Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease

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The CRISP study of polycystic kidney disease (PKD) found that urinary sodium excretion associated with the rate of total kidney volume increase. Whether sodium restriction slows the progression of Autosomal Dominant PKD (ADPKD) is not known. To evaluate this we conducted a post hoc analysis of the HALT-PKD clinical trials of renin-angiotensin blockade in patients with ADPKD. Linear mixed models examined whether dietary sodium affected rates of total kidney volume or change in estimated glomerular filtration rate (eGFR) in patients with an eGFR over 60 ml/min/1.73 m^2 (Study A) or the risk for a composite endpoint of 50% reduction in eGFR, end-stage renal disease or death, or the rate of eGFR decline in patients with an eGFR 25–60 ml/min/1.73 m^2 (Study B) all in patients initiated on an under100 mEq sodium diet. During the trial urinary sodium excretion significantly declined by an average of 0.25 and 0.41 mEq/24 hour per month in studies A and B, respectively. In Study A, averaged and time varying urinary sodium excretions were significantly associated with kidney growth (0.43%/year and 0.09%/year, respectively, for each 18 mEq urinary sodium excretion). Averaged urinary sodium excretion was not significantly associated with faster eGFR decline (–0.07 ml/min/1.73m^2/year for each 18 mEq urinary sodium excretion). In Study B, the averaged but not time-varying urinary sodium excretion significantly associated with increased risk for the composite endpoint (hazard ratio 1.08 for each 18 mEq urinary sodium excretion) and a significantly faster eGFR decline (–0.09 ml/min/1.73m^2/year for each mEq 18 mEq urinary sodium excretion). Thus, sodium restriction is beneficial in the management of ADPKD.

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Hypertension is the most common manifestation of autosomal dominant polycystic kidney disease (ADPKD).[1] Factors contributing to its development include activation of the intrarenal renin-angiotensin-aldosterone system (RAAS), increase in sympathetic tone, and possibly a primary vascular dysfunction. It is associated with progression to end-stage renal disease (ESRD) and cardiovascular morbidity and mortality. Early detection, lifestyle modification, and medical treatment are essential for optimal management. Angiotensin converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) have become the first-line therapy, based more on evidence that supports the importance of the intrarenal RAAS in the pathogenesis of hypertension in ADPKD rather than on results of randomized clinical trials.[1–5] Sodium restriction may be particularly important because patients with ADPKD usually have sodium-sensitive hypertension and moderation of dietary sodium has been shown to potentiate the renal- and cardiovascular-protective effects of RAAS blockade in other renal diseases.[6,7]

The importance of dietary salt restriction in ADPKD has received little attention. Nevertheless, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease showed an association between urine sodium excretion (UNaE), a surrogate marker for dietary sodium, and the rate of increase in total kidney volume (TKV) at relatively early stages of the disease.[8] Furthermore, dietary sodium has been shown to influence clinical outcomes from RAAS blockade in several randomized clinical trials for other kidney diseases. UNaE was associated with the risk for doubling serum creatinine level or ESRD in the Ramipril Efficacy in Nephropathy[9] clinical trial and with the frequency of renal and cardiovascular adverse events in the Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan and Irbesartan Diabetic Nephropathy Trial.[10] On the

other hand, overzealous sodium restriction in combination with ACEi therapy may induce tubulointerstitial damage under certain experimental conditions.[11]

HALT PKD was a randomized clinical trial to test whether rigorous blood pressure control slows the progression of ADPKD compared with standard blood pressure control, both with drugs blocking the renin-angiotensin system in healthy patients with hypertension aged 15 to 49 years, with good kidney function (Study A), and whether an ACEi plus ARB combination would slow the progression of the disease compared with treatment with an ACEi alone in patients with good (Study A) or moderately reduced (Study B) kidney function. All participants were instructed to follow a sodium-restricted diet ($\leq$ 2.4 g/d). The goals of the present *post hoc* analysis were to examine the compliance of the HALT PKD participants with the diet instructions, the effect of dietary salt on the rates of change in TKV and estimated glomerular filtration rate (eGFR), and its influence on the effects of the trial interventions on the main trial endpoints.

RESULTS

The baseline characteristics of Study A and Study B participants are summarized in Table 1.

Compliance with dietary instructions during HALT PKD

At baseline, UNaE was 178.1 ± 79.9 mEq/24 hr in Study A and 177.8 ± 81.0 mEq/24 hr in Study B. During the studies UNaE declined by 0.25 ± 0.04 mEq/24 hr per month of follow-up ($P < 0.001$) in Study A and by 0.41 ± 0.04 mEq/24 hr per month of follow-up ($P < 0.001$) in Study B (Figure 1A). At the final follow-up, varying from 60 to 96 months, UNaE was 166.5 ± 77.5 mEq/24 hr in Study A and 152.1 ± 66.0 mEq/24 hr in Study B, and was > 100 mEq/24 hr in more than 80% of study participants. Therefore, reductions in UNaE were modest overall (on average, 6.5% and 14.5% reductions from baseline in Study A and Study B, respectively), but highly variable from patient to patient in Study A only (estimate of random slope standard deviation = 0.37 and $P < 0.001$ in Study A and standard deviation = 0.00007 and $P \geq 0.999$ in Study B) (Figure 1B). Changes in UNaE over time were similar regardless of assignment to blood pressure group in Study A or to telmisartan or placebo in both studies (not shown).

Association of study-averaged and time-varying UNaE with disease progression in Study A

A linear mixed model showed a significant association of averaged UNaE on the annual rate of TKV growth in Study A (0.43%/yr for each 18-mEq increase in UNaE; $P<0.001$) (Table 2A). A similar model showed an insignificant trend for an association between UNaE and a faster decline in eGFR (–0.067 ml/min/yr for each 18-mEq increase in UNaE; $P = 0.09$) (Table 2B). When time-varying UNaE rather than averaged UNaE was used as a covariate, there was an association between within-person change in UNaE and the annual rate of TKV growth (0.086%/yr for each 18-mEq increase in UNaE; $P = 0.005$) (Table 2C), but the association of UNaE with the rate of change in eGFR was insignificant (–0.004 ml/min per 1.73 m^2/yr for each 18 mEq increase; $P = 0.79$) (Table 2D). Neither averaged nor time-varying UNaE differentially influenced the effect of low versus standard blood pressure control, nor the effect of ACEi plus ARB combination versus ACEi monotherapy (not shown).

Table 1 | Baseline clinical and laboratory data of Study A and Study B participants

	Study A (N = 558)		Study B (N = 486)	
	% or mean	n	% or mean	n
Male	50.7	558	48.4	486
Age at baseline	36.6 ± 8.3	558	48.7 ± 8.3	486
Height (cm)	173.8 ± 10.2	547	173.2 ± 10.4	476
Body surface area (m^2)	2.0 ± 0.2	546	2.0 ± 0.3	476
Body mass index	27.2 ± 5.2	546	28.0 ± 5.2	476
Office average systolic blood pressure (mm Hg)	126.7 ± 13.9	554	129.1 ± 14.6	484
Office average diastolic blood pressure (mm Hg)	80.1 ± 11.1	554	79.4 ± 10.2	484
Height-adjusted total kidney volume	692 ± 402	540	–	–
Renal blood flow (mL/min per 1.73 m^2)	609 ± 206	372	–	–
Height-adjusted TLV	1123 ± 460	539	–	–
Liver cyst volume	286 ± 805	408	–	–
Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate (mL/min per 1.73 m^2)	91.5 ± 17.5	557	48.2 ± 11.8	486
Serum sodium (mEq/l)	139.2 ± 2.1	558	139.5 ± 2.4	485
Serum potassium (mEq/l)	4.1 ± 0.4	558	4.3 ± 0.5	486
Urine volume (ml/24 hr)	2565 ± 1175	553	2685 ± 1072	475
Urine sodium (mEq/24 hr)	178.1 ± 79.9	542	177.8 ± 81.0	462
Urine potassium (mEq/24 hr)	58.3 ± 26.9	536	62.6 ± 26.5	462
Urine creatinine (mg/24 hr)	1501 ± 671	542	1448 ± 618	462
Urine aldosterone (μg/24 hr)	12.2 ± 9.5	534	9.7 ± 7.3	450
Urine albumin (mg/24 hr)	41.5 ± 137.3	542	89.8 ± 170.2	462

TLV, total liver volume.

Association of study-averaged UNaE with disease progression in Study B

A Cox proportional hazards model showed a significant association of the averaged UNaE with an increased risk to reach the composite endpoint of 50% reduction from the baseline eGFR, ESRD, or death in Study B (hazard ratio, 1.083 for each 18 mEq/24 hr increase in UNaE; $P = 0.010$) (Table 3A) and with a greater annual rate of decline in eGFR (–0.086 ml/min/yr for each 18 mEq/24 hr increase in UNaE; $P < 0.001$) (Table 3B) using a similar linear mixed model as in Study A. When time-varying UNaE rather than averaged UNaE was used as a covariate, these associations were not statistically significant (Tables 3C and 3D). Neither averaged nor time-varying UNaE differentially influenced the effect of ACEi plus ARB combination versus ACEi monotherapy.

Changes in urine potassium and creatinine excretions and relationship to disease progression

At baseline, urinary excretion of potassium (UKE) and urinary excretion of creatinine (UCrE) were 58.3 ± 26.9 mEq/24