ORIGINAL ARTICLE

Volume Progression in Polycystic Kidney Disease

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ABSTRACT

BACKGROUND

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive enlargement of cyst-filled kidneys.

METHODS

In a three-year study, we measured the rates of change in total kidney volume, total cyst volume, and iothalamate clearance in patients with ADPKD. Of a total of 241 patients, in 232 patients without azotemia who were 15 to 46 years old at baseline we used magnetic-resonance imaging to correlate the total kidney volume and total cyst volume with iothalamate clearance. Statistical methods included analysis of variance, Pearson correlation, and multivariate regression analysis.

RESULTS

Total kidney volume and total cyst volume increased exponentially, a result consistent with an expansion process dependent on growth. The mean (±SD) total kidney volume was 1060±642 ml at baseline and increased by a mean of 204±246 ml (5.27±3.92 percent per year, P<0.001) over a three-year period among 214 patients. Total cyst volume increased by 218±263 ml (P<0.001) during the same period among 210 patients. The baseline total kidney volume predicted the subsequent rate of increase in volume, independently of age. A baseline total kidney volume above 1500 ml in 51 patients was associated with a declining glomerular filtration rate (by 4.33±8.07 ml per minute per year, P<0.001). Total kidney volume increased more in 135 patients with *PKD1* mutations (by 245±268 ml) than in 28 patients with *PKD2* mutations (by 136±100 ml, P=0.03).

CONCLUSIONS

Kidney enlargement resulting from the expansion of cysts in patients with ADPKD is continuous and quantifiable and is associated with the decline of renal function. Higher rates of kidney enlargement are associated with a more rapid decrease in renal function.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common renal disorder involving a single gene and the fourth leading cause of end-stage renal disease in adults.[1,2] Renal cysts contribute to morbidity and can impair the quality of life early in the course of the disease. Pain and gross hematuria are reported in approximately 60 percent of patients.[3,4] ADPKD ultimately leads to the destruction of renal parenchyma in more than 50 percent of patients.[5-9]

Serum creatinine levels rise late in the course of the disease, only after the noncystic parenchyma has incurred serious, irreversible damage. The lack of a sensitive measure of disease progression in the early stages of ADPKD has hindered the development of therapeutic agents.

In the present study, we quantified renal enlargement, the hallmark of ADPKD, to determine the rate of disease progression as part of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). The goal of this study group is to make prospective, longitudinal measurements of cyst and kidney growth in a large cohort of patients with ADPKD.

METHODS

ORGANIZATION OF THE STUDY

Detailed descriptions of the CRISP study protocol and the baseline characteristics of the cohort have been published previously.[10-13] We enrolled 241 patients with ADPKD who were 15 to 46 years of age and who were evaluated annually (for a total of four visits) over a period of three years between January 5, 2001, and August 26, 2005. Eligible patients had received a diagnosis of ADPKD,[14] had an actual or estimated (by the Cockcroft–Gault equation) creatinine clearance of at least 70 ml per minute, and had a serum creatinine level of 1.6 mg per deciliter (141 μmol per liter) or less in the case of male patients and 1.4 mg per deciliter (124 μmol per liter) or less in the case of female patients. Patients were ineligible if they had other medical conditions besides hypertension that could affect renal function (e.g., diabetes mellitus).[10]

Clinical centers included the University of Alabama at Birmingham, Emory University in Atlanta, the Kansas University Medical Center in Kansas City, and the Mayo Clinic College of Medicine in Rochester, Minnesota. Washington University in St. Louis served as the data-coordinating and image-analysis center; the statistical analysis was performed there.[15] The protocols were approved by the institutional review board at each center. All patients provided informed written consent.

All the authors contributed to the design and execution of the study. Ms. Zhang and Mr. Miller analyzed the data. Dr. Grantham wrote the manuscript. All authors read and approved the manuscript.

Histories were taken and physical examinations were performed at the time of enrollment of the patients. Creatinine clearance was estimated by the Cockcroft–Gault equation. The glomerular filtration rate was determined at each visit from iothalamate clearance (coefficient of variance, 4.9 percent).[10,16]

DNA samples from the patients were screened for mutations in the two ADPKD genes (*PKD1* and *PKD2*) by denaturing high-performance liquid chromatography.[17] Mutation-negative samples and control samples were also analyzed by direct sequencing according to a commercial clinical protocol (Athena Diagnostics).

IMAGING

Magnetic resonance imaging was used to determine total kidney volume and total cyst volume.[12] Coronal T_2-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 T_1-weighted images were obtained (slice thickness, 3 mm). The volumes of individual kidneys were measured in T_1-weighted images with use of a stereologic method[10,12] and calculated from the set of contiguous images by summing the products of the area measurements and slice thickness. A region-based threshold method was used to calculate cyst volumes.

The reliability coefficients were 0.998 for total kidney volume and 0.961 for total cyst volume in serially acquired images from individual patients. The average coefficients of variation of the measurements of total kidney volume and total cyst volume in the repeated analysis of 99 images were 0.01 percent and 0.26 percent, respectively.

STATISTICAL ANALYSIS

The kidney and cyst volumes of individual kidneys were measured in milliliters, and the values from

both kidneys were combined to yield the total kidney volume and the total cyst volume. The annual percent change in kidney volume and cyst volume for each kidney or for both kidneys combined was determined by regressing log-transformed (on a base-10 scale) kidney and cyst volumes against time (baseline to year 3) for each patient. Paired changes within patients were also determined as the differences between the baseline value and the value obtained at year 3 divided by the actual interval. Multivariate linear regression analysis was used to validate the relationships between total kidney volume and the age of the patients at baseline and the changes in total kidney volume and the glomerular filtration rate.

The percent change in renal function was determined by regressing log-transformed glomerular filtration rates against time. Paired changes in the glomerular filtration rate, serum creatinine level, the reciprocal of serum creatinine, and blood urea nitrogen between baseline and year 3 were also measured. To determine whether kidney enlargement led to decreasing renal function, the cohort was stratified into three groups according to total kidney volume: less than 750 ml, 750 to 1500 ml, or more than 1500 ml. To assess the effect of age, each group was divided further according to age (less than 30 years or 30 years or older).

Genotype data were available for 185 patients, and the renal volumes of those with *PKD1* mutations and those with *PKD2* mutations were compared.

Data are presented as means ±SD. Statistical methods included analysis of variance, Pearson correlation, multivariate linear regression analysis, the two-tailed Student's t-test, and the paired t-test. All P values were two-sided.

RESULTS

The mean age of the cohort at baseline was 32.4±8.9 years, 60.0 percent were female, and 61.4 percent had hypertension. Among the patients, 43.5 percent were receiving an angiotensin-converting–enzyme (ACE) inhibitor and 21.1 percent an angiotensin-receptor blocker. The use of ACE inhibitors was more common among the patients with the largest kidneys. At baseline, the mean rate of iothalamate clearance, measured in 236 patients, was 107±28 ml per minute; after adjustment, the rate was 98±25 ml per minute per 1.73 m^2 of body-surface area.

At baseline, the mean total kidney volume was 1076±670 ml and the total cyst volume was 534±529 ml among the 241 patients, as compared with a mean volume of 196 ml in single normal kidneys (range, 136 to 295 ml).[18] The mean dif-

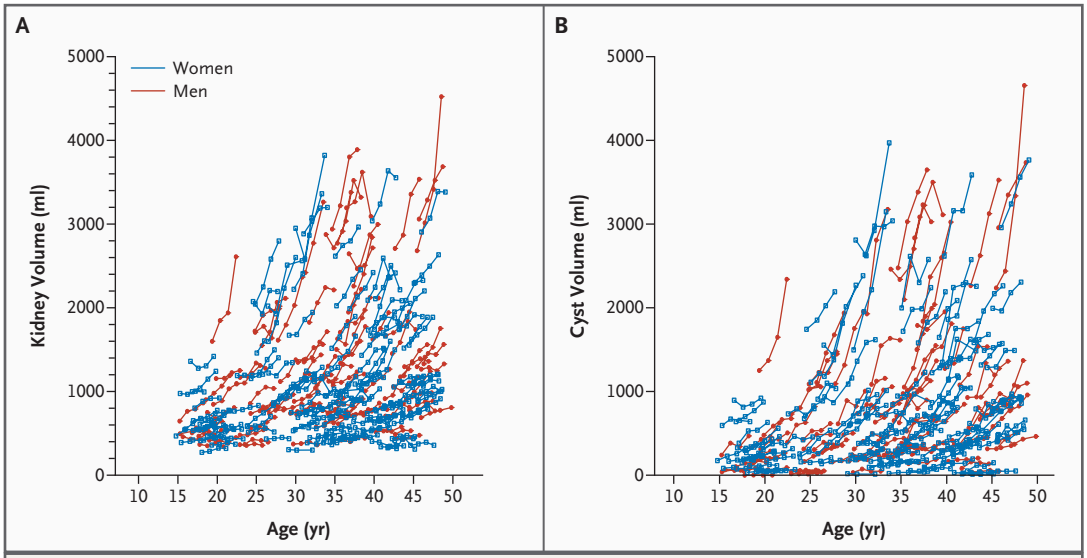

Figure 1. Total Kidney Volume (Panel A) and Total Cyst Volume (Panel B) in Relation to Age in Women (Blue) and Men (Red).

The lines connecting the four measurements for each patient in the three years of follow-up exhibit a concave upward sweep suggestive of an exponential growth process.

ference between total kidney volume and total cyst volume was 540±180 ml. In most patients, polycystic kidneys and cysts increased in volume from year to year (Fig. 1A and 1B). The total kidney volume increased during the three-year period by an average of 204±246 ml (P<0.001 for the comparison with baseline) in 214 patients, and total cyst volume increased by an average of 218±263 ml (P<0.001) in 210 patients. The rates of kidney and cyst enlargement varied widely within the group. The concave upward sweep of the data in Figure 1 resembled a growth curve, and the data after log-transformation were consistent with the occurrence of an exponential growth process (Fig. 2). Sufficient information was available from 232 of the 241 patients in the study to determine the slopes of the increase in total kidney volume from baseline to year 3. The mean slope of the increase of total kidney volume from a mean intercept baseline of 1060±642 ml was 63.4±69.8 ml per year — this increase of 5.27±3.92 percent per year was significantly different from zero (P<0.001).

There was a direct correlation (r=0.95, P<0.001) between the change in total kidney volume and the change in total cyst volume (Fig. 3A). The change in volume in the left kidney correlated directly with the change in volume in the right kidney (r=0.67, P<0.001) (Fig. 3B), as did the respective changes in cyst volumes (data not shown). We plotted the baseline intercepts and slopes of log total kidney volume against age in the left and right kidneys. The mean intercept was greater for the left than for the right kidney (560 vs. 500 ml, P<0.001); however, the annual rate of increase in total kidney volume did not differ significantly between the left and right kidneys (5.1±4.5 percent per year and 5.4±4.4 percent per year, respectively; P=0.27).

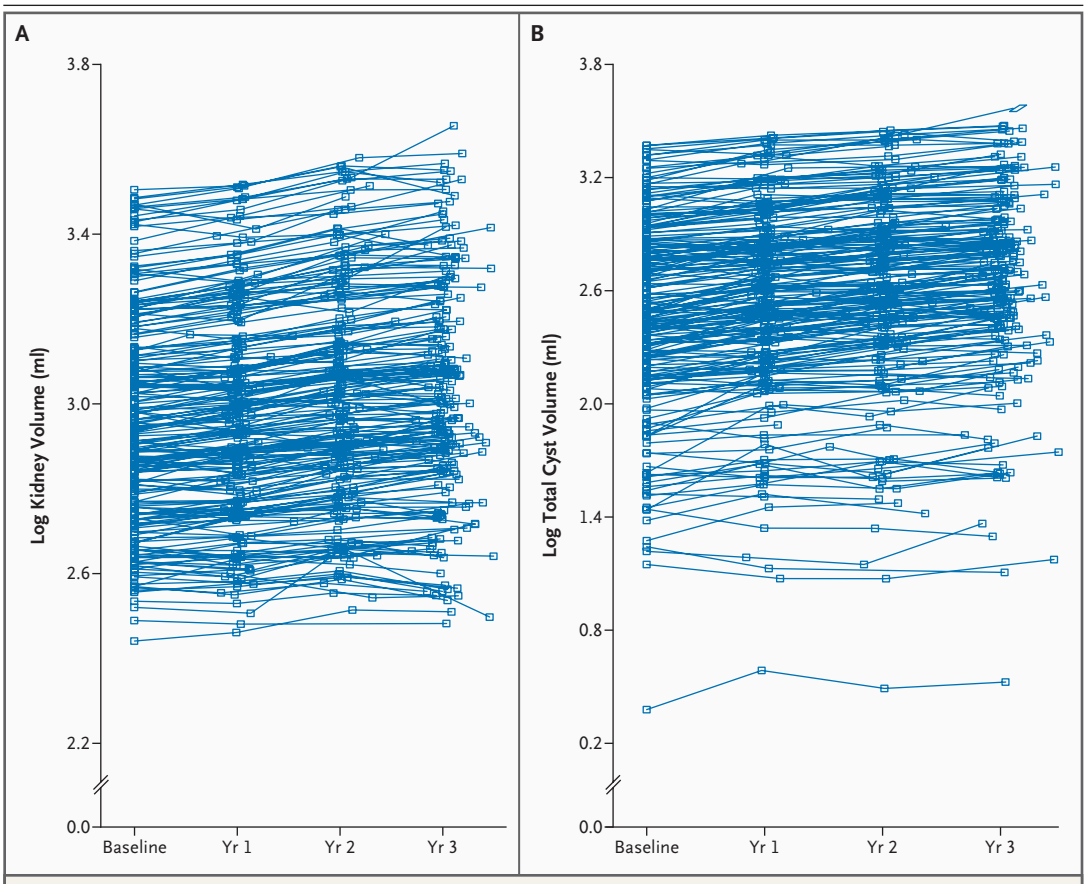

Figure 2. Log-Transformed Total Kidney Volume (Panel A) and Total Cyst Volume (Panel B) in Relation to Time.
The linear relationship of the four measurements for each patient during the three years of follow-up is suggestive of an exponential growth process. A base-10 log scale was used.

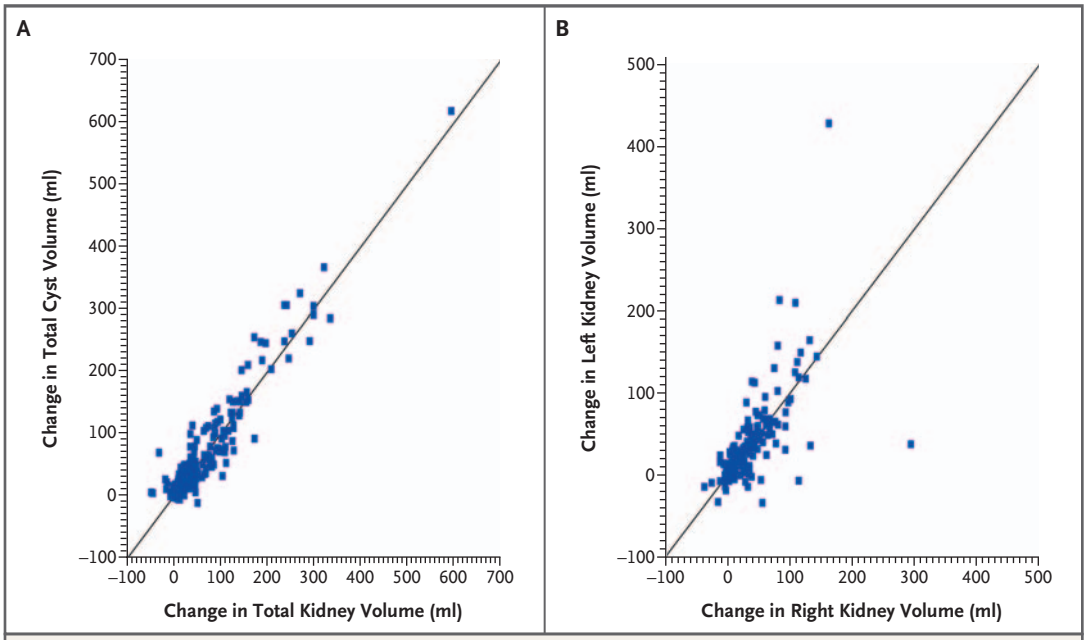

Figure 3. Relation between Changes in Total Kidney Volume and Total Cyst Volume (Panel A) and between Changes in Left and Right Kidney Volumes (Panel B) in Individual Patients over Three Years.

Lines of identity are shown. Changes in total kidney volume and total cyst volume are directly correlated, as are changes in left and right kidney volumes.

The slope of the change in the glomerular filtration rate from baseline to year 3 was determined in 234 patients. The correlation coefficient (−0.186) for the overall plot of the slope of the change in total kidney volume (milliliters per year) as compared with the slope of the change in the glomerular filtration rate (milliliters per year) in 232 patients was significant (P=0.005). To determine whether kidney enlargement was uniformly associated with decreasing renal function, we stratified the cohort into three groups according to baseline total kidney volume (Table 1). Analysis of variance was used to assess the independent effects on the glomerular filtration rate of the total kidney volume and age and their interaction. The mean baseline intercepts for total kidney volume determined by regression analysis differed from the measured baseline values by less than 1.5 percentage points. The mean slopes of individual measurements of total kidney volume over the three-year period are shown as absolute values (in milliliters per year, as determined from differences in the measurements of total kidney volume between baseline and year 3) or as percent changes from the intercept (in percent per year, as determined from the regression of log total kidney volume against time since baseline).

Among the subgroups defined according to the initial total kidney volume, the differences between the slopes of total kidney volume (expressed as milliliters per year or percent per year) were significant (P<0.001). Among the age subgroups, the slopes expressed as percent per year were significantly lower in the older age group (P=0.02). There was no significant interaction between total kidney volume and age, even for the slope of percent of total kidney volume, where age was significant. The slopes of total kidney volume were different among the subgroups of total kidney volume within each age group. Overall, the slopes of total kidney volume differed between the subgroup with initial total kidney volumes of 750 to 1500 ml and the subgroup with initial total kidney volumes greater than 1500 ml (P<0.001) and between the subgroup with initial total kidney volumes under 750 ml and the subgroup with initial total kidney volumes above 1500 ml (P<0.001).

The slopes of the glomerular filtration rate were not significantly different from zero in the subgroup of 86 patients with initial total kidney volumes under 750 ml (1.39±6.61 ml per minute per year, P=0.063) and the subgroup of 84 patients with initial total kidney volumes of 750 to 1500 ml

Table 1. Relationship between Total Kidney Volume and Glomerular Filtration Rate.

Variable	Total Kidney Volume			Glomerular Filtration Rate	
	Baseline Intercept	Slope	Slope	Baseline	Slope
	ml	*ml/yr*	*%/yr*	*ml/min*	*ml/min/yr*
Total kidney volume and age — mean ±SD (no. of patients)					
<750 ml and <30 yr	506±109 (45)	25.9±22.0 (45)	4.70±3.80 (45)	114±24.7 (47)	2.88±12.1 (46)
<750 ml and ≥30 yr	572±130 (48)	23.0±22.2 (48)	3.70±3.42 (48)	108±24.2 (49)	1.03±7.06 (48)
750–1500 ml and <30 yr	978±193 (28)	53.4±36.1 (28)	5.33±3.15 (28)	122±30.8 (28)	−0.38±7.66 (28)
750–1500 ml and ≥30 yr	1052±191 (61)	55.4±44.0 (61)	5.16±3.88 (61)	101±26.8 (61)	−1.62±10.9 (61)
>1500 ml and <30 yr	1859±333 (12)	173±81.3 (12)	9.48±4.61 (12)	99.6±23.8 (13)	−2.69±10.2 (12)
>1500 ml and ≥30 yr	2155±543 (38)	144±92.2 (38)	6.76±3.78 (38)	94.0±29.2 (38)	−5.04±5.86 (39)
P values for analysis-of-variance factors					
Total-kidney-volume group		<0.001	<0.001	0.009	0.005
Age group		0.20	0.02	0.005	0.20
Interaction		0.30	0.24	0.15	0.95

(−0.69±9.47 ml per minute per year, P=0.57). On the other hand, the slope decreased significantly in the subgroup of 51 patients with initial total kidney volumes greater than 1500 ml (by 4.33±8.07 ml per minute per year, P<0.001). Analysis of variance revealed that the slopes of glomerular filtration rate differed among subgroups with different initial total kidney volumes (P=0.005), whereas the slopes of glomerular filtration rate did not differ significantly among subgroups with different initial ages (P=0.20); there was no significant interaction between total kidney volume and age (P=0.95). Thus, the relationship between the increase in total kidney volume and the decrease in glomerular filtration rate does not appear to be confounded by age. Similar analysis showed that for the subgroup of patients with data on total kidney volume, there were significant differences between the mean slopes of the serum creatinine level (0.028±0.066 mg per deciliter per year [2.5 μmol per liter per year], P<0.001), measured in 215 patients; the reciprocal of the serum creatinine level (−0.020±0.060 dl per milligram per year [1.75 liters per micromole per year], P=0.04), measured in 215 patients; and blood urea nitrogen level (0.161±1.424 mg per deciliter per year [0.057 μmol per liter per year], P=0.001), measured in 233 patients. Corresponding multivariate models that used continuous measures of age and total kidney volume produced similar results.

Mutations were identified in 185 patients: 83 percent were *PKD1* mutations, and 17 percent were *PKD2* mutations. Patients with *PKD2* mutations tended to be in the lowest third of total kidney volume, irrespective of age (Fig. 4). The mean baseline total kidney volume among 32 patients with *PKD2* mutations (711±298 ml) was less than that among the 153 patients with *PKD1* mutations (1197±683 ml, P=0.001). Total kidney volume increased significantly from baseline to year 3 in 28 patients with *PKD2* mutations (by 136±100 ml); however, the increase was greater among 135 patients with *PKD1* mutations (245±268 ml, P=0.03). The difference in the change in iothalamate clearance over the three-year period between 135 patients in the *PKD1* group (a decrease of 2.4±27.6 ml per minute) and 30 patients in the *PKD2* group (an increase of 8.2±27.0 ml per minute) did not reach statistical significance (P=0.06). Among 139 patients with *PKD1* mutations, serum creatinine levels increased (by 0.12±0.22 mg per deciliter [10.6 μmol per liter], P<0.001) and the reciprocal of the serum creatinine level decreased (by 0.09±0.18 dl per milligram [7.9 liters per micromole], P<0.001), but no significant changes were observed in the *PKD2* group. The following values were obtained from 31 patients with *PKD2* mutations: an increase in the serum creatinine level by 0.01±0.14 mg per deciliter (0.88 μmol per liter) (P=0.70) and a decrease in the reciprocal of the serum creatinine level by 0.001±0.15 dl per milligram (0.088 liter per micromole) (P=0.89).

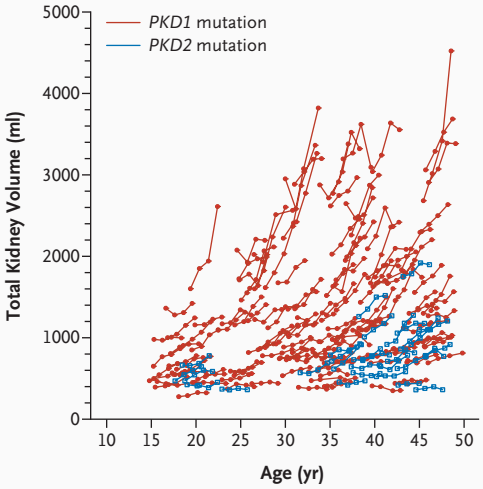

Figure 4. Total Kidney Volume in Relation to Age in the 185 Patients with Identified *PKD1* (Red) or *PKD2* (Blue) Mutations.

The kidneys of patients with *PKD1* mutations were generally larger at baseline and expanded at faster rates than those of patients with *PKD2* mutations.

DISCUSSION

Our findings provide a glimpse into the wide variation in the rates of renal-volume evolution in patients with ADPKD. It is clear that in patients with mature polycystic kidneys, the increase in renal volume is due to the increase in cyst volume. Our findings also establish that renal-cyst and kidney enlargement is a continuous process in most patients with ADPKD. Unexpectedly, we found that the kidneys behaved as though the cysts within them enlarged at a steady rate specific to the patient. Just as surprisingly, in most patients, both kidneys grew at a similar rate. Thus, it would appear that most pairs of polycystic kidneys behave as if the cysts within them were programmed to grow at a uniform rate, although exceptions exist in which local or regional factors may stimulate some cysts to grow at a faster rate than others.[19]

Cross-sectional studies have demonstrated considerable heterogeneity in the size of cysts within and between kidneys, a finding that we confirmed.[20,21] Despite this heterogeneity, overall renal growth, as reflected by the total kidney volume and total cyst volume, appeared to be coordinated within and between the kidneys of an individual patient. The absolute (in milliliters per year) and fractional (in percent per year) rates of renal enlargement are directly associated with absolute renal volume. Further study will be needed to determine whether small kidneys enlarge at a slower rate than large kidneys because they contain fewer cysts or because the individual cysts within them grow at a slower "signature" rate.

Since kidney growth is a continuous and relatively constant process, patients with the largest kidneys at a given age should have the fastest rates of renal enlargement. This supposition has practical value in judging the prognosis in individual patients. Since larger kidneys appear to be associated with hypertension, pain, hematuria, and renal hemorrhage, young patients with elevated total kidney volumes may have a more difficult course than patients of the same age with smaller kidneys.[9]

Previous studies that used ultrasonography or computed tomography to determine total kidney volumes have suggested that the cysts are a major factor contributing to renal insufficiency in ADPKD.[20-23] The CRISP study was designed to include patients with normal function who were at high risk for renal insufficiency in order to demonstrate a clear-cut reduction in the glomerular filtration rate at some point during the study. Indeed, we found a strong relationship between kidney volume at the beginning of the study and the subsequent change in the glomerular filtration rate. This information, when analyzed together with data from several longitudinal and cross-sectional studies, provides support for the view that enlarging cysts have an important role in promoting the ultimate decline in glomerular filtration rate.

It is well known that end-stage renal disease and hypertension develop earlier in patients with the *PKD1* genotype than in those with the *PKD2* genotype.[7,24-26] Over the age spectrum of patients in this study, we observed that the kidneys of patients with the *PKD1* genotype were larger at baseline and expanded at faster rates than the kidneys of patients with the *PKD2* genotype. Renal function remained within normal limits in patients with the *PKD2* genotype, whereas the serum creatinine level rose (while the reciprocal of the creatinine level declined) and the glomerular filtration rate tended to decline in patients with the *PKD1* genotype.

Therapeutic strategies have focused on patients with ADPKD who have established renal insufficiency, rather than on patients with the troubling complications that occur in the early stages of the

disease.[10] Currently, physicians and patients monitor changes in serum creatinine levels to determine the extent of progression and to assess prognosis. However, serum creatinine levels do not typically rise in patients with ADPKD until the fourth or fifth decade of life, when massive renal enlargement has occurred. Unfortunately, this often lulls patients with normal serum creatinine levels and their physicians into the false belief that little renal damage has been done despite the grotesque distortions of the parenchyma caused by the cysts.

Our study has implications for the design of clinical trials in ADPKD. Several potential therapeutic agents on the horizon are targeted to slow the early growth and expansion of cysts.[27-29] It may be futile to administer such agents late in the course of ADPKD, when a host of different processes have combined to produce the fibrotic end-stage kidney. Since renal enlargement due to cysts is the underlying disease process, it would seem more prudent to find an agent with efficacy early in the course of the disease. Our findings provide potential tools and a rationale for evaluating therapeutic agents in patients in the early stages of the disease.

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Dr. Grantham reports having served as a consultant for and receiving a grant in aid from Otsuka. (Otsuka is examining tolvaptan in clinical trials for the treatment of polycystic kidney disease but has no relationship with the CRISP study. Otsuka, or any other company performing clinical trials on patients with polycystic kidney disease, may benefit from the technology described in this article.) Dr. Chapman reports having received a research contract with Otsuka to study the effects of tolvaptan in patients with autosomal dominant polycystic kidney disease. Dr. Khlar reports having received research support from the Barnes–Jewish Hospital unrelated to the study. Dr. Harris reports holding a patent on the *PKD1* gene that generates minor revenues from licensing. Dr. Bennett reports having served as a consultant to Roche Laboratories and Astellas Pharma for research unrelated to polycystic kidney disease. Dr. Torres reports having received a grant from Otsuka. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The members of the CRISP study were as follows: Steering Committee — J.J. Grantham, V.E. Torres, A.B. Chapman, L.M. Guay-Woodford, K.T. Bae, B.F. King, L.H. Wetzel, P.J. Kenney, J.P. Miller, G.N. Hirschman, C.M. Meyers, W.M. Bennett (chair); Writing Committee — J.J. Grantham, V.E. Torres, A.B. Chapman, L.M. Guay-Woodford, K.T. Bae, P.C. Harris, C.M. Meyers, J.P. Miller, W.M. Bennett, S. Klahr, D.A. Baumgarten, P.J. Kenney, X. Zhang, and F. Zhu; Data Collection and Analysis — J.J. Grantham, V.E. Torres, A.B. Chapman, L.M. Guay-Woodford; Radiologic Analysis — K.T. Bae, B.F. King, L.H. Wetzel, P.J. Kenney, D.A. Baumgarten; Biostatistics — J.P. Miller, X. Zhang; Design and Supervision, Design, and Analysis of MRI Protocol — K.T. Bae, F. Zhu.

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