Analysis of baseline parameters in the HALT polycystic kidney disease trials

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HALT PKD consists of two ongoing randomized trials with the largest cohort of systematically studied patients with autosomal dominant polycystic kidney disease to date. Study A will compare combined treatment with an angiotensin-converting inhibitor and receptor blocker to inhibitor alone and standard compared with low blood pressure targets in 558 early-stage disease patients with an eGFR over 60 ml/min per 1.73 m^2. Study B will compare inhibitor-blocker treatment to the inhibitor alone in 486 late-stage patients with eGFR 25–60 ml/min per 1.73 m^2. We used correlation and multiple regression cross-sectional analyses to determine associations of baseline parameters with total kidney, liver, or liver cyst volumes measured by MRI in Study A and eGFR in both studies. Lower eGFR and higher natural log-transformed urine albumin excretion were independently associated with a larger natural log–transformed total kidney volume adjusted for height (ln(HtTKV)). Higher body surface area was independently associated with a higher ln(HtTKV) and lower eGFR. Men had larger height-adjusted total kidney volume and smaller liver cyst volumes than women. A weak correlation was found between the ln(HtTKV) and natural log–transformed total liver volume adjusted for height or natural log liver cyst volume in women only. Women had higher urine aldosterone excretion and lower plasma potassium. Thus, our analysis (1) confirms a strong association between renal volume and functional parameters, (2) shows that gender and other factors differentially affect the development of polycystic disease in the kidney and liver, and (3) suggests an association between anthropomorphic measures reflecting prenatal and/or postnatal growth and disease severity.

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Autosomal dominant polycystic kidney disease (ADPKD) occurs in 1/400–1/1000 live births and accounts for ~4.6% of the prevalent kidney replacement population in the United States.[1] Hypertension is its most common manifestation and an important risk factor for its progression to end-stage renal disease (ESRD) and cardiovascular morbidity and mortality.[2]

Substantial experimental and clinical data have implicated the renin–angiotensin–aldosterone system (RAAS) in the pathogenesis of ADPKD and associated hypertension. However, evidence that treatments targeting the RAAS are superior to other antihypertensive therapies is inconclusive. Past studies have been limited by small sample sizes with inadequate power, short periods of follow-up, study of relatively late stages of disease, and/or use of low doses of angiotensin I–converting enzyme inhibitors (ACEIs), which may not effectively block the RAAS.[2]

Because of the importance of hypertension in ADPKD and uncertainties surrounding its treatment, the NIH/NIDDK funded two distinct multicenter double-blind randomized clinical trials, adequately powered to assess the effect of RAAS blockade on renal progression at early (Study A) and late (Study B) stages of the disease (NCT00283686, http://clinicaltrials.gov). Their rationale, design, and implementation have been discussed in detail elsewhere.[3]

Here we perform a cross-sectional analysis of the baseline characteristics in this large cohort of patients to identify factors affecting the development and progression of this disease.

RESULTS

Baseline patient characteristics

Gender, race, education level, marital status, employment, ages at the time of enrollment into the study and diagnoses of ADPKD and hypertension, and manifestations leading to ADPKD and mode of diagnosis of ADPKD, by study and, in Study A, blood pressure (BP) target assignment, are shown in Table 1.

The baseline clinical, laboratory, and imaging characteristics of participants in Studies A and B are shown in Table 2. Study B participants, who by design have lower estimated glomerular filtration rate (eGFR) than Study A patients, are older, have higher body mass index, higher serum concentration of potassium and urine excretion of albumin, and lower urine excretion of aldosterone and urine sodium/potassium ratio. Serum potassium concentration is lower in women in both studies, whereas urine aldosterone excretion is higher in women compared with men in Study A.

Kidney and liver volumes were measured only in Study A. Total kidney volume (TKV) and TKV adjusted for height (HtTKV) or body surface area (BSA) are significantly greater in men than in women (Table 2). Liver cyst volume (LCV) is greater in women.

Baseline clinical, laboratory, and imaging characteristics of participants in Study A by BP group assignment are shown in Table 3. Except for slightly lower urine aldosterone excretion in participants assigned to rigorous BP control, there are no significant differences between the standard and rigorous BP control groups.

Table 1 | Demographic characteristics of the study population

	Study A (Standard, *n*=284)	Study A (Low, *n*=274)	Study B (*n*=486)
Gender			
Male (*n*, %)	143 (50.4)	140 (51.2)	235 (48.4)
Race			
Caucasian (*n*, %)	258 (90.9)	259 (94.5)	454 (93.6)
African American (*n*, %)	7 (2.5)	7 (2.6)	12 (2.5)
Age at enrollment			
Years (mean ± s.d.)	35.9 ± 8.4	36.5 ± 8.2	48.2 ± 8.3
Educational level			
Some high school (*n*, %)	12 (4.2)	7 (2.6)	2 (0.4)
Completed high school (*n*, %)	33 (11.6)	31 (11.4)	53 (11.0)
Some college (*n*, %)	70 (24.7)	57 (21.0)	117 (24.2)
Completed college (*n*, %)	104 (36.6)	111 (40.8)	160 (33.1)
Graduate studies (*n*, %)	65 (22.9)	66 (24.3)	152 (31.4)
Marital status			
Single (*n*, %)	82 (29.0)	80 (29.4)	52 (10.7)
Married (*n*, %)	171 (60.4)	175 (64.3)	363 (74.9)
Divorced/separated (*n*, %)	27 (9.5)	16 (5.9)	57 (11.8)
Widowed/other (*n*, %)	3 (1.1)	1 (0.4)	13 (2.6)
Employment			
Student (*n*, %)	25 (8.8)	27 (9.9)	11 (2.3)
Homemaker (*n*, %)	18 (6.3)	22 (8.0)	43 (8.9)
Part-time employment (*n*, %)	34 (12.0)	32 (11.7)	50 (10.3)
Full-time employment (*n*, %)	204 (71.8)	197 (71.9)	342 (70.5)
Other/disabled/retired (*n*, %)	13 (4.6)	11 (4.0)	60 (12.4)
Diagnosis of ADPKD, age			
Years (mean ± s.d.)	27.1 ± 9.7	28.0 ± 10.3	33.1 ± 12.3
Diagnosis due to			
Screening (*n*, %)	113 (39.8)	93 (34.2)	184 (37.9)
Incidental imaging (*n*, %)	37 (13.0)	30 (11.0)	47 (9.7)
Pain (*n*, %)	42 (14.8)	34 (12.5)	52 (10.7)
Hypertension (*n*, %)	36 (12.7)	50 (18.4)	69 (14.2)
Routine physical (*n*, %)	10 (3.5)	8 (2.9)	26 (5.4)
Hematuria (*n*, %)	15 (5.3)	25 (9.2)	33 (6.8)
UTI (*n*, %)	5 (1.8)	9 (3.3)	9 (1.9)
Other (*n*, %)	26 (9.1)	23 (8.5)	65 (13.4)
Diagnosis of ADPKD, mode			
Ultrasound (*n*, %)	205 (72.2)	195 (71.7)	350 (72.2)
CT (*n*, %)	46 (16.2)	42 (15.4)	54 (11.1)
MRI (*n*, %)	17 (6.0)	16 (5.9)	23 (4.7)
IVP (*n*, %)	7 (2.5)	11 (4.0)	31 (6.4)
Other (*n*, %)	9 (0.1)	8 (0.0)	27 (0.6)
Diagnosis of hypertension, age			
Years (mean ± s.d.)	30.2 ± 8.7	30.9 ± 9.1	36.2 ± 10.6

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography; IVP, intravenous pyelogram; MRI, magnetic resonance imaging; UTI, urinary tract infection.

Associations of baseline parameters with kidney volume

Age and natural log–transformed HtTKV, ln(HtTKV), are significantly correlated in men, but not in women (Table 4). BSA and height are positively correlated with ln(HtTKV); these correlations are seen in men but not in women. BSA and height are also positively correlated with unadjusted lnTKV or with lnTKV adjusted for BSA (not shown). Office (and home, not shown) BPs and ln(urine albumin excretion) correlate positively, whereas eGFR and renal blood flow (RBF) correlate negatively with ln(HtTKV). Weak positive correlations exist between urine volume, urine sodium excretion, natural log–transformed total liver volume adjusted for height and ln(HtLCV), with ln(HtTKV) in women only.

Multiple regression analysis shows independent associations of baseline BSA, ln(urine albumin excretion), and eGFR with baseline ln(HtTKV) (Table 5), unadjusted lnTKV, or lnTKV adjusted for BSA. The association of BSA with baseline ln(HtTKV) remains statistically significant if kidney weights (estimated from TKV) are subtracted from body weights to calculate BSA, indicating that the association is not due to a bias introduced by the contribution of kidney volume to body weight. Body mass index cannot replace BSA in the model.

Associations of baseline parameters with eGFR

Age, office systolic BP, serum potassium, and ln (urine albumin excretion) are negatively correlated, whereas sodium/potassium ratio is positively correlated with baseline eGFR (Table 6). BSA, body mass index, office diastolic BP, and urine potassium excretion are negatively correlated with eGFR in men only. Urine aldosterone excretion is positively correlated with eGFR in women only. In Study A, age and ln(HtTKV) are negatively correlated and RBF is positively correlated with eGFR.

Table 2 | Baseline characteristics by gender in Study A and Study B

	Study A			Study B		
	Male	Female	Both	Male	Female	Both
	Mean ± s.d. (*N*)	Mean ± s.d. (*N*)	Mean ± s.d.	Mean ± s.d. (*N*)	Mean ± s.d. (*N*)	Mean ± s.d.
Age (years)	**35.2 ± 8.1** (283)	**37.2 ± 8.4**** (275)	**36.2 ± 8.3**	**47.4 ± 8.7** (235)	**49.0 ± 7.9*** (251)	**48.2 ± 8.3*****
Height (cm)	**181.0 ± 7.8** (275)	**166.3 ± 7.8***** (271)	173.7 ± 10.7	**180.3 ± 8.9** (231)	**166.4 ± 20.5***** (246)	173.1 ± 17.4
BSA (m^2)	**2.1 ± 0.2** (274)	**1.8 ± 0.2***** (271)	2.0 ± 0.2	**2.1 ± 0.2** (231)	**1.8 ± 0.2***** (246)	2.0 ± 0.3
BMI (kg/m^2)	27.6 ± 4.7 (274)	27.2 ± 10.4 (271)	**27.4 ± 8.0**	29.0 ± 5.9 (231)	28.2 ± 12.9 (246)	**28.6 ± 10.1***
Office systolic BP (mm Hg)	**127.2 ± 14.3** (280)	**122.9 ± 14.5***** (274)	125.1 ± 14.5	127.9 ± 15.0 (235)	125.4 ± 15.8 (251)	126.6 ± 15.4
Office diastolic BP (mm Hg)	80.0 ± 11.4 (280)	78.6 ± 11.8 (274)	79.3 ± 11.6	**80.3 ± 9.7** (234)	**76.8 ± 10.9***** (251)	78.5 ± 10.5
HtTKV (ml/m)	**780.7 ± 419.5** (262)	**608.9 ± 367.2***** (266)	694.1 ± 403.0	NA	NA	NA
RBF (ml/min per 1.73 m^2)	**665.0 ± 224.3** (130)	**610.5 ± 205.4*** (138)	636.9 ± 216.1	NA	NA	NA
HtTLV (ml/m)	1114 ± 402 (265)	1137 ± 513 (269)	1126 ± 461	NA	NA	NA
Liver cyst volume (ml)	**146.2 ± 703.0** (226)	**343.9 ± 795.6*** (241)	248.2 ± 757.9	NA	NA	NA
eGFR (ml/min per 1.73 m^2)	90.4 ± 17.8 (282)	92.7 ± 17.1 (275)	**91.5 ± 17.5**	47.1 ± 11.3 (235)	49.2 ± 12.3 (251)	**48.2 ± 11.8*****
Serum sodium (mEq/l)	139.3 ± 2.2 (283)	138.6 ± 7.8 (275)	138.9 ± 5.7	138.6 ± 11.8 (234)	139.3 ± 2.4 (249)	138.9 ± 8.4
Serum potassium (mEq/l)	**4.2 ± 0.4** (283)	**4.0 ± 0.4***** (275)	**4.1 ± 0.4**	**4.3 ± 0.5** (234)	**4.2 ± 0.5*** (249)	**4.3 ± 0.5*****
Urine volume (ml)	2639 ± 1201 (272)	2457 ± 1150 (265)	2550 ± 1179	**2794 ± 1114** (222)	**2541 ± 974*** (240)	2662 ± 1050
Urine sodium (mEq/24 h)	**194.0 ± 75.3** (254)	**161.0 ± 78.5***** (260)	177.3 ± 78.6	**202.7 ± 86.6** (211)	**153.8 ± 68.1***** (224)	177.5 ± 81.3
Urine potassium (mEq/24 h)	**62.9 ± 26.4** (251)	**53.5 ± 25.0***** (257)	**58.1 ± 26.1**	**68.7 ± 28.3** (211)	**56.3 ± 23.0***** (224)	**62.3 ± 26.4***
Urine sodium/potassium ratio	3.5 ± 1.6 (251)	3.3 ± 1.6 (257)	**3.4 ± 1.6**	3.2 ± 1.2 (211)	3.0 ± 1.5 (224)	**3.1 ± 1.3****
Urine aldosterone (μg/24 h)	**10.0 ± 5.9** (217)	**15.8 ± 12.0***** (223)	**12.9 ± 9.9**	10.0 ± 7.7 (173)	10.3 ± 7.6 (190)	**10.2 ± 7.6*****
Urine albumin (mg/24 h)	40.8 ± 73.2 (254)	42.3 ± 183.6 (260)	**41.5 ± 140.2**	**109.1 ± 195.6** (210)	**64.9 ± 124.1*** (224)	**86.3 ± 163.9*****

Abbreviations: BMI, body mass index; BP, blood pressure; BSA, body surface area; eGFR, estimated glomerular filtration rate; HtTKV, total kidney volume adjusted for height; HtTLV, total liver volume adjusted for height; NA, not applicable; RBF, renal blood flow.
Characters in bold indicate statistically significant differences between the genders within Study A and Study B or between Study A and Study B.
P*-values ⩽ 0.05, ** ⩽ 0.005, * ⩽ 0.0005.

Table 3 | Baseline characteristics in Study A by blood pressure group assignment

	Study A (Standard)		Study A (Low)		
	N	Mean ± s.d.	*N*	Mean ± s.d.	*P*-value
Age (years)	284	35.9 ± 8.4	274	36.5 ± 8.2	0.401
Female	284	49.6%	274	48.9%	0.861
Height (cm)	280	173.4 ± 11.5	266	174.0 ± 9.8	0.533
BSA (m^2)	279	2.0 ± 0.2	266	2.0 ± 0.2	0.938
BMI (kg/m^2)	279	27.8 ± 10.1	266	27.0 ± 5.1	0.225
Office systolic BP (mm Hg)	282	125.2 ± 14.6	272	125.0 ± 14.5	0.883
Office diastolic BP (mm Hg)	282	79.9 ± 11.7	272	78.7 ± 11.5	0.227
HtTKV (ml/m)	269	704.2 ± 406.1	259	683.7 ± 400.2	0.558
RBF (ml/min per 1.73 m^2)	131	623.2 ± 215.0	137	650.0 ± 217.2	0.311
HtTLV (ml/m)	273	1128.4 ± 380.4	261	1122.9 ± 532.4	0.892
Liver cyst volume (ml)	241	237.1 ± 596.9	226	260.1 ± 899.6	0.751
eGFR (ml/min per 1.73 m^2)	283	91.7 ± 17.8	274	91.4 ± 17.2	0.820
Serum sodium (mEq/l)	284	139.1 ± 2.3	274	138.8 ± 7.8	0.572
Serum potassium (mEq/l)	284	4.1 ± 0.4	274	4.1 ± 0.4	0.368
Urine volume (ml)	271	2577 ± 1223	266	2522 ± 1133	0.595
Urine sodium (mEq/24 h)	260	176.4 ± 77.7	254	178.2 ± 79.7	0.786
Urine potassium (mEq/24 h)	257	57.9 ± 24.4	251	58.4 ± 27.8	0.818
Urine sodium/potassium ratio	257	3.4 ± 1.6	251	3.4 ± 1.6	0.784
Urine aldosterone (μg/24 h)	226	**13.9 ± 11.1**	214	**11.9 ± 8.3**	**0.033**
Urine albumin (mg/24 h)	260	34.9 ± 56.6	254	48.3 ± 191.0	0.284

Abbreviations: BMI, body mass index; BP, blood pressure; BSA, body surface area; eGFR, estimated glomerular filtration rate; HtTKV, total kidney volume adjusted for height; HtTLV, total liver volume adjusted for height; RBF, renal blood flow.
Characters in bold indicate statistically significant differences.

Multiple regression analysis shows independent associations of baseline age, RBF, and ln(HtTKV) with eGFR (Table 7). Excluding RBF and ln(HtTKV) from the model, age, BSA, ln(urine albumin), serum potassium, and urine aldosterone are independently associated with eGFR (Table 7). Body mass index cannot replace BSA in the model.

DISCUSSION

The HALT PKD A and B populations constitute the largest cohort of systematically analyzed hypertensive ADPKD patients published to date. Analysis of the baseline characteristics of the study population demonstrates adequate randomization between the low and standard BP arms of

Table 4 | Correlations between ln(htTKV) and other baseline parameters in Study A

	ln(htTKV)								
	Men			Women			Both		
	N	*r*-value	*P*-value	*N*	*r*-value	*P*-value	*N*	*r*-value	*P*-value
Age (years)	262	0.233	**0.0001**	266	0.049	0.4288	528	0.109	**0.0121**
Height (cm)	262	0.142	**0.0215**	266	0.075	0.2198	528	0.236	**<0.0001**
BSA (m^2)	261	0.243	**<0.0001**	266	0.101	0.0998	527	0.275	**<0.0001**
BMI (kg/m^2)	261	0.157	**0.0112**	266	0.055	0.3675	527	0.084	0.0541
Office systolic BP (mm Hg)	261	0.190	**0.0020**	266	0.106	0.0840	527	0.178	**<0.0001**
Office diastolic BP (mm Hg)	261	0.193	**0.0017**	266	0.088	0.1533	527	0.152	**0.0005**
RBF (ml/min per 1.73 m^2)	128	−0.241	**0.0062**	137	−0.169	**0.0489**	265	−0.181	**0.0032**
eGFR (ml/min per 1.73 m^2)	262	−0.375	**<0.0001**	266	−0.289	**<0.0001**	528	−0.339	**<0.0001**
Serum sodium (mEq/l)	262	0.043	0.4916	266	0.018	0.7691	528	0.035	0.4184
Serum potassium (mEq/l)	262	0.056	0.3647	266	−0.054	0.3765	528	0.044	0.3101
Urine volume (ml)	254	−0.042	0.5020	256	0.129	**0.0397**	510	0.055	0.2156
Urine sodium (mEq/24 h)	236	0.044	0.5018	251	0.139	**0.0276**	487	0.142	**0.0017**
Urine potassium (mEq/24 h)	233	0.027	0.6777	248	0.069	0.2775	481	0.096	**0.0351**
Urine sodium/potassium ratio	233	−0.005	0.9342	248	0.008	0.9054	481	0.015	0.7423
Urine aldosterone (μg/24 h)	201	0.058	0.4135	216	−0.017	0.7997	417	−0.062	0.2031
ln(Urine albumin)	236	0.286	**<0.0001**	251	0.446	**<0.0001**	487	0.360	**<0.0001**
ln(HtTLV) (in ml/m)	262	0.081	0.1895	262	0.136	**0.0264**	527	0.112	**0.0098**
ln(Liver cyst volume) (in ml)	215	0.040	0.5581	233	0.171	**0.0088**	448	0.066	0.1641

Abbreviations: BMI, body mass index; BP, blood pressure; BSA, body surface area; eGFR, estimated glomerular filtration rate; HtTKV, total kidney volume adjusted for height; HtTLV, total liver volume adjusted for height; ln(HtTKV), natural log–transformed TKV adjusted for height; ln(HtTLV), natural log–transformed TLV adjusted for height; RBF, renal blood flow.
Characters in bold indicate statistically significant correlations.

Table 5 | Final regression model to predict ln(HtTKV)

	R^2=0.287 (*n*=486)	
	β-value	*P*-value
BSA (m^2)	0.247	**<0.001**
ln(Urine albumin) (in mg/24 h)	0.324	**<0.001**
eGFR (ml/min per 1.73 m^2)	−0.286	**<0.001**

Abbreviations: BSA, body surface area; eGFR, estimated glomerular filtration rate; HtTKV, total kidney volume adjusted for height; ln(HtTKV), natural log–transformed TKV adjusted for height.
Characters in bold indicate statistically significant independent predictors.

Study A. It also identifies novel factors affecting the development and progression of ADPKD.

Associations of baseline parameters with ln(HtTKV)

Baseline eGFR, ln(urine albumin excretion), and BSA independently associate with ln(HtTKV) in the current study. Previous studies had shown a negative correlation between TKV and GFR[4] and direct associations of TKV with urine protein and albumin excretions.[5] More recently, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) used magnetic resonance imaging (MRI) to measure TKV annually in a cohort of ADPKD patients with well-preserved renal function at the initiation of the study. Age-adjusted TKV was negatively correlated with GFR and urine albumin excretion at baseline.[6] During the initial CRISP study period of 3 years, TKV was modestly associated with a decline in GFR measured by iothalamate clearance.[7] A more recent CRISP report with 8 years of follow-up has found increasingly strong associations between baseline HtTKV and the follow-up iothalamate clearances and progression through the K/DOQI stages.[8] These observations demonstrate that renal cyst burden, reflected by HtTKV, is a very important determinant of renal functional decline in ADPKD.

In the current study, BSA is independently associated with ln(HtTKV), unadjusted lnTKV, or lnTKV adjusted for BSA. The association between the anthropomorphic marker BSA and TKV, even when TKV is adjusted for height or BSA, points to biological factor or factors associated with, but distinct from, body size. Genetic and environmental factors affect birth weights and postnatal growth velocities, which ultimately determine adult height, weight, and BSA. Genome-wide association studies have identified loci associated with height variation.[9,10] Associations between height and risks for particular diseases may reflect common genetic effects on growth and disease predisposition, rather than direct associations of phenotypic traits. Low birth weights increase the risk for insulin resistance, type 2 diabetes, obesity, and hypertension in adult life,[11] whereas high birth weights are associated with increased risk for various childhood[12–15] and adult[16–19] malignancies. Low birth weights have been associated with lower nephron numbers, which in turn could increase the risk for hypertension, proteinuria, and GFR decline in ADPKD, as it has been reported in other renal diseases.[20,21] On the other hand, enhanced nephrogenesis could accelerate cyst development as shown in conditional mouse models[22–24], and a higher nephron number could make larger number of cells susceptible to somatic mutations and cyst development in the same way that a large nephron number and mammary gland

Table 6 | Correlations between eGFR and other baseline parameters in both studies (A and B)

	eGFR								
	Men			Women			Both		
	N	*r*-value	*P*-value	*N*	*r*-value	*P*-value	*N*	*r*-value	*P*-value
Age (years)	517	−0.666	**<0.0001**	526	−0.658	**<0.0001**	1043	−0.656	**<0.0001**
Height (cm)	505	0.019	0.6627	517	0.035	0.4280	1022	0.012	0.7043
BSA (m^2)	504	−0.147	**0.0010**	517	0.000	0.9961	1021	−0.073	**0.0202**
BMI (kg/m^2)	504	−0.188	**<0.0001**	517	−0.026	0.5618	1021	−0.072	**0.0219**
Office systolic BP (mm Hg)	514	−0.093	**0.0360**	525	−0.093	**0.0330**	1039	−0.095	**0.0022**
Office diastolic BP (mm Hg)	513	−0.136	**0.0020**	525	0.061	0.1621	1038	−0.035	0.2571
Serum sodium (mEq/l)	516	0.021	0.6331	524	−0.035	0.4214	1040	−0.003	0.9228
Serum potassium (mEq/l)	516	−0.198	**<0.0001**	524	−0.246	**<0.0001**	1040	−0.223	**<0.0001**
Urine volume (ml)	494	−0.088	0.0506	505	−0.070	0.1158	999	−0.081	**0.0104**
Urine sodium (mEq/24 h)	465	−0.001	0.9881	484	0.050	0.2712	949	0.014	0.6675
Urine potassium (mEq/24 h)	462	−0.100	**0.0311**	481	−0.063	0.1680	943	−0.088	**0.0068**
Urine sodium/potassium ratio	462	0.178	**0.0001**	481	0.125	**0.0059**	943	0.148	**<0.0001**
Urine aldosterone (μg/24 h)	390	0.003	0.9496	413	0.279	**<0.0001**	803	0.173	**<0.0001**
ln(Urine albumin)	464	−0.308	**<0.0001**	484	−0.263	**<0.0001**	948	−0.287	**<0.0001**
Study A	517	0.818	**<0.0001**	526	0.824	**<0.0001**	1043	0.820	**<0.0001**

Abbreviations: BMI, body mass index; BP, blood pressure; BSA, body surface area; eGFR, estimated glomerular filtration rate.
Characters in bold indicate statistically significant correlations.

Table 7 | Final regression models to predict eGFR

	Including ln(HtTKV) and RBF R^2=0.404 (n=265)		Excluding ln(HtTKV) and RBF R^2=0.740 (n=770)	
	β-value	*P*-value	*β*-value	*P*-value
Age (years)	−0.433	**<0.001**	−0.288	**<0.001**
BSA (m^2)	—	—	−0.047	**0.012**
Serum potassium (mEq/l)	—	—	−0.048	**0.013**
Urine aldosterone (μg/24 h)	—	—	0.046	**0.015**
ln(Urine albumin) (in mg/24 h)	—	—	−0.111	**<0.001**
ln(HtTKV) (in ml/m)	−0.182	**<0.001**	—	—
RBF (ml/min per 1.73 m^2)	0.300	**<0.001**	—	—
Study A	—	—	0.606	**<0.001**

Abbreviations: BSA, body surface area; eGFR, estimated glomerular filtration rate; HtTKV, total kidney volume adjusted for height; ln(HtTKV), natural log-transformed TKV adjusted for height; RBF, renal blood flow.
Characters in bold indicate statistically significant independent predictors.

mass increase the risk for renal cell and breast cancers.[16,25] Postnatal growth may be as important as, or more important than, prenatal growth for programming pathways predisposing to adult diseases. Faster postnatal growth associated with high nutrient formula feeding increases the risk for obesity, insulin resistance, low high-density lipid cholesterol, hypertension, and cardiovascular disease.[26–30] As newborns with low birth weights usually show faster postnatal growth, whereas large newborns show growth deceleration, it has been suggested that the association of low birth weight with higher risk for cardiovascular disease reflects at least in part the adverse effects of postnatal growth acceleration.[28,31–33] At present, we can only speculate on which genetic and environmental factors affecting growth can also affect the progression of ADPKD. A large body of evidence, for example, indicates that the insulin-like growth factor-I system has a major role in prenatal and postnatal growth[34–37] and mediates epithelial cell proliferation in polycystic kidney disease.[38,39]

The fact that the association between BSA and ln(HtTKV) in the current study is mostly restricted to men is intriguing but not unique. Gender differences are common in animal[40–43] and human[44,45] examples of developmental programming. Men appear more susceptible to perinatal programming of metabolic and cardiovascular homeostasis than women. The associations of birth weight with development of chronic kidney disease[46–48] and of renal cell cancer[16] are stronger in men. Gender differences in hormonal systems affecting fetal and renal development, such as the insulin-like growth factor-I[37] and the RAS,[49] may be responsible for these gender effects.

Associations of baseline parameters with eGFR

In Study A, age, RBF, and ln(HtTKV) were independently associated with baseline eGFR. These results are consistent with those of the CRISP study.[50] In Studies A and B, age, BSA, serum potassium, ln(urine albumin excretion), and urine aldosterone excretion were independently associated

with eGFR. As in the case of ln(HtTKV), the association of BSA and eGFR is restricted to men. The positive correlation between urine aldosterone excretion and eGFR and the lower urinary aldosterone excretion in Study B compared with Study A participants, despite higher serum potassium concentrations, suggests that as renal function declines extracellular fluid volume expansion suppresses the circulating RAS. In chronic kidney disease, aldosterone production depends on the extracellular volume status, increases in response to sodium restriction, and may contribute to renal disease progression regardless of its level.[51–53]

Distinct factors affect the severity of polycystic kidney and liver disease

A number of observations in this study suggest that the renal involvement in ADPKD may be more severe in men than in women. In Study A, TKV is significantly greater in men than in women, even when adjusted by height or BSA and despite the fact that men are significantly younger than women. The significant direct correlation between age and ln(HtTKV) in men, but not in women, may reflect a higher rate of renal enlargement in men. In Study B, men have significantly higher BP and urine albumin excretion than women. The significantly older age of women in both studies, A and B, probably reflects a selection bias introduced by the fact that men have more progressive disease than women and therefore had to be younger at enrollment into the study in order to meet the eGFR entry criteria. Nevertheless, we cannot find an independent association of gender with disease severity reflected by a higher ln(HtTKV) or a lower eGFR in the multiple regression analysis. Interestingly, a recent study based on data from the Danish National Registry on Regular Dialysis and Transplantation has shown that during 1990–2007 the mean age of ESRD increased by 5.0 and 4.4 years in male and female ADPKD patients and that the age-adjusted male/female ratio at onset of ESRD decreased from 1.6 to 1.1, suggesting that male gender has become less important as a risk factor for progression in ADPKD in the past two decades.[54]

It has been hypothesized that patients with more severe polycystic kidney disease also have more severe liver involvement, reflecting a higher systemic severity of the disease.[55] This was not confirmed by the CRISP study where a correlation between LCV and TKV became nonsignificant when adjusted for age.[56] The current study detects only a weak association between ln(HtTKV) and either natural log–transformed total liver volume adjusted for height or ln(LCV) in women, but not in men. Furthermore, whereas men had higher HtTKV than women, women had higher LCV than men, suggesting opposite sex–linked hormonal effects on disease progression in polycystic kidneys and polycystic livers. These observations indicate that, in addition to the *PKD* mutations, other factors distinct for each organ are important for the development and progression of polycystic kidney and polycystic liver disease.

Gender differences in urine aldosterone excretion and plasma potassium concentrations

Other observations in this analysis deserve comment. Higher urine aldosterone excretions in women compared with men in Study A are consistent with higher serum aldosterone values in women compared with men and in premenopausal compared with postmenopausal women in the Framingham Heart Study.[57] Aldosterone production significantly increases in the luteal phase owing to high progesterone levels[58,59] because progesterone is a precursor of aldosterone[60,61] and a mineralocorticoid receptor antagonist with a natriuretic effect that can activate the RAS.[62] Luteinizing hormone may also stimulate aldosterone synthesis in the adrenal cortex.[63]

Lower plasma potassium concentrations in women compared with men have been reported in previous human and animal studies[64–66] and attributed to estrogen effects, enhancing the action of mineralcorticoids on the kidney and increasing β_2-adrenoreceptor density, affinity, or G protein coupling to adenylate cyclase in skeletal muscle and red blood cells, thus causing an intracellular influx of potassium into the cells.[66,67]

In summary, a cross-sectional analysis of baseline parameters in HALT PKD, the largest cohort of systematically studied ADPKD patients to date that confirms a strong association between renal volume and functional parameters, shows that gender and other factors differentially affect the development of polycystic disease in the kidney and liver, and suggests the intriguing possibility that intrauterine development and developmental programming (reflected by BSA and height) affect the natural history of this disease.

MATERIALS AND METHODS

The design and implementation of the HALT PKD trials have been described in detail elsewhere.[3] The Polycystic Kidney Disease Treatment Network (HALT PKD) includes four participating clinical centers, three satellite clinical sites, and a coordinating center. The participating clinical centers include the Emory University, Mayo Clinic with Kansas University Medical Center and the Cleveland Clinic, Tufts Medical Center with Beth Israel Deaconess Medical Center, and University of Colorado Health Sciences. The Coordinating Center initially at the Washington University is now at the University of Pittsburgh. HALT PKD began enrolling subjects in 2006, and concluded enrollment in mid-2009. Follow-up will continue until 2014.

Organization of the HALT PKD trials

The HALT PKD trials are prospective randomized double-blind placebo-controlled multicenter interventional trials comparing treatment with ACEI—angiotensin receptor blocker combination vs. ACEI alone and standard vs. low BP target in 15- to 49-year-old ADPKD patients with eGFR >60 ml/min per 1.73 m^2 ($n=558$, Study A) and ACEI-angiotensin receptor blocker vs. ACEI alone in 18- to 64-year-old patients with eGFR 25–60 ml/min per 1.73 m^2 ($n=486$, Study B). All participants have hypertension or high-normal BP defined as systolic BP $\geqslant 130$ mm Hg and/or diastolic BP $\geqslant 80$ mm Hg on three separate readings within the past year, or current use of antihypertensive agents for BP control. Standard

BP control for this study is defined as 120–130/70–80 mm Hg and low BP as 95–110/60–75 mm Hg.

Washout period and home BP measurements

Participants are trained at the screening visit to perform home BP measurements at least every other day during the drug washout period. BP measurements are obtained at least 30 min after awakening, before eating breakfast, smoking or consuming caffeine, after sitting for at least 5 min with the arm resting at heart level. The average of the second and third of three measurements 30 s apart is used for decision making. If the difference between the two systolic or diastolic readings is >10 mm Hg, participants record a fourth and fifth reading and the average of the last four readings is used. For those patients taking antihypertensive medications, existing antihypertensives are gradually discontinued and a 2- to 4-week drug washout period is completed. Labetalol or clonidine is taken during the washout period for BP control, unless indicated otherwise. BP drugs taken for non-hypertensive indications are continued at the discretion of the principal investigator.

Participant baseline visits and randomization procedures

Within 10 weeks of the screening visit, participants return to the center for a standardized baseline visit including complete history taking and physical examinations, recording sitting and standing clinic BP measurements following the same protocol used for home BP measurements, as well as serum creatinine (see below) and biochemical measurements, MRI acquisitions in Study A patients, and completion of 24-h urine collections for determination of albumin and aldosterone excretion. They also had to complete health-related questionnaires.

Two blood samples, drawn a minimum of 1-h apart, are sent to the central laboratory (Cleveland Clinic Foundation Reference Laboratory) for analysis to establish the baseline serum creatinine measurement. Consistency of the two serum creatinine measurements ($<20\%$ variation) is required. If the two measurements differ by greater than 20%, a second set of serum creatinine samples is obtained shortly after and sent for repeat analysis. Glomerular filtration rate is estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[68] A 24-hour urine collection is performed for measurements of sodium, potassium, creatinine, albumin, and aldosterone excretions, which are carried out at the Diagnostic Laboratory Facility at Brigham and Women's Hospital, Boston. Adequacy of the collection is assessed based on creatinine excretion compared with the predicted value from lean body weight for age and gender.

MRI is performed in Study A patients for the determination of TKV, total liver volume, LCV, left ventricular mass, and RBF. MR images (including RBF images) are obtained at each center using a protocol developed by the HALT PKD Imaging Subcommittee. Following acquisition, MR images are reviewed locally and then transferred electronically to the Image Analysis Center at the University of Pittsburgh. The cardiac MR imaging results will be reported separately.

Randomization procedures

Randomization was performed by the coordinating center at the baseline visit in equal proportions to combined lisinopril plus telmisartan or lisinopril plus placebo using random permuted blocks with stratification by center, participant age, gender, race, and baseline eGFR. Study A patients were additionally randomized in equal proportions to either a standard BP (120–130/70–80 mm Hg) or low BP (95–110/60–75 mm Hg) target.

Statistical methods

The data were analyzed using STATA/SE 11.1 (College Station, TX). Group comparisons were conducted using two-sample t-tests, and correlations were reported using Pearson's correlation coefficients. The comparison of categorical variables across groups was conducted using χ^2-tests. Continuous data were investigated for violations of normality, as well as outliers. In the event that these violations occurred, suitable transformations were taken (i.e., natural logarithm).

Multiple regression models were built to examine how clinical and laboratory baseline variables were associated with baseline TKV or eGFR. Predictor variables for each of the initial multivariate models were chosen based on significant ($P<0.10$) univariate correlations with the respective outcome. The predictor variables were also checked for multicollinearity using variance inflation factors. Stepwise selection, with probabilities to enter and remove as 0.05 and 0.10, respectively, was used for model building. Only variables with $P<0.05$ were further considered for the final models. Finally, standardized regression coefficients were used to facilitate the comparison of predictor variables. Standardized regression coefficients were calculated within STATA11 as follows: $\beta_{\text{std}} = \beta_{\text{unstd}}[S_x/S_y]$, where β_{unstd} is the unstandardized coefficient from a multiple regression model, and S_x and S_y are the standard deviations for the covariate of interest and the outcome variable, respectively. Because of the exploratory nature of the analyses, adjustments for multiplicity were not performed.

DISCLOSURE

VET is an investigator and Chair of the Steering Committee for several Otsuka studies on ADPKD, is an investigator in a clinical trial for ADPKD sponsored by Novartis Pharmaceuticals, and has served as consultant for Wyeth Pharmaceuticals, Hoffman-La Roche, and Primrose Therapeutics. RDP is an investigator and member of the Steering Committee for several Otsuka studies on ADPKD and is the coordinating and site investigator for a clinical trial for ADPKD sponsored by Novartis Pharmaceuticals. ABC is an investigator and member of the Steering Committee for several Otsuka studies on ADPKD.

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