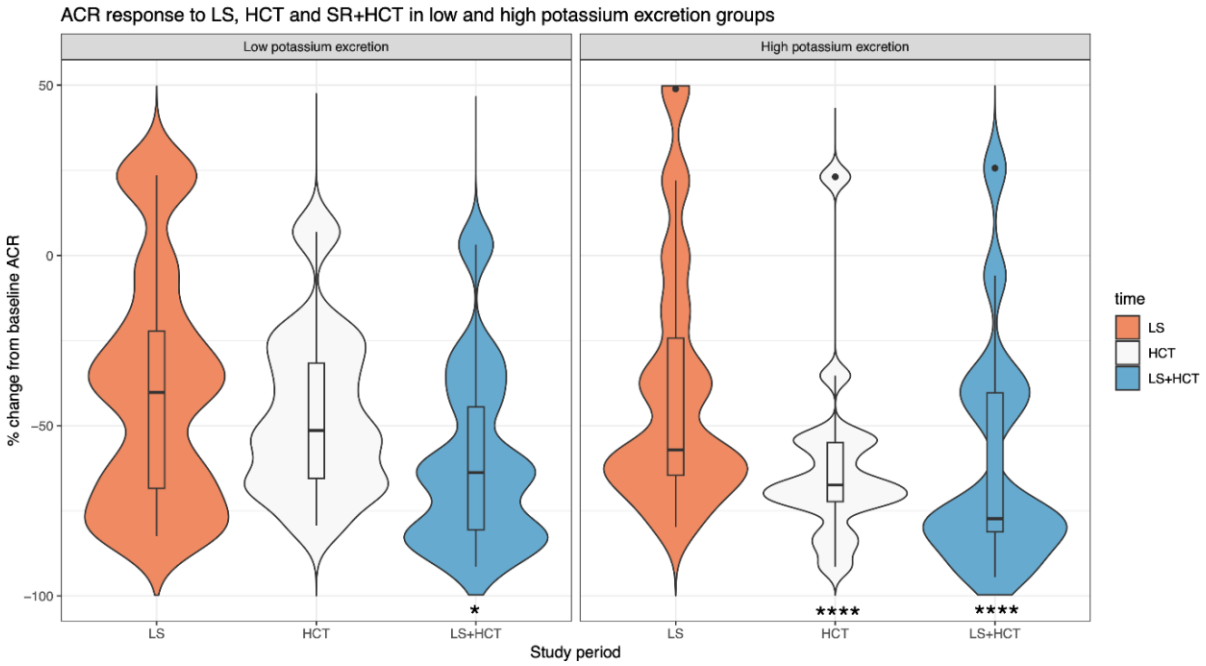

Figure 1: Violin plot showing the relative change from baseline albumin-creatinine ratio (ACR) at each study period, for the low and high potassium excretion subgroups. The high potassium group showed a significant reduction in ACR at low sodium (LS; $P = .011$), hydrochlorothiazide (HCT, $p < 0.0001$) and their combination ($p < 0.0001$). For the low potassium group, ACR was only significantly reduced from baseline at combined LS+HCT ($P = .034$).