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.