Magnetic Resonance Imaging of Kidney and Cyst Volume in Children with ADPKD

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Summary

Background and objectives Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease and has important clinical manifestations in childhood. Numerous studies have documented the superiority of magnetic resonance imaging (MRI) for serial monitoring of kidney and cyst volume in this condition in adults. However, no studies have examined the utility of MRI for serial assessment of kidney and cyst volume in children with ADPKD.

Design, setting, participants, & measurements Subjects 4 to 21 years of age with ADPKD underwent abdominal MRI on an annual basis for 5 years. Subjects were grouped according to BP as hypertensive (HBP; BP $\geq$ 95th percentile for age, height, and gender) or as normotensive (NBP; BP $<$ 95th percentile). Total kidney volume (TKV), cyst volume, and cyst number were assessed by stereology.

Results MRI studies (n = 302) were obtained in 77 children with ADPKD. TKV and cyst volume were significantly increased in HBP *versus* NBP subjects. HBP subjects demonstrated a greater increase in fractional cyst volume over time *versus* NBP subjects. Cyst number increased more rapidly in HBP ADPKD children.

Conclusions This is the first large-scale clinical study examining the utility of MRI for serial assessment of TKV, cyst volume, and cyst number in children with ADPKD. These results demonstrate that MRI is an acceptable means to follow these parameters in children with ADPKD. Because of the embryonic occurrence of cysts, interventional trials are needed in ADPKD children and MRI may be the preferred renal imaging approach.

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease, affecting 1 in 400 to 1 in 1000 people (1). This condition is associated with the progressive development of renal cysts with subsequent distortion of normal kidney architecture, renal enlargement, and loss of kidney function over time such that approximately half of those affected reach ESRD by 60 years of age (1). The term "adult-onset polycystic kidney disease" has now been discarded because ADPKD is known to occur in childhood and can be detected as early as fetal life by prenatal ultrasonography (2,3). However, thus far more is known regarding this condition in adults as compared with children.

Because renal function is not impaired until marked structural damage has occurred, recent studies have focused on kidney volume as an early and important marker of disease progression in patients with ADPKD (4–7). An early marker of disease progression is of critical importance in the design of interventional trials in children with ADPKD, in whom systemic and renal manifestations may be present for decades before any detectable change in renal function. In this regard, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) has documented the advantages of magnetic resonance imaging (MRI) for the assessment of renal and cyst growth in adults with ADPKD (8–10). An inverse correlation between renal volume or cyst volume and GFR has been observed in adults with ADPKD, and increased renal volume has been directly related to the presence of hypertension and increased urinary albumin excretion in subjects with ADPKD and normal renal function (8). However, there are no reports regarding the reliability of renal MRI in children with ADPKD. The purpose of the study presented here was to describe the first large-scale study on the use of renal MRI to assess volume changes in renal parenchyma and cysts over time in children with ADPKD.

Materials and Methods

The full clinical protocol was approved by the Colorado Multiple Institutional Review Board and has been detailed extensively elsewhere (11,12). Eligible subjects ranged in age from 4 to 21 years and had a documented history of ADPKD. Patients were considered to have ADPKD when radiographic imaging demonstrated at least two renal cysts in the setting of a family history of ADPKD or when multiple cysts

were present and were clinically consistent with a new diagnosis of ADPKD. All subjects had normal renal function upon entry to the study as determined within the 6 months before enrollment by 24-hour urine creatinine clearance or by estimation from the patient's height and serum creatinine concentration using the Schwartz formula (13). BP was assessed at the initial study visit and interpreted according to guidelines set forth by the National High Blood Pressure Education Program (14–16). On the basis of these results, subjects were designated either hypertensive (HBP), defined as systolic and/or diastolic BP greater than or equal to the 95th percentile for age, height, and gender, or normotensive (NBP), defined as systolic and/or diastolic BP below the 95th percentile for age, height, and gender. The NBP group consisted of subjects with more than ten kidney cysts and BP less than the 75th percentile, as well as subjects with at least two kidney cysts and BP between the 75th and the 95th percentiles. The NBP group included subjects who were felt to be at higher risk of disease progression; this included subjects with high-normal BP who were shown to have an increased risk of progressive renal and cardiovascular disease (12,17) and subjects with more severe structural disease. Subjects were seen annually for 5 years. Clinical data obtained at each visit included serum creatinine and standardized BP measurement. The clinical trial occurred between 1998 and 2007. Abdominal MRI was added to the study protocol in 2001 and thereafter participating subjects underwent abdominal ultrasound and MRI on an annual basis. Results of ultrasonography have been previously reported (17).

Abdominal MRI

MRI was performed annually. A combination of T1, T2, and proton density spin echo sequences were combined with gradient echo sequences with imaging in axial and coronal planes. Sections of 5- to 10-mm thickness were acquired depending on patient size and renal volume. Ultrafast single breath-hold sequences were used as appropriate. A phased array surface coil was used for image acquisition. Imaging was performed on a 1.5-T Visart System (Toshiba America Medical Systems) with image data transferred to a Vitria 3D workstation (Vital Images).

Digital Imaging and Communications in Medicine images were deidentified and evaluated by a single investigator (A.M.) with no knowledge of the subject's hypertensive status using the Analyze software system (Analyze 9.0, Mayo Foundation, Biomedical Imaging Resource, Rochester, MN). Kidney volumes were measured from T1-weighted images using the stereology method. This method has been used extensively for evaluation of kidney and cyst volume in adult subjects with ADPKD (8,9,18,19) as well as for assessment of MRI-acquired images in other organs (20–23). Stereology is a simple and fast method of segmenting an object by counting the number of intersections of a randomly oriented and positioned grid over the object. In this technique, the area of the kidney in each image was calculated from the collection of selected points that overlaid the kidney regions and by converting the point count to a pixel count to obtain the area measurements. The total kidney volume (TKV) was calculated from the set of contiguous images by summing the products of the area measurements and the slice thickness.

Renal cyst volume was calculated from T2-weighted images using the region-based thresholding method (18). The analyst (A.M.) interactively selected a threshold using T2-weighted images. Cysts were brighter than the renal parenchyma in T2-weighted images and were segmented from voxels with intensity values greater than the threshold. Cyst areas were calculated in each image, and the total cyst volume (TCV) was calculated from each set of contiguous images by summing the products of the area measurements and the slice thickness. Fractional cyst volume was determined from the ratio of cyst volume to total renal volume.

To count the number of cysts, a middle section of the left kidney was chosen from coronal T2-weighted images, and the analyst (A.M.) recorded any cyst with a diameter of $\geq$4 mm.

The measurement variability of the kidney volume was expressed as a coefficient of variation for repeated measurements of the same images performed at least a few weeks apart. A single analyst (A.M.) performed all measurements for this study. The reliability coefficients for repeated measurements were 0.972 for kidney volume, 0.987 for cyst volume, and 0.995 for cyst number.

Statistical Analyses

Renal volume and cyst volume by MRI were highly skewed. Therefore, a natural log transformation was applied, and all analyses were performed on the transformed data. Estimates were back transformed and reported as geometric mean and 95% confidence intervals. Mixed-model longitudinal data analysis was performed to compare HBP to NBP ADPKD children for all patients with at least two MRI observations. To address the effects of somatic growth on total kidney and cyst volume in this pediatric population, values were corrected for a body surface area (BSA) of 1.73 m^2. For BSA-corrected renal and cyst volumes, gender was included as a covariate. Left kidney and cyst volumes were compared with right kidney and cyst volumes by paired *t* tests at each time point. The addition of serial MRI to the study protocol after the start of the clinical trial resulted in fewer MRI studies obtained at baseline and year 1 as compared with later follow-up visits. To address this, we did not include baseline measurements in the analysis designed to detect change in kidney and cyst volume. Regression lines were created for each individual starting at year 1, and mixed models were used to provide estimates for each year on the basis of the population regression line.

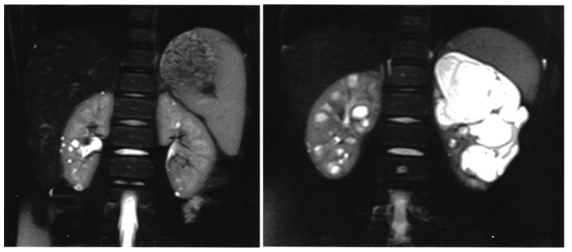

Figure 1. | Representative T2-weighted coronal MRI images from two male participants, each 12 years of age, demonstrating heterogeneity of renal cystic disease.

Table 1. Number of abdominal MRI studies obtained in pediatric ADPKD subjects by study group and year of study

Year of Study	HBP	NBP	Total
Baseline	9/28	20/57	29/85
1	15/27	29/49	44/76
2	16/26	38/47	54/73
3	17/20	42/45	59/59
4	18/19	40/40	58/59
5	18/18	40/48	58/66
Total	93	209	302/418

Denominator reflects the total number of subjects participating in the clinical trial (17). The mean number of MRI studies obtained per subject was 4 ± 2.

Results

A total of 302 abdominal MRI studies were obtained at 418 study visits in 77 children. Representative images are provided in Figures 1 and 2. The number of abdominal MRI studies performed at each time point in the longitudinal study is shown in Table 1. Demographic characteristics for the HBP and NBP children during study participation are shown in Table 2.

TKV was significantly increased in HBP as compared with borderline hypertensive subjects throughout the study period (Figure 3A), with similar trends seen between right and left kidney volumes (Figure 3B). For all subjects, left kidneys were on average 35

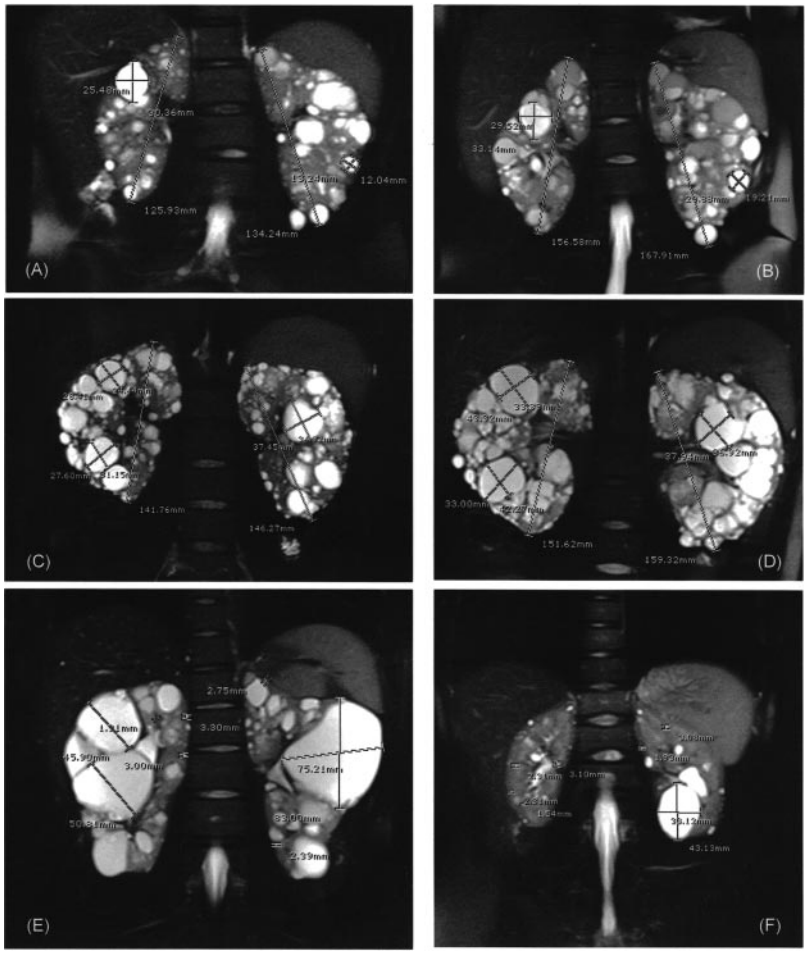

Figure 2. | Representative T2-weighted coronal MRI images from study participants. Interval change in female subject at (A) 15 and (B) 19 years of age. Interval change in male subject with very early-onset ADPKD at (C) 16 and (D) 21 years of age. MRI images demonstrating range of cyst sizes in (E) female subject at 18 years of age and (F) in a different female subject at 10 years of age. The smallest cyst size that could be documented was approximately 2 mm.

Table 2. Demographic characteristics of ADPKD children

Characteristic	HBP, $n = 28$	NBP, $n = 49$	Between-Group, P
Age (years)	14 ± 4	12 ± 4	0.02
Male/female	16/12	22/27	0.30
Height (cm)	159 ± 23	149 ± 23	0.07
BSA (m^2)	1.68 ± 0.49	1.41 ± 0.43	0.02
Systolic BP (mmHg)			
baseline	130 ± 16	112 ± 10	<0.0001
year 5	132 ± 14	118 ± 11[b]	0.0002
Diastolic BP (mmHg)			
baseline	73 ± 11	64 ± 6	0.0012
year 5	72 ± 9	70 ± 8[b]	0.4350
Serum creatinine (mg/dl)			
baseline	0.78 (0.69 to 0.87)	0.65 (0.60 to 0.69)	0.0055
year 5	1.08 (0.98 to 1.19)[a]	0.75 (0.70 to 0.81)[b]	<0.0001

Values are mean ± SEM or geometric mean ± 95% confidence interval as appropriate.
[a]HBP baseline *versus* year 5, $P < 0.0001$. [b]NBP baseline *versus* year 5, $P < 0.001$. Borderline hypertensive = 22/49 (45%).

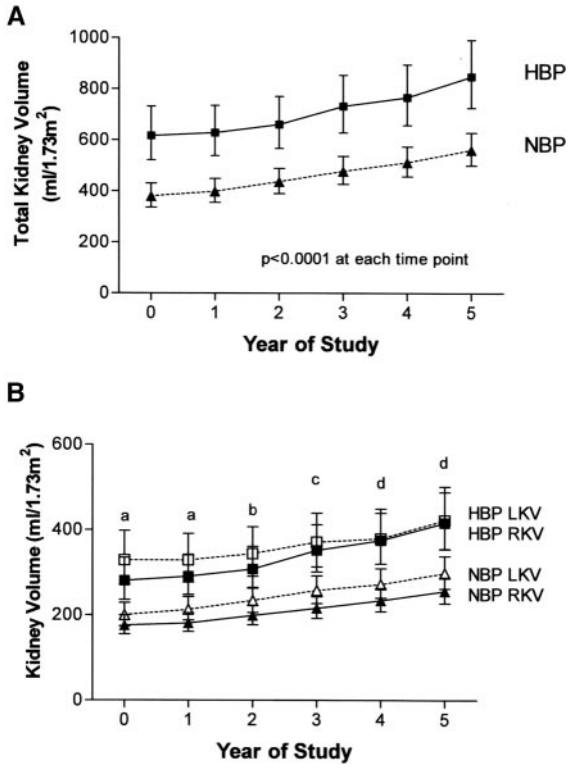

Figure 3. | (A) TKV was significantly increased in HBP as compared with NBP children. Left kidneys tended to be larger. However, there were no significant differences between right and left kidney volumes within HBP or NBP groups (B). Values are geometric mean ± 95% confidence interval adjusted for gender and reported in ml/1.73 m^2. LKV, left kidney volume; RKV, right kidney volume. P values are for HBP *versus* NBP. For RKV, all $P < 0.0001$. For LKV, [a]$P < 0.0001$, [b]$P < 0.0005$, [c]$P < 0.001$, and [d]$P < 0.005$.

ml larger than right kidneys ($P < 0.0001$) across all time points.

TCV was increased at baseline in HBP as compared with NBP subjects and remained elevated over time in HBP subjects (Figure 4A). There were no significant differences noted between right and left kidneys within either group (data not shown). Fractional cyst volume (the percent of TKV occupied by cysts) was similar at baseline in HBP and NBP subjects. However, HBP subjects demonstrated a greater fractional cyst volume as compared with NBP subjects starting at year 2 and continuing through the end of the research study (Figure 4B). The absolute increase in renal cyst volume per year after adjustment for BSA was 81 ± 13 ml/1.73 m^2 per year in HBP subjects as compared with 45 ± 8 ml/1.73 m^2 per year ($P = 0.02$) in NBP subjects. BSA-adjusted fractional cyst volume increased 4.7 ± 1.2%/yr ($P = 0.0002$) in the HBP group and 1.7 ± 1.2%/yr ($P < 0.04$) in the NBP group. These rates of increase were significantly different ($P < 0.03$).

Cyst number was similar between HBP and borderline hypertensive subjects until year 3 of the study, after which time HBP subjects showed a significantly higher number of cysts than NBP subjects (Figure 5). HBP patients had an increase of 19 ± 3 cysts/yr as compared with 11 ± 2 cysts/yr for NBP patients ($P = 0.009$). There were no significant differences noted between right and left kidneys within either group (data not shown).

With serial MRI, we were able to detect a mean increase in TKV of 67 ± 24 ml/1.73 m^2 ($P < 0.005$) and a mean increase in TCV of 71 ± 25 ml/1.73 m^2 ($P = 0.005$) between the first- and second-year observations. For all subjects, when TKV and TCV were regressed against age, a curvilinear relationship was demonstrated, consistent with exponential growth (Figure 6). The natural log of TKV was regressed

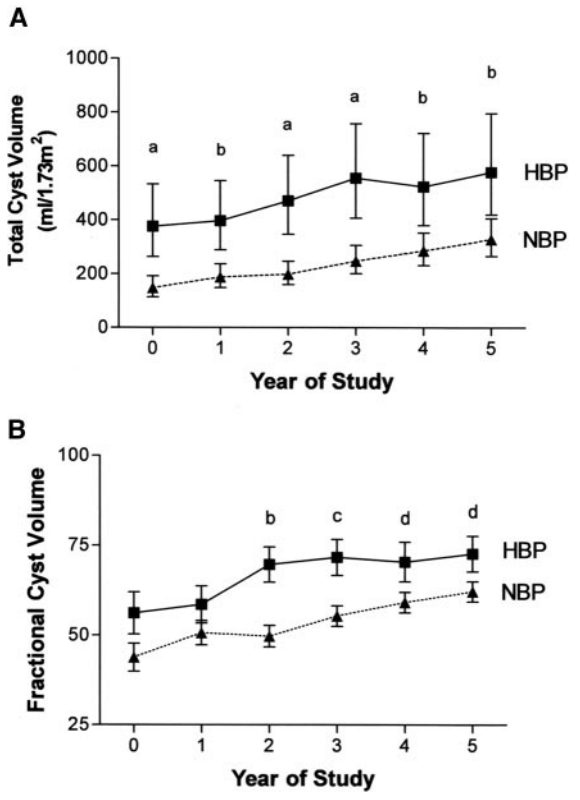

Figure 4. | (A) TCV was increased at baseline and over time in HBP subjects as compared with NBP subjects. Values are geometric mean ± 95% confidence intervals adjusted for gender and reported in ml/1.73 m^2. Although the fractional cyst volume (percent of TKV occupied by cysts) was similar in HBP and NBP subjects at baseline, HBP subjects demonstrated a higher fractional cyst volume over time than did NBP subjects (B). For HBP *versus* NBP, $^{a}P < 0.0001$, $^{b}P < 0.0005$, $^{c}P < 0.005$. $^{d}P < 0.05$.

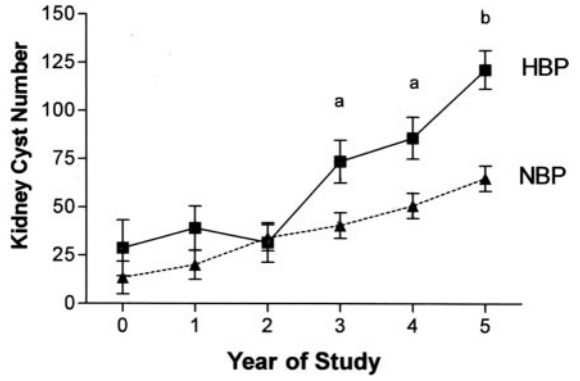

Figure 5. | HBP subjects demonstrated a significant increase in kidney cyst number as compared with NBP subjects beginning at year 3 of the study. Values are mean number of cysts adjusted for gender ± SEM. Cyst number was determined from a single midsection MRI image of the left kidney. For HBP *versus* NBP, $^{a}P < 0.01$, $^{b}P = 0.001$.

against age to assess the annual rate of growth in TKV. The annual rate of growth for all subjects was 7.4%/yr. There was no difference in the annual growth rate between subjects ≤18 years of age as compared with those >18 years of age (7.2 *versus* 8.1%/yr; $P = 0.2$).

TKV by was compared by MRI and ultrasound techniques (17). A Bland–Altman plot demonstrated that the differences in MRI and ultrasound techniques varied randomly around zero. The intraclass correlation coefficient was 0.83. On average, TKV by ultrasound was 27 ml less than by MRI. Greater differences were apparent with larger kidneys. Accurate assessment of TCV could not be obtained with ultrasound.

The study design was such that the NBP group included children with BP below the 75th percentile for age, height, and gender but with severe structural disease (more than ten renal cysts). Therefore, it is likely that differences in TKV, TCV, and cyst number would be more marked between HBP ADPKD children and a randomly selected group of NBP ADPKD children. Our previous studies have suggested that children with borderline hypertension (BP between the 75th and the 95th percentile for age, height, and gender) are at particular risk for progressive renal and cardiovascular disease (12,17). With these considerations, we therefore performed a subgroup analysis comparing results between HBP and borderline hypertensive ADPKD children in the study presented here. HBP subjects demonstrated a significantly greater increase in TKV per year (89 ± 14 *versus* 28 ± 14 ml/1.73 m^2 per year, $P = 0.004$) as compared with borderline hypertensive subjects. HBP subjects also demonstrated a greater increase in renal cyst volume per year (97 ± 18 *versus* 23 ± 18 ml/1.73 m^2 per year, $P = 0.0034$) as compared with borderline hypertensive subjects. Fractional cyst volume increased 4.9 ± 1.6%/yr in the HBP group, whereas there was no perceptible change in percent cyst volume over time in the borderline hypertensive group (0.6 ± 1.5%/yr, $P < 0.006$). HBP patients demonstrated an addition of 19 ± 3 cysts/yr as compared with 11 ± 3 cysts/yr in the borderline hypertensive group ($P = 0.07$).

Discussion

There are 4 to 5 million individuals with ADPKD worldwide, and currently no definitive treatment is available to slow or prevent the renal cystic disease that ultimately leads to renal dysfunction and ESRD in most patients. The earlier term for ADPKD was "adult-onset" polycystic kidney disease. However, studies have shown that clinically relevant renal and cardiac changes actually occur in a large percentage of children with ADPKD (5,24,25). ADPKD children with larger kidneys have more age-adjusted hypertension and larger left ventricular mass indices (11,12,17,26). In this regard, cardiovascular complications actually exceed renal complications as a cause of death in ADPKD (27).

The most recent evidence demonstrates that renal ultrasonography in children with a positive family history can establish the diagnosis of ADPKD by 15 years of age in >90% of patients if bilateral cysts are identified (28). Therefore, ultrasonography is ade-

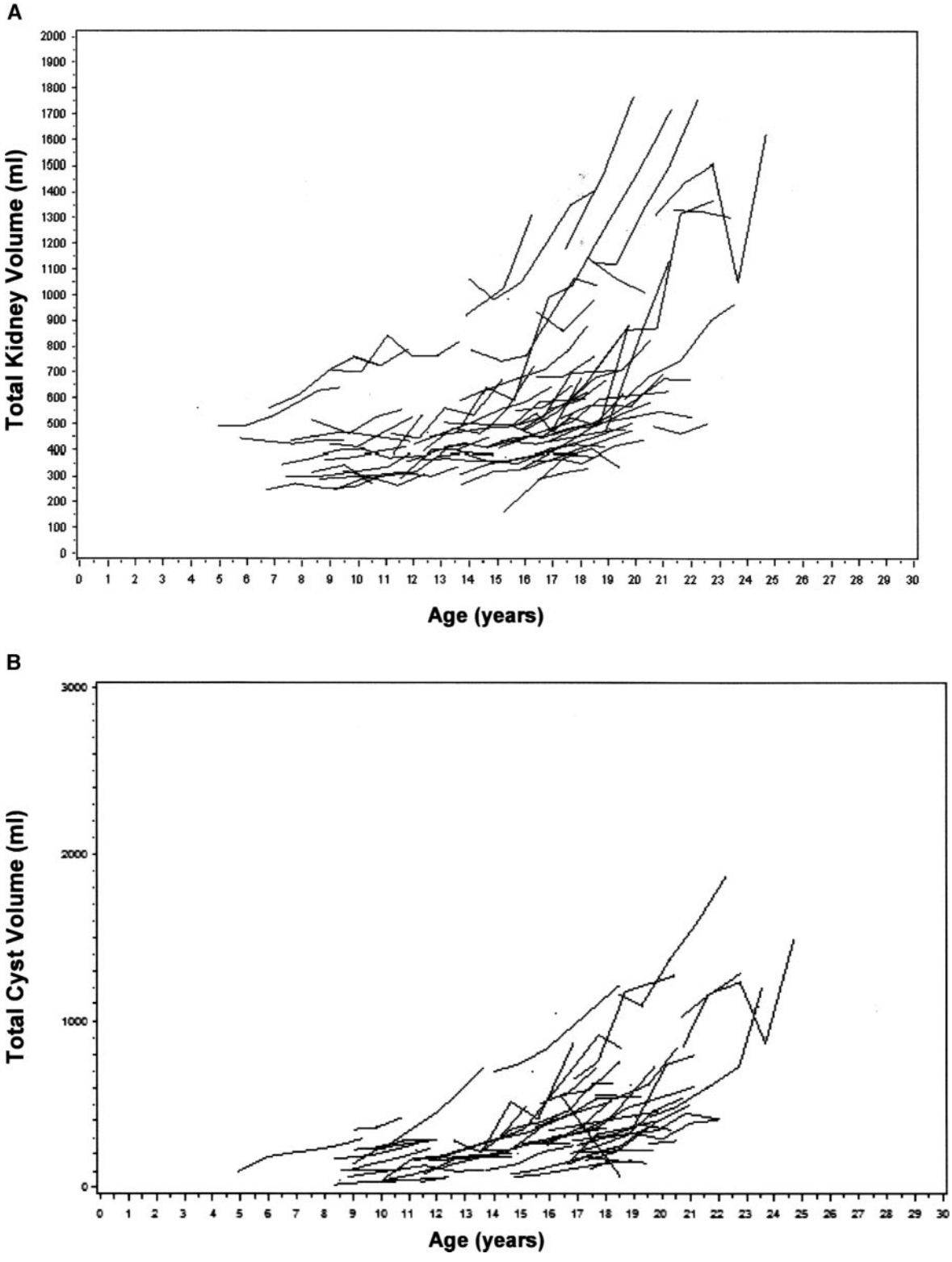

Figure 6. | When (A) TKV and (B) TCV were regressed against age, a curvilinear relationship was demonstrated, consistent with exponential growth.

quate for the clinical diagnosis of ADPKD in adults and children. However, recent studies in adults with ADPKD have shown that MRI is more sensitive than ultrasonography (9) and is therefore necessary for the performance of interventional randomized studies on the basis of demonstrating a slowing or prevention of increased TKV and TCV. However, there has been no prospective, large-scale study on the use of MRI to

assess kidney and cyst volume over time in ADPKD children.

Recent results suggest that the fastest growth of kidney and cyst volume may actually occur *in utero* rather than postnatally, and that most large cysts in adults with ADPKD may develop *in utero* (29,30). Therefore, the optimal time for intervention in ADPKD may be in childhood utilizing MRI to assess the effect of the intervention on renal volume (17).

The results presented here were obtained from 302 MRI studies in 77 ADPKD children at 418 annual study visits. The imaging studies analyzed the kidney and cyst volume as well as cyst number. The MRIs were performed in ADPKD children as young as 4 to 5 years of age, and no subject required sedation. There was a highly significant difference in TKV throughout the entire 5-year follow-up between NBP and HBP children; there was no significant difference between left and right kidneys. Because kidneys grow in normal children, it is important in ADPKD children to assess cyst volume. This is most feasible with MRI as compared with ultrasonography in children with ADPKD. In the study presented here, cyst volume increased over the 5-year follow-up period and was significantly greater in the ADPKD children with hypertension. This increase in cyst volume was a primary contributor to increased kidney volume over time and resulted in a larger fractional cyst volume over time in both study groups. Over the 5-year follow-up, there was an increased number of cysts detectable in both groups of patients, although the cyst numbers were significantly greater in the HBP ADPKD children. However, it is impossible to document whether these are new cysts or smaller cysts that were present *in utero* and with growth became detectable.

A subgroup analysis was undertaken to compare results between HBP and borderline hypertensive subjects because our previous studies have shown that the latter group may represent a prime target for intervention with angiotensin converting enzyme inhibition to prevent decreased GFR and increased left ventricular mass over time (12,17). Our results suggest that this subgroup of children is at less risk of progressive renal structural disease in childhood as compared with HBP ADPKD children. Efforts to prevent the development of hypertension in this group may be of value.

Thus, taken together the results presented here demonstrate that MRI is an acceptable means to follow kidney and cyst volume as well as cyst number in ADPKD children. Because of the embryonic occurrence of cysts, interventional trials are needed in ADPKD children, and MRI may be the preferred renal imaging approach.

Acknowledgments

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Disclosures

None.

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