Potentially Modifiable Factors Affecting the Progression of Autosomal Dominant Polycystic Kidney Disease

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Summary

Background and objectives The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) was created to identify markers of disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD).

Design, setting, participants, & measurements Linear mixed models were utilized to model effects of baseline parameters on changes in natural-log (ln)-transformed total kidney volume (TKV) and iothalamate clearance (GFR) across time in CRISP participants (creatinine clearance at entry >70 ml/min). Stepwise selection was used to obtain a final main effect model.

Results TKV increased from year to year, whereas GFR uncorrected for body surface area (BSA) decreased only at year 6. Higher lnTKV and urine sodium excretion ($U_{Na}V$), lower serum HDL-cholesterol, and younger age at baseline associated with greater lnTKV growth from baseline to year 3 and to year 6. Higher lnTKV at baseline associated with greater GFR decline from year 1 to year 3 and to year 6. Higher BSA and 24-hour urine osmolality at baseline associated with greater GFR decline from year 1 to year 6. Higher $U_{Na}V$ and lower serum HDL-cholesterol at baseline associated with greater GFR decline from year 1 to year 6 by univariate analysis only. Associations seen during year 1 to year 6 (not seen during year 1 to year 3) reflect the time lag between structural and functional disease progression.

Conclusions Serum HDL-cholesterol, $U_{Na}V$, and 24-hour urine osmolality likely affect ADPKD progression. To what extent their modification may influence the clinical course of ADPKD remains to be determined.

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Introduction

The National Institutes of Health-sponsored Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) was created to develop imaging techniques and analyses to follow disease progression and evaluate treatments for autosomal dominant polycystic kidney disease (ADPKD) (1–5). CRISP followed 241 subjects (age 15 to 46 years; creatinine clearance at entry >70 ml/min) between January 5, 2001 and August 26, 2005 (CRISP I) at Emory University, Kansas University Medical Center, the Mayo Clinic, and the University of Alabama–Birmingham with baseline and three yearly (YR1 to YR3) visits including measurements of total kidney volume (TKV) by magnetic resonance (MR) and GFR by iothalamate clearance.

CRISP I participants seen at Emory University and the Mayo Clinic (n = 131) had renal blood flow (RBF) measurements by MR. Analysis of baseline predictors of disease progression in this subset showed that TKV, RBF, and urinary sodium excretion ($U_{Na}V$) independently predicted TKV increase during 3 years of follow-up (5). Only TKV and total cyst volume (TCV) were independent predictors of GFR decline. Short follow-up and stability of GFR during CRISP I limited the ability to detect significant predictors of GFR decline.

To further evaluate the association of baseline covariates with structural (increase in TKV) or functional (decline in GFR) disease progression, we have extended the analysis to include the entire CRISP I cohort and up to 6 years of follow-up in most patients (CRISP II).

Materials and Methods

Study Organization

CRISP clinical centers included the Mayo Clinic and University of Alabama–Birmingham, Emory University, and the University of Kansas Medical Center.

Washington University during CRISP I and the University of Pittsburgh during CRISP II served as the data coordinating and image analysis center (1–5), which collected images transferred from the collaborating institutions in Digital Imaging and Communications in Medicine format, segmented and analyzed images, stored and recorded results, and performed statistical analysis.

Study Protocol

Detailed descriptions of the study protocol and baseline characteristics have been published (1–5). ADPKD subjects were eligible if they were older than 15 and younger than 46 years of age and had a creatinine clearance >70 ml/min (1). Hypertension status was defined as previous diagnosis and current use of antihypertensive medications or as systolic and diastolic BP >140/90 mmHg on three consecutive visits.

After informed written consent, enrolled subjects were scheduled for two-day evaluations in the General Clinical Research Center at baseline and 1 (YR1), 2 (YR2), and 3 (YR3) between January 5, 2001 and August 26, 2005. Approximately 2 years after completion of CRISP I, participants were contacted and after informed written consent enrolled subjects were scheduled for a baseline CRISP II visit (YR6). Enrollment into CRISP II started in July 2007. CRISP II participants are followed by telephone or in center visits every 6 months; measurements of serum creatinine every year; and MR measurements of TKV, TCV, and iothalamate clearance every 2 years. Before each visit, participants were instructed to continue their medications, to discontinue any nonsteroidal anti-inflammatory medications for at least 7 days before evaluation, and not to initiate diuretic therapy within 14 days of evaluation. During CRISP I, subjects collected a 24-hour urine sample for determination of creatinine, urea nitrogen, $U_{Na}V$, and urine albumin excretion ($U_{alb}V$) on the day before admission. Weight, height, body surface area (BSA), and body mass index (BMI) were measured at admission. BP was measured in the morning, before antihypertensive medication intake, in the left and right arms after being seated for at least 5 minutes on three occasions 3 minutes apart using an oscillometric measuring device. Blood was obtained before GFR studies for the determination of blood hemoglobin, serum electrolytes, liver enzymes, and lipid profile during CRISP I and serum electrolytes and lipid profile only during CRISP II. GFR was measured by a nonradiolabeled iothalamate clearance technique with sonographic monitoring of bladder emptying (4). The mean coefficient of variation is 4.9%. GFR was also estimated (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation: $186.3 \times \textit{serum creatinine}^{-1.154} \times \textit{age}^{-0.203} \times 0.742$ (*if female*) $\times$ 1.212 (*if black*) (6). Protein intake (g/d) was estimated using the equation $6.25 \times$ [*urine urea nitrogen in g/d* + (0.03 × *weight in kg*)] (7). Urine osmolality averaged over 24 hours (24-h U_{osm}) was estimated using the equation *urine urea nitrogen in mg/L*/28 + 2 × (*urine sodium* + *potassium in mEq/L*) in a 24-hour urine collection.

Measurements of TKV

MR imaging studies were performed in the morning before medication intake and breakfast. During CRISP I, coronal T2-weighted images (single-shot fast spin echo/half-Fourier acquired single-shot turbo spin-echo) and gadolinium-enhanced, three-dimensional, volume-interpolated, spoiled-gradient echo coronal T1-weighted images were obtained (3-mm slice thickness). The volumes of individual kidneys were measured in T1-weighted images with a stereology method and calculated from the set of contiguous images by summing the products of the area measurements and slice thickness. The reliability coefficient was 0.998 for TKV. The average coefficient of variation of the TKV in repeated analysis of 99 images was 0.01%. A region-based thresholding method was used to calculate cyst volumes using T2-weighted images. During CRISP II, gadolinium enhanced T1-weighted images are no longer obtained because of concerns raised in 2006 about the role of gadolinium in nephrogenic systemic fibrosis (8). In addition to T2-weighted imaging, a fast imaging sequence, 2D true-FISP T2/T1-weighted imaging of the kidneys without fat saturation, is obtained to help delineate the kidney borders. The image analyst displayed these images concurrently as a visual guide and performed kidney volume measurement on T1-weighted images using the stereology method just as in the CRISP I image analysis.

Statistical Methods

The data were analyzed using Stata version 10 (StataCorp, College Station, TX). Changes in baseline covariates across time were examined by comparing each of the follow-up years to the baseline year using paired *t* tests or the McNemar test. Descriptive statistics for TKV and GFR were calculated to investigate the nature of the outcome variables. Because of the skewed nature of TKV, the natural log (lnTKV) was taken to normalize the data. Linear mixed models were utilized to model the change in outcome across time. In each model, there were fixed effects for year, the baseline covariates of interest, and their pairwise interactions. To account for the correlated observations within each subject, a random effect was also included. Of interest is a significant interaction between a particular baseline covariate and year, which would suggest that the covariate affects the trajectory of the outcome across time. This analysis was done for CRISP I subjects (baseline to YR3) as well as CRISP II subjects (baseline to YR6). Because of the nonlinear nature of the GFR outcome, the baseline year was not included in the assessment of change. This also helped mitigate regression to the mean.

Regression analyses were conducted in the following way. For each of the outcomes, univariate relationships were investigated by fitting a linear mixed model with year, the baseline covariate, and their respective interaction. Baseline covariates of interest are shown in Table 1. Covariates that significantly affected the outcome across time at the 0.15 level were included in a "full" model. Subsequently, if baseline covariates were significant at the 0.10 level in the full model, they were included in the pool of potential covariates for the "final" model. Backward selection was used in the final model by removing nonsignificant interactions (and, if possible, nonsignificant main effects) at the 0.05 significance level.

Table 1. Relevant clinical, radiologic, and laboratory parameters at baseline and at YR1 to YR6

Parameter	Baseline (n = 195 to 241)	Y1 (n = 174 to 241)	Y2 (n = 163 to 241)	Y3 (n = 168 to 241)	Y6 (n = 169 to 241)
Female gender (%)	60.2	60.2	60.2	60.2	60.3
Age (years)	32.4 ± 8.9	33.6 ± 8.9[c]	34.9 ± 8.8[c]	35.8 ± 8.8[c]	39.1 ± 8.7[c]
BSA (m^2)	1.89 ± 0.25	1.90 ± 0.25[a]	1.92 ± 0.25[c]	1.92 ± 0.25[c]	1.93 ± 0.25[c]
BMI (kg/m^2)	25.9 ± 5.3	26.1 ± 5.3[b]	26.4 ± 5.6[c]	26.8 ± 5.8[c]	27.1 ± 5.2[c]
Protein intake (g/day)	71.9 ± 22.9	74 ± 28.1	76.8 ± 23.4[a]	81.8 ± 27.5[c]	NA
Hypertension (%)	61.0	64.2[b]	69.3[c]	73.3[c]	74.2[c]
MAP (mmHg)	92.7 ± 11.8	90.8 ± 11.7[a]	90.8 ± 11.1[a]	92 ± 11.9	91.8 ± 11.2
TKV (ml)	1073 ± 663	1123 ± 692[c]	1240 ± 789[c]	1277 ± 826[c]	1510 ± 1106[c]
TCV (ml)	534 ± 528	610 ± 586[c]	686 ± 651[c]	744 ± 714[c]	—
iGFR (ml/min)	106.5 ± 27.8	108.2 ± 29.4	106.3 ± 33.6	104.6 ± 34.8	92 ± 41.4[c]
iGFR (ml/min per 1.73 m^2)	97.8 ± 24.7	98.8 ± 25.7	96.2 ± 29.7	94.5 ± 28.7[a]	83.5 ± 38.3[c]
eGFR (ml/min per 1.73 m^2)	89.1 ± 27.7	85.3 ± 23.7[c]	83.6 ± 26.9[c]	81 ± 25.4[c]	72.1 ± 28.3[c]
Serum sodium (mEq/L)	138.1 ± 2.2	138 ± 2.7	138.3 ± 2.3	138.2 ± 2.3	137.6 ± 2.3[a]
Serum potassium (mEq/L)	4.04 ± 0.46	3.97 ± 0.42[a]	3.99 ± 2.07	3.81 ± 0.49[c]	3.92 ± 0.42[a]
Serum HDL (mg/dl)	47.8 ± 13.3	45.4 ± 12.9[c]	44.6 ± 12.9[c]	45.7 ± 12.1[b]	46.4 ± 14.7
Serum LDL (mg/dl)	102 ± 34	101.1 ± 27.7	103.4 ± 28.9	100.9 ± 28.5	101.6 ± 31.6
Serum uric acid (mg/dl)	5 ± 1.51	5.09 ± 1.51	5.26 ± 1.58[b]	5.42 ± 1.54[c]	NA
Urine volume (ml/24 h)	2452 ± 1140	2777 ± 1216[c]	2763 ± 1170[b]	2794 ± 1231[c]	NA
Urine osmolality (mOsm/L)	368 ± 159	332 ± 138[b]	348 ± 162[a]	342 ± 144[a]	NA
Urine albumin (mg/24 h)	45.8 ± 63	43.3 ± 52.9	44.8 ± 62.5	53.1 ± 84.3[a]	NA
Urine citrate (mg/24 h)	509 ± 350	490 ± 272	444 ± 238[a]	441 ± 235	NA
Urine urea nitrogen (mg/24 h)	9194 ± 3396	9527 ± 4237	9947 ± 3416[b]	10740 ± 4114[c]	NA
Urine potassium (mEq/24 h)	58.9 ± 23.3	59.4 ± 23.9	59.5 ± 20.4	59.9 ± 21.3	NA
Urine sodium (mEq/24 h)	193.2 ± 86.1	203.1 ± 83.5	195.3 ± 75.9	190.6 ± 69.2	NA

Data are shown as mean ± SD. Numbers in parentheses represent minimal and maximal sample sizes. iGFR, GFR measured by iothalamate clearance; NA, data not available.
[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ compared to baseline.

Results

Baseline Characteristics and Longitudinal Changes

Two-hundred and forty-one patients participated in CRISP I and 203 re-enrolled into CRISP II. Table 1 summarizes the relevant clinical, radiologic, and laboratory parameters. Sixty percent of participants in CRISP I and in CRISP II are female. BSA and BMI increased steadily from baseline to YR6. Protein intake (estimated from urine urea nitrogen excretion) was significantly higher at YR2 and YR3 compared with baseline; urine urea nitrogen excretion was not measured at YR6. TKV and TCV increased significantly from year to year, whereas GFR uncorrected for BSA remained unchanged from baseline to YR3 and decreased significantly at YR6. This is consistent with a lag time between structural and functional changes in ADPKD.

Potential Baseline Predictors of lnTKV Slopes across Time

Table 2 shows which baseline covariates significantly predicted the change in lnTKV as reflected by a significant year × covariate interaction coefficient in the univariate models. Models were built to assess lnTKV change from baseline to YR3 or from baseline to YR6. Male gender and presence of hypertension at baseline were associated with higher TKV slopes. In addition, the higher the baseline BSA, BMI, estimated protein intake, mean arterial pressure, lnTKV, lnTCV, serum sodium and uric acid concentrations, $lnU_{alb}V$, and $U_{Na}V$, the higher was the increase in lnTKV over time. Baseline GFR and eGFR and serum HDL-cholesterol were negatively correlated with baseline to YR3 changes in lnTKV slopes, implying that the larger the baseline values, the lesser the increase in lnTKV over time. Associations between baseline covariates and lnTKV slopes from baseline to YR6 were similar to those between baseline covariates and baseline to YR3 slopes.

Regression Analysis for Changes in lnTKV across Time

When stepwise selection was used to obtain a final main effect model (Table 3), baseline lnTKV and $U_{Na}V$ were positively and HDL-cholesterol and age were negatively and independently associated with changes in lnTKV slopes across time from baseline to YR3 and from baseline to YR6. The higher the baseline $U_{Na}V$, the greater was the increase of lnTKV over the 3 and 6 years on study. Higher baseline HDL and older age at the start of the study were independently associated with slower lnTKV growth.

Potential Baseline Predictors of GFR Slopes across Time

Table 4 shows which baseline covariates significantly predicted the change in GFR across time from YR1 to YR3 or from YR1 to YR6 as reflected by a significant year × covariate interaction coefficient in the univariate models. Baseline GFR values were not used in the analysis to minimize regression to the mean. Higher lnTKV, lnTCV, MAP, age, and hypertension status at baseline were significantly associated with steeper GFR declines over time from YR1 to YR3 and more significantly from YR1 to YR6.

Table 2. Baseline variables as univariate predictors of lnTKV across time

Variable	Baseline YR3		Baseline YR6	
	Year*Variable Coefficient	*P*	Year*Variable Coefficient	*P*
Gender (% female)	−0.011	**0.002**	−0.016	**<0.001**
Hypertension	0.015	**<0.001**	0.008	**0.023**
Age (years)	−0.0002	0.465	−0.001	**<0.001**
BMI (kg/m^2)	0.001	**<0.001**	0.0004	0.172
BSA (m^2)	0.037	**<0.001**	0.032	**<0.001**
Protein intake (g/day)	0.0003	**0.002**	0.0002	**0.013**
MAP (mmHg)	0.0003	**0.048**	0.0001	0.668
lnTKV (ml)	0.024	**<0.001**	0.015	**<0.001**
lnTCV (ml)	0.013	**<0.001**	0.007	**<0.001**
iGFR (ml/min)	−0.000003	0.967	0.00001	0.898
iGFR (ml/min per 1.73 m^2)	−0.0002	**0.008**	−0.0002	**0.020**
Serum sodium (mEq/L)	0.002	**0.039**	0.002	**0.008**
Serium potassium (mEq/L)	0.004	0.292	−0.001	0.814
Serum HDL (mg/dl)	−0.001	**<0.001**	−0.001	**<0.001**
Serum LDL (mg/dl)	0.0001	0.318	0.00002	0.696
Serum uric acid (mg/dl)	0.006	**<0.001**	0.006	**<0.001**
Urine volume (mL)	0.000003	0.067	0.000004	**0.011**
Urine osmolality (mOsm/L)	0.00001	0.472	0.000003	0.781
lnU_{alb} (mg/24 h)	0.008	**<0.001**	0.004	**0.033**
Urine citrate (mg/24 h)	0.000001	0.899	−0.00001	0.064
Urine urea nitrogen (mg/24 h)	0.000002	0.009	0.000001	**0.037**
Urine potassium (mEq/24 h)	0.0001	0.136	0.00001	0.883
Urine sodium (mEq/24 h)	0.0001	**<0.001**	0.0001	**<0.001**

Bold values indicate $P \leq 0.05$. MAP, mean arterial pressure.

Table 3. Final regression models predicting structural disease progression measured as lnTKV across time from baseline parameters

Parameter	Baseline to YR3 ($n = 205$)		Baseline to YR6 ($n = 165$)	
	Coefficient	*P*	Coefficient	*P*
Year	−0.072	**0.004**	0.011	0.655
Age	0.0002	0.705	0.001	0.466
lnTKV	1.001	**<0.001**	1.014	**<0.001**
Serum HDL	0.00004	0.915	0.001	0.205
Urine sodium	−0.000003	0.960	0.00001	0.930
Year*age	−0.0005	**0.049**	−0.001	**<0.001**
Year*lnTKV	0.022	**<0.001**	0.014	**<0.001**
Year*serum HDL	−0.001	**<0.001**	−0.001	**<0.001**
Year*urine sodium	0.0001	**0.001**	0.0001	**0.008**
Intercept	−0.017	0.776	−0.155	0.118

Bold values indicate $P \leq 0.05$.

Higher baseline protein intake, serum uric acid, 24-h U_{osm}, $lnU_{alb}V$, and $U_{Na}V$ were associated with steeper declines, whereas higher serum HDL-cholesterol values were associated with less decline in GFR from YR1 to YR6, but not from YR1 to YR3. Higher significance of associations and emerging new associations between baseline covariates and GFR slopes from YR1 to YR6 as compared with slopes from YR1 to YR3 are consistent with the stability of the GFR during CRISP I and a time lag between structural and functional disease progression. Female gender was negatively associated with GFR slopes from YR1 to YR3, but not from YR1 to YR6.

Regression Analysis for Changes in GFR across Time

In the final stepwise regression model (Table 5), higher baseline lnTKV and serum uric acid concentration were associated with lower baseline GFR. Higher baseline lnTKV was also associated with a steeper decline in GFR, but higher baseline serum uric acid was associated with lower changes in GFR over time between YR1 and YR3. The relationship between lnTKV and GFR remained when adding YR6, but serum uric acid was no longer significant. Instead, higher baseline BSA was associated with higher baseline GFR and steeper decreases in GFR over time. This was also true for 24-h U_{osm}. Although $U_{Na}V$ was nega-

Table 4. Baseline variables as univariate predictors of uncorrected GFR across time

	YR1 to YR3		YR3 to YR6	
	Year*Variable Coefficient	*P*	Year*Variable Coefficient	*P*
Gender (% female)	−4.8917	**0.002**	1.1240	0.148
Hypertension	−3.3713	**0.036**	−2.7624	**<0.001**
Age (years)	−0.1745	**0.051**	−0.1175	**0.008**
BMI (kg/m^2)	−0.0690	0.638	−0.2982	**<0.001**
BSA (m^2)	2.4554	0.427	−6.9990	**<0.001**
Protein intake (g/day)	0.0372	0.315	−0.0615	**0.001**
MAP (mmHg)	−0.1694	**0.011**	−0.0926	**0.005**
lnTKV (ml)	−4.7005	**0.001**	−3.7777	**<0.001**
lnTCV (ml)	−2.6099	**<0.001**	−1.6222	**<0.001**
iGFR (ml/min)	0.0575	**0.043**	−0.0029	0.833
iGFR (ml/min per 1.73 m^2)	0.0479	0.141	0.0375	**0.023**
eGFR (ml/min per 1.73 m^2)	0.0175	0.560	0.0257	0.073
Serum sodium (mEq/L)	0.2920	0.414	0.0520	0.764
Serum HDL (mg/dl)	−0.0797	0.188	0.0630	**0.036**
Serum LDL (mg/dl)	0.0278	0.251	0.0051	0.694
Serum uric acid (mg/dl)	1.5012	**0.003**	−0.8473	**0.002**
Urine volume (mL)	0.0005	0.471	0.0003	0.333
Urine osmolality (mOsm/L)	0.0094	0.067	−0.0084	**<0.001**
lnU_{alb} (mg/24 h)	−1.0919	0.211	−1.3488	**<0.001**
Urine citrate (mg/24 h)	0.0019	0.446	0.0004	0.737
Urine urea nitrogen (mg/24 h)	0.0003	0.314	−0.0003	**0.007**
Urine sodium (mEq/24 h)	0.0205	**0.035**	−0.0116	**0.010**

Bold values indicate $P \leq 0.05$.

Table 5A. Final regression models predicting functional disease progression measured as GFR (uncorrected iothalamate clearance) across time from baseline parameters, YR1 to YR3

	YR1 to YR3 (n = 235)	
	Coefficient	*P*
Year	26.41	**0.005**
lnTKV	−10.29	**0.016**
Serum uric acid	−1.728	0.270
Year*lnTKV	−5.483	**<0.001**
Year*serum uric acid	1.821	**<0.001**
Intercept	189.1	**<0.001**

Bold values indicate $P \leq 0.05$.

Table 5B. Final regression models predicting functional disease progression measured as GFR (uncorrected iothalamate clearance) across time from baseline parameters, YR1 to YR6

	YR1 to YR6 (n = 182)	
	Coefficient	*P*
Year	29.94	**<0.001**
BSA	60.97	**<0.001**
lnTKV	−18.26	**<0.001**
Urine osmolality	0.0533	**<0.001**
Year*BSA	−4.799	**0.004**
Year*lnTKV	−3.230	**<0.001**
Year*urine osmolality	−0.0065	**0.009**
Intercept	103.2	**<0.001**

Bold values indicate $P \leq 0.05$.

tively and serum cholesterol concentration was positively associated with the change in GFR from YR1 to YR6, neither was an independently significant predictor of GFR decline in the final regression model.

Serum HDL-Cholesterol, $U_{Na}V$, and 24-h U_{osm} Are Constant Throughout CRISP

This analysis of CRISP data has revealed three potentially modifiable predictors of disease progression in ADPKD: serum HDL-cholesterol (a possible surrogate marker of vascular disease), $U_{Na}V$ (a surrogate marker of salt intake), and U_{osm} (a surrogate marker of vasopressin effect on the kidney). During CRISP, average (Table 1) and within-patient (Table 6) serum HDL-cholesterol concentration, $U_{Na}V$, and 24-h U_{osm} remained mostly constant over time.

Discussion

The effects of multiple baseline covariates on the rate of renal enlargement in CRISP I and CRISP II participants followed for 6.3 years in the study presented here confirm and extend the conclusions of the previous study in a subset of CRISP I patients with 3 years of follow-up (5). As in that study, TKV and $U_{Na}V$ are independently predictive of renal growth. RBF, which was found to be an important predictor of disease progression, is not included in the study presented here because it was measured in only two of the four participating clinical centers. Exclusion of RBF from this analysis may have uncovered HDL-cholesterol as an independent predictor of renal growth (see below).

Table 6. Spearman correlation coefficients among baseline, YR1, YR2, and YR3 serum HDL-cholesterol, $U_{Na}V$, and 24-h U_{osm} values

Year	Y1	Y2	Y3	Y6
Serum HDL-cholesterol				
baseline				
r	0.705	0.712	0.703	0.708
P	<0.0001	<0.0001	<0.0001	<0.0001
n	226	215	192	195
Y1				
r	—	0.800	0.759	0.672
P	—	<0.0001	<0.0001	<0.0001
n	—	213	191	192
Y2				
r	—	—	0.817	0.715
P	—	—	<0.0001	<0.0001
n	—	—	182	181
Y3				
r	—	—	—	0.703
P	—	—	—	<0.0001
n	—	—	—	170
$U_{Na}V$				
baseline				
r	0.425	0.395	0.369	NA
P	<0.0001	<0.0001	<0.0001	NA
n	168	166	172	NA
Y1				
r	—	0.444	0.418	NA
P	—	<0.0001	<0.0001	NA
n	—	161	166	NA
Y2				
r	—	—	0.335	NA
P	—	—	<0.0001	NA
n	—	—	166	NA
24-h U_{osm}				
baseline				
r	0.408	0.495	0.467	NA
P	<0.0001	<0.0001	<0.0001	NA
n	210	201	205	NA
Y1				
r	—	0.682	0.601	NA
P	—	<0.0001	<0.0001	NA
n	—	207	210	NA
Y2				
r	—	—	0.684	NA
P	—	—	<0.0001	NA
n	—	—	206	NA

NA, data not available.

The effects of dietary salt on the development of hypertension, cardiovascular health, and progression of chronic kidney disease have received much attention (9–11). The study presented here suggests that it may also affect the progression of ADPKD. This can occur by several mechanisms. Modest increases in salt intake cause changes in plasma sodium, which are partially buffered by the movement of fluid from the intracellular to the extracellular compartment (12,13). Concomitant small increases in osmolality activate mechanisms to retain water (stimulation of vasopressin secretion and thirst) and elimination of salt (release of natriuretic factors such as atrial natriuretic factor) (13–15). Persistent high salt intake increases plasma levels of endogenous cardiotonic steroids and renal production of TGF-β (16–18). Vasopressin promotes cystogenesis (19). Atrial natriuretic peptide could have a cystogenic effect via generation of cGMP (20). Cardiotonic steroids induce extracellular signal-regulated kinase activation and proliferation of human ADPKD cyst-derived epithelial cells (18). TGF-β plays a role in the development of epithelial-mesenchymal transition and interstitial fibrosis in ADPKD (17). Increased salt consumption in the last decades underscores the relevance of dietary salt as a potential modifying factor in ADPKD (21,22).

Another observation of this study is the association of lower baseline serum HDL-cholesterol levels with faster renal enlargement. An association of lower HDL-cholesterol and steeper GFR decline had been observed in MDRD

Study A, but renal volume was not measured (23). Several mechanisms could account for an effect of HDL on cyst growth. The detection of an HDL-cholesterol effect in this but not our previous study when baseline RBF was included in the model suggests that the effect may be indirect through an effect on the vasculature. Indeed, HDL exerts antiatherogenic and anti-inflammatory actions on the vasculature through its role in the reverse transport of cholesterol and through the sphingosine-1-phosphate (S1P)-$S1P_{1–5}$ receptor (a family of five G-protein-coupled receptors) and apolipoprotein A1-scavenging receptor class B type1 receptor interactions (24,25). S1P or apolipoprotein A1 could directly affect the development of polycystic kidney disease because renal sphingolipid metabolism is altered (26,27) and renal expression of apolipoprotein A1 is downregulated (28) in animal models of polycystic kidney disease.

In our previous study, no significant association was detected between $U_{Na}V$ or serum HDL-cholesterol and GFR decline (5). Because of the lag time between structural and functional changes in ADPKD, we re-examined the associations between baseline parameters and GFR decline in the study presented here with longer follow-up. Consistent with this lag time, we find a higher number and significance of associations between baseline covariates and GFR slopes during YR1 to YR6 compared with YR1 to YR3. With longer follow-up from YR1 to YR6, higher $U_{Na}V$ and lower serum HDL-cholesterol concentrations become significantly associated with faster GFR decline. However, $U_{Na}V$ and serum HDL-cholesterol are not independently significant in the final main effect model. It is possible that longer follow-up will be needed to detect a larger and independent effect of these parameters on renal function.

In the final regression model to predict GFR decline, two baseline covariates, in addition to lnTKV, have an independent significant effect: BSA and 24-h U_{osm}. In both cases, they are positively associated with GFR at baseline and negatively with GFR changes over time. The explanation for the positive association between baseline BSA and GFR uncorrected for BSA is obvious. The association between baseline 24-h U_{osm} and GFR likely reflects better urine concentrating capacity in the patients with higher GFR and/or the known relationship between urinary concentrating activity and GFR (29). On the other hand, negative associations of baseline BSA and 24-h U_{osm} with GFR change over time suggest detrimental effects on renal function. The association between BSA and rate of disease progression in ADPKD is consistent with a recent analysis in the large HALT-PKD clinical trial cohort showing a highly significant independent association between baseline BSA and renal disease severity ascertained by BSA- or height-adjusted TKV and eGFR (V.E. Torres *et al.*, submitted). This may point to an effect of developmental programming on the clinical course of ADPKD. The association between 24-h U_{osm} and rate of GFR decline is consistent with a large body of evidence suggesting that vasopressin contributes to the progression of ADPKD and chronic kidney disease because 24-h U_{osm} can be considered a surrogate marker for vasopressin effect on the kidney (29,30–32).

A *post hoc* analysis of the MDRD Study A patients with ADPKD (GFR 25 to 55 ml/min per 1.73 m^2; $n = 139$) showed an association between high urine volume or low urine osmolality with faster GFR decline (33). Because patients with the highest urine volumes tended to have lower serum sodium concentrations and hypostenuria, excess water intake and not a renal concentrating defect was deemed responsible for the high urine volumes. Pushing fluids was suggested to be detrimental, possibly by increasing intratubular pressure and promoting cyst growth. In the study presented here, urine volume and 24-h U_{osm} are not independent predictors of renal growth. Contrary to the observation in the MDRD study that serum sodium concentrations tended to be lower in the patients with faster GFR decline, we find a statistically significant direct correlation between serum sodium level and the rate of renal enlargement, possibly reflecting more severe disease and impaired concentrating ability or lower fluid intake. As discussed above, baseline 24-h U_{osm} was positively associated with GFR, but negatively associated with GFR change across time. Taken together, these results do not support the hypothesis that high fluid intake promotes cyst growth or is detrimental to renal function in ADPKD.

In summary, this study has identified three potentially modifiable phenotypic traits that likely affect the progression of ADPKD: serum HDL-cholesterol (possibly a surrogate marker of vascular disease) and $U_{Na}V$ and 24-h U_{osm} (surrogate markers of salt and vasopressin effect on the kidney). To what extent their modification may influence the clinical course of ADPKD remains to be determined.

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Disclosures

None.

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