Article

Kidney Volume and Functional Outcomes in Autosomal Dominant Polycystic Kidney Disease

Arlene B. Chapman,* James E. Bost,[†] Vicente E. Torres,[‡] Lisa Guay-Woodford,[§] Kyongtae Ty Bae,[†] Douglas Landsittel,[†] Jie Li,[†] Bernard F. King,[‡] Diego Martin,* Louis H. Wetzel,[‖] Mark E. Lockhart,[§] Peter C. Harris,[‡] Marva Moxey-Mims,[¶] Mike Flessner,[¶] William M. Bennett,** and Jared J. Grantham[‖]

Summary

Background and objectives Autosomal dominant polycystic kidney disease (ADPKD) is characterized by increased total kidney volume (TKV) and renal failure. This study aimed to determine if height-adjusted TKV (htTKV) predicts the onset of renal insufficiency.

Design, setting, participants, & measurements This prospective, observational, longitudinal, multicenter study included 241 adults with ADPKD and preserved renal function. Magnetic resonance imaging and iothalamate clearance were used to measure htTKV and GFR, respectively. The association between baseline htTKV and the attainment of stage 3 CKD (GFR $<$60 ml/min per 1.73 m^2) during follow-up was determined.

Results After a mean follow-up of 7.9 years, stage 3 CKD was attained in 30.7% of the enrollees. Using baseline htTKV, negative correlations with GFR increased from -0.22 at baseline to -0.65 at year 8. In multivariable analysis, a baseline htTKV increase of 100 cc/m significantly predicted the development of CKD within 8 years with an odds ratio of 1.48 (95% confidence interval: 1.29, 1.70). In receiver operator characteristic curve analysis, baseline htTKV of 600 cc/m most accurately defined the risk of developing stage 3 CKD within 8 years with an area under the curve of 0.84 (95% confidence interval: 0.79, 0.90). htTKV was a better predictor than baseline age, serum creatinine, BUN, urinary albumin, or monocyte chemotactic protein-1 excretion ($P<0.05$).

Conclusions Baseline htTKV $\geq$600 cc/m predicted the risk of developing renal insufficiency in ADPKD patients at high risk for renal disease progression within 8 years of follow-up, qualifying htTKV as a prognostic biomarker in ADPKD.

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*Emory University School of Medicine, Atlanta, Georgia; [†]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [‡]Mayo College of Medicine, Rochester, Minnesota; [§]University of Alabama, Birmingham, Alabama; [‖]Kansas University Medical Center, Kansas City, Kansas; [¶]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; and **Legacy Good Samaritan Hospital, Portland, Oregon

Correspondence: Dr. Arlene B. Chapman, Emory University School of Medicine, 1364 Clifton Road, Suite GG23, Atlanta, GA 30322. Email: Arlene_chapman@emory.org

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder that leads to ESRD (1–3). It is characterized by the gradual expansion of renal cysts resulting in bilateral kidney enlargement measured as increased total kidney volume (TKV) (4). Although increased TKV usually precedes the development of renal insufficiency by >4 decades, the extent to which TKV predicts the onset of renal insufficiency within a specified period of time has not been established.

TKV associates with the development of ESRD and significantly affects patients' quality of life (5–8). Women have smaller kidneys and develop ESRD later than men (9–11) and the two major genotypes, *PKD1* and *PKD2*, are also differentially associated with disease severity. PKD1 patients have larger kidneys with more cysts and develop ESRD approximately 20 years earlier than PKD2 patients (12–15). These findings suggest that TKV forecasts the later development of renal insufficiency. However, prospectively defined renal insufficiency endpoints have not been examined rigorously in relation to antecedent measurements of TKV.

Imaging methods that reliably and accurately measure TKV in ADPKD patients have been developed utilizing magnetic resonance imaging (MRI) and computerized tomography (4,5,16–22). The Consortium for Radiologic Imaging Studies of PKD (CRISP) (ClinicalTrials.gov identifier NCT 01039987) has developed reliable and accurate MRI-based protocols to measure TKV in ADPKD patients that detect relatively small changes in TKV over a short period of time (19,20). The association between baseline TKV and baseline iothalamate clearance (GFR) was modestly significant in 241 participants ($r=-0.39$, $P<0.001$), However, only 29 participants reached stage 3 CKD (GFR of 60 ml/min per 1.73 m^2), and only those with the largest kidneys (>1500 cc) demonstrated a significant decline in GFR (-4.33 ml/min per yr) in the first 3 years of follow-up (4). Results from three recent prospective clinical trials of relatively short duration have not demonstrated an association between changes in TKV and GFR (23–25), questioning the value of TKV as a disease marker in ADPKD (26). We present the results of 8 years of follow-up in study participants to determine the

extent to which baseline TKV predicts the future development of renal insufficiency.

Materials and Methods

Participants were studied between 2001 and 2010. The initial study enrolled 241 participants (96 men, 145 women; mean age 32.4 years) with a creatinine clearance >70 ml/min. All participants were provided current dietary guidelines regarding sodium and potassium restriction for patients with hypertension and underlying renal disease. Sixty-seven percent of participants were hypertensive at baseline. Enrolled participants were followed between 2001 and 2005 (CRISP I) with yearly visits including TKV and GFR measurements by MRI and iothalamate clearance (4,19). Telephone evaluations were completed every 3 months. Two years after completion of the initial study, 201 participants (80 men, 121 women; mean age 39.2 years) were re-enrolled into a 5-year follow-up study (CRISP II). Re-enrollees were interviewed by telephone every 6 months and were evaluated in standardized fashion during clinic visits every 12 months. TKV and GFR were measured every 2 years in identical fashion to the initial study.

At each visit, medical history, adverse events, physician visits, medication changes, and hospitalizations were recorded. Blood and urine samples were obtained for determination of serum creatinine, electrolytes, PKD genotype, urinary albumin (27), monocyte chemotactic protein-1 (MCP-1) excretion (28), and iothalamate clearance. Serum creatinine values were validated by the Cleveland Clinic. Ten patients were found to have stage 3 CKD at baseline utilizing iothalamate GFR and were excluded from the predictive studies.

Renal insufficiency defined as stage 3 CKD or an GFR <60 ml/min per 1.73 m^2 is the primary endpoint of interest in this study. We also evaluated stage 4 CKD or an GFR of <30 ml/min per 1.73 m^2, as well as relative decreases of >20% and >40% from the individual patient's baseline GFR. Both iothalamate clearance (GFR) and serum creatinine (eGFR) using the Modification of Diet in Renal Disease equation (29) were used for these evaluations.

TKV was referenced to height (htTKV, cc/m) and GFR was referenced to body surface area adjusted to a fixed norm (milliliters per minute per 1.73 m^2; see Results for details). Means and SDs are provided to show the trend of change over time for both htTKV and GFR. Paired t tests were used to determine a significant change from baseline in those participants with complete data. Pearson correlation coefficients and their corresponding P values were calculated to assess the relationship between baseline htTKV and GFR measured at each visit. For htTKV, which followed a skewed distribution, summary statistics by group were also presented in terms of medians and interquartile ranges (displayed as the median [IQR]).

To compare the changes in htTKV and GFR from baseline on the same scale and at the same time points, we normalized the data by subtracting the baseline mean value from individual values and then dividing the residual value by the baseline SD. Baseline htTKV and GFR were assigned a mean value of 0 and a SD of 1, and the graphic display of the relative change from baseline was provided to indicate the degree to which their time courses differed.

To determine if baseline htTKV predicted the development of renal insufficiency within the follow-up period, multivariable logistic regression was used to examine the primary endpoint, stage 3 CKD using iothalamate GFR <60 ml/min per 1.73 m^2. Other endpoints used to assess the association of baseline htTKV and renal function were stage 3 CKD estimated from serum creatinine concentration (eGFR), GFR changes (>20% and >40%) relative to baseline iothalamate clearance, and stage 4 CKD using GFR and eGFR measures. The multivariable model controlled for the following: baseline age, body mass index (BMI), sex, ethnicity, genotype, and baseline corrected iothalamate clearance as covariates. Genotype was determined in 221 individuals but was not a significant variable in the model and thus was excluded from the final model to preserve sample size. Adjusted odds ratios (ORs) and their 95% confidence intervals (95% CIs) are presented.

Receiver operator characteristic (ROC) curves were built to determine the area under the curve (AUC) and optimal cut points for baseline htTKV to predict the development of stage 3 CKD. Statistical comparisons of two AUCs were done for baseline htTKV and other potential predictors, including baseline serum creatinine, BUN, urine albumin excretion, urine MCP-1, and age.

Analyses were conducted using SAS version 9.2 and Stata version 11.0 software.

Results

The studies comprised 241 original enrollees and 201 re-enrollees. After 7.9±0.6 years of follow-up (year 8), 194 participants remained in the study. Of the remaining patients, 2 died, 9 reached ESRD, 13 were lost to follow-up, and 23 did not re-enroll.

To accurately correlate TKV and severity of cystic disease, we sought to correct for other factors influencing TKV, such as sex and body size. At the baseline initial study visit, adult men (n=96) had greater mean TKV than adult women (n=145), with a ratio of 1.15 (1161±732 cc versus 1014±609 cc, respectively; median [IQR], 911 [786]; P=0.11). Referencing initial study TKV to baseline height, weight, body surface area, or BMI diminished the sex differences (Supplemental Table 1). From this analysis, height was the best reference for TKV (htTKV), with a male/female ratio of 1.037, and was used thereafter in this study. For GFR, we chose body surface area as the reference because this is the conventional notation in nephrology and values for height and body surface area made a similar degree of adjustment (1.036 and 0.965, respectively).

Baseline htTKV for the total cohort was similar to the values for the 201 re-enrollees (620±373 cc/m and 504 [407] versus 623±363 cc/m and 507 [420], respectively), as was the overall annual rate of increase in htTKV (5.3%±4.0%/yr versus 5.5%±3.8%/yr). The exponential relationship between TKV and age observed after 3 years (4,30) was also seen throughout the extended period of follow-up with htTKV (data not shown).

The development of renal dysfunction in this cohort increased steadily with age (Figure 1). Reductions in GFR
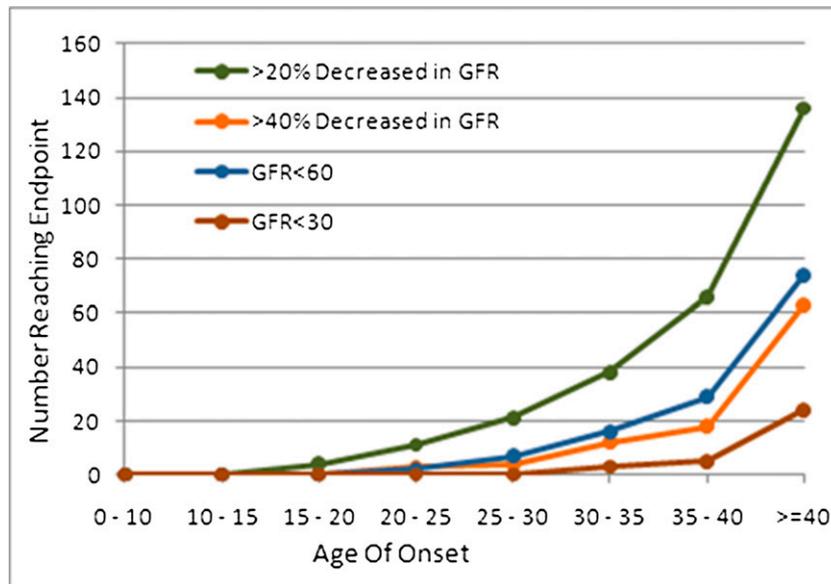
Figure 1. | Age-related development of renal insufficiency. Cumulative number of participants reaching specified renal insufficiency end points >20% or >40% decline in iothalamate GFR from baseline or a GFR <60 (stage 3 CKD) or <30 ml/min per 1.73 m^2 (stage 4 CKD).

>20% from baseline were first observed in the second decade, whereas stage 3 CKD or >40% reduction of GFR were first seen in the third decade. More severe reduction to stage 4 CKD initially appeared in the fourth decade. The majority of the participants (55.9%) entered the CRISP I study with a GFR >90 ml/min per 1.73 m^2, and 42.3% continued to maintain this level of renal function by year 8 (Table 1). The remaining patients had reached at least stage 2 CKD (57.7%), stage 3 CKD (30.7%), or stage 4 CKD (10.0%). The GFR decreased >20% from baseline in 56.4% and >40% in 26.4% at the end of follow-up. eGFR showed similar trends and distributed similarly to the iothalamate determinations of GFR, as did the numbers of patients in whom eGFR decreased >20% and >40% below baseline (Table 1). eGFR estimated from serum creatinine values distributed similarly to the iothalamate determinations of GFR, as did the numbers of patients in whom eGFR decreased >20% and >40% below baseline (Table 1). Mean htTKV when patients reached stage 3 CKD was 1211±650 cc/m and 1311±571 cc/m for women and men, respectively. Only 3 (8.6%) PKD2 participants, compared with 67 (36%) PKD1 participants, developed stage 3 CKD.

Changes in htTKV and GFR were assessed in those who had studies completed at every visit (n=93; Figure 2). HtTKV increased significantly from baseline each year, reaching a mean increase of 55% after 7.9 years of follow-up. In contrast, GFR declined significantly from baseline much later, beginning in year 6 (−10.6%) and continuing in year 8 (−22.3%). Similar changes in htTKV and GFR were seen over time when data from the entire cohort, including those with incomplete data, were analyzed (Supplemental Figure 1).

Given the different time course for change in htTKV and GFR, it seems unlikely that a significant association between htTKV and GFR would be found by linear correlation of differences extending from baseline. On the other hand, if htTKV and GFR are causally but inconstantly associated, there may be a limiting value of htTKV that must be breached to reveal the dependency of GFR on TKV. To test this hypothesis, we correlated baseline htTKV with each iothalamate GFR measured at six visits over 7.9 years in 114 participants in whom both measurements were completed (Figure 3). There was a significant negative correlation between baseline htTKV and GFR at each subsequent visit that increased from baseline (r=−0.22, P=0.02) to year 8 (r=−0.65, P<0.001). Similar increases in the strength of the association between baseline htTKV and GFR were found when data from the entire cohort, including those with incomplete data, were analyzed (Supplemental Figure 2).

Multivariable analyses of the independent contribution of baseline htTKV (in 100-cc/m increments) to a decline in GFR to stage 3 CKD or to a >20% or >40% decline in GFR showed significant ORs of 1.48, 1.39, and 1.47, respectively (Table 2). For each 100-cc/m change in htTKV, we estimate a 48% increase (which is multiplicative for each 100-unit change) in odds of progression to stage 3 CKD. Similar ORs and levels of significance were seen with eGFR determinations. Using estimated htTKV at age 18 years (30) also showed a similar capacity to predict renal insufficiency from this earlier age (Table 2). Supplemental Table 3 provides the coefficients of the multivariable logistic models that generated the ORs for baseline htTKV or htTKV at age 18 years.

We used ROC curves and AUCs to determine the likelihood that baseline htTKV and other variables (serum creatinine, BUN, urine albumin excretion, urine MCP-1 excretion, and age) would predict the development stage 3 CKD based on iothalamate GFR (Figure 4 and Table 3). HtTKV had an AUC (0.84; 95% CI: 0.79, 0.90) that was significantly greater than any of the other variables

($P<0.05$). The optimum combined sensitivity (74.0%) and specificity (75.0%) for htTKV was observed at a baseline value of 600 cc/m, in which 75% of patients were correctly classified. The percentages correctly classified at this cut point were 73% for female participants and 77% for male participants, indicating little differences in predictive power by sex. Cut points were also selected that gave optimum values for sensitivity and specificity for the compared variables (Table 3). These findings indicate that in the CRISP cohort, a htTKV value of 600 cc/m forecasts stage 3 CKD within 8 years.

Discussion

The primary goal of CRISP is to determine the extent to which TKV forecasts the development of renal insufficiency in ADPKD. This study provides strong evidence to indicate that baseline htTKV predicts, with good sensitivity and specificity, the development of renal insufficiency within 8 years. Multivariable analysis further indicated that for each 100-cc increment of htTKV at baseline, the odds of reaching a stage 3 CKD endpoint within 7.9 years increase 1.48-fold. Operationally, if these findings are substantiated in a validation study, it means that a single determination of htTKV in an adult patient could be used to determine the likelihood of developing significant renal insufficiency.

We previously showed that kidney enlargement in ADPKD is continuous, proceeding at a uniform rate unique for each patient, thus making it possible to estimate TKV in the CRISP study at almost any adult age (4,30). We found by multivariable analysis that htTKV values estimated at age 18 years also predicted the odds of developing stage 3 CKD. Although it seems encouraging that htTKV determined over a substantial span of adulthood will be a useful measurement to predict the future onset of renal insufficiency in ADPKD, confirmatory studies initiated in children are needed.

The htTKV-based prediction of stage 3 CKD was independent of variables known to associate with renal insufficiency in ADPKD, including genotype, sex, race, and age. As reported previously, patients with the PKD2 genotype have smaller kidneys and fewer cysts than those

Table 1.   Frequency of renal insufficiency at baseline and year 8

Renal Insufficiency Endpoint	Baseline (%)	Year 8 (%)
GFR (CKD stage)		
<30 stage 4	0 (0.0)	24 (10.0)
30–<60 stage 3	10 (4.2)	50 (20.7)
60–<90 stage 2	94 (39.8)	65 (27.0)
≥90 stage 1	132 (55.9)	102 (42.3)
GFR decreased >20%		136 (56.4)
GFR decreased >40%		63 (26.1)
eGFR (MDRD formula)		
<30	0 (0.0)	26 (10.8)
30–<60	24 (10.0)	61 (25.3)
60–<90	121 (50.2)	81 (33.6)
≥90	96 (39.8)	73 (30.3)
eGFR decreased >20%		132 (54.8)
eGFR decreased >40%		63 (26.1)

GFR measured in milliliters per minute per 1.73 m^2. eGFR, estimated GFR; MDRD, Modified Diet in Renal Disease formula.
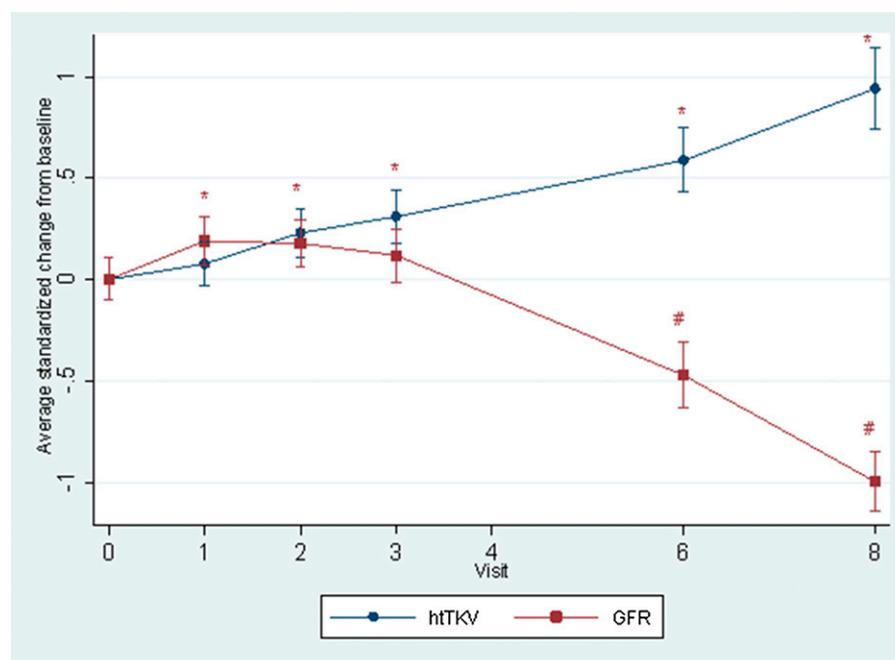

Figure 2. | Average standardized change in htTKV and iothalamate GFR. htTKV determined at baseline and iothalamate GFR at baseline and five subsequent visits until year 8 ($n=93$ with complete data). $P<0.01$ based on paired t test comparing each year to baseline for htTKV (*) and GFR (#). htTKV, height-adjusted total kidney volume.
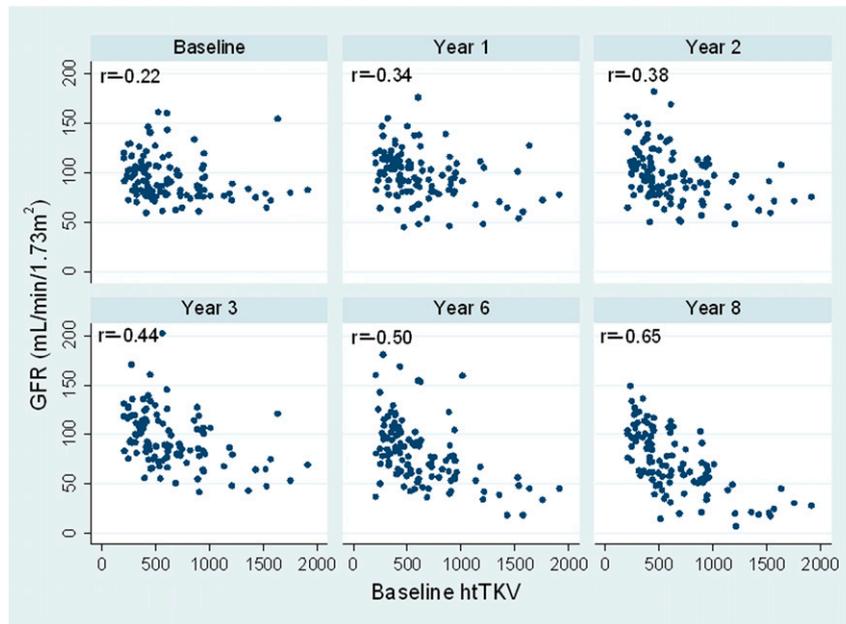
Figure 3. | **Correlations between baseline htTKV and GFR during follow-up**. Pearson correlation coefficients determined for baseline htTKV and iothalamate GFR at baseline and five subsequent visits (n=114 with complete data) to year 8. The degree of correlation at each time point is shown. htTKV, height-adjusted total kidney volume.

Table 2. Multivariable analyses to evaluate baseline htTKV and age 18 years htTKV prediction of CKD endpoints at final visit

Renal Insufficiency Endpoint	htTKV at Baseline			htTKV at Age 18 yr		
	OR	95% CI	P Value	OR	95% CI	P Value
GFR (iothalamate clearance)						
stage 3 CKD	1.48	(1.29, 1.70)	<0.001	1.33	(1.12, 1.57)	0.001
ΔGFR >20%↓	1.39	(1.22, 1.59)	<0.001	1.23	(1.04, 1.44)	0.01
ΔGFR >40%↓	1.47	(1.29, 1.68)	<0.001	1.27	(1.10, 1.48)	0.002
eGFR (MDRD formula)						
stage 3 CKD	1.41	(1.23, 1.61)	<0.001	1.23	(1.04, 1.46)	0.01
ΔGFR >20%↓	1.24	(1.11, 1.39)	<0.001	1.23	(1.05, 1.44)	0.01
ΔGFR >40%↓	1.38	(1.22, 1.55)	<0.001	1.23	(1.06, 1.44)	0.01

GFR measured in milliliters per minute per 1.73 m². htTKV, height-adjusted total kidney volume; OR, odds ratio; 95% CI, 95% confidence interval; eGFR, estimated GFR; MDRD, Modified Diet in Renal Disease formula.

with PKD1 (12). The observation that few PKD2 participants (8.6% versus 36%) progressed to renal insufficiency in CRISP is not unexpected because previous epidemiologic studies reveal that they reach ESRD about 20 years later than patients with the PKD1 genotype (12–14,31,32). In addition, that PKD2 was not a significant and independent covariate with htTKV in predicting renal insufficiency in this study is consistent with renal volume being closely correlated with genotype (12). Taken together, these data support the view that TKV is a biomarker that forecasts the future development of renal insufficiency in individuals with ADPKD.

In ADPKD, the kidneys begin to enlarge in childhood but the GFR typically remains in the normal range for 3–5 decades before there is loss of kidney function. This makes it extremely difficult to establish mechanistic linkages between the formation and enlargement of cysts and the ultimate decline of function. Previous cross-sectional and longitudinal studies have reported significant associations between kidney volume and kidney function (5,16), but we can now quantify the relationship between baseline htTKV and the propensity to develop renal insufficiency. We selected a cohort of participants at relatively high risk for developing renal insufficiency, but who had relatively intact renal function upon recruitment. Most of the patients we selected in CRISP I had stage 1 or stage 2 CKD based on the original Kidney Disease Outcomes Quality Initiative criteria, and selection for enrollment in CRISP required that two-thirds had risk factors for disease progression including onset of hypertension or gross hematuria before age 35 years or proteinuria >300 mg/d. As shown in Figure 1, the cohort developed renal insufficiency
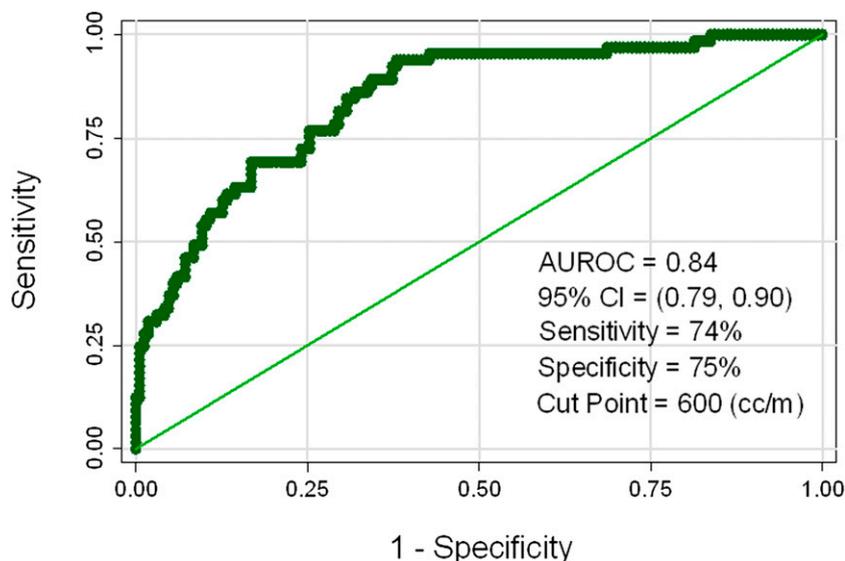
Figure 4. | Receiver operating characteristic curve defining baseline height-adjusted total kidney volume prediction of stage 3 CKD end point. Area under the curve is 0.84, with 74% sensitivity, 75% specificity, and a cut point of 600 cc/m. Ten participants who had reached stage 3 CKD at baseline were excluded. AUROC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval.

Table 3. Baseline predictors of CKD stage 3 endpoint						
Variable	AUC	Sensitivity	Specificity	Cut Point	95% CI of AUC	P Value*
htTKV (cc/m)	0.84	0.74	0.7	600	(0.79, 0.90)	
Serum creatinine (mg/dl)	0.75	0.58	0.81	1.1	(0.67, 0.82)	0.02
BUN (mg/dl)	0.76	0.63	0.79	16	(0.70, 0.83)	0.04
Urine albumin (mg/d)	0.70	0.66	0.67	30	(0.61, 0.78)	0.002
MCP-1 (pg/mg)	0.75	0.80	0.62	410	(0.68, 0.83)	0.02
Baseline age (yr)	0.66	0.60	0.65	35	(0.59, 0.74)	<0.001

AUC, area under the curve; 95% CI, 95% confidence interval; htTKV, height-adjusted total kidney volume; MCP-1, monocyte chemotactic protein-1.

with an increasing pace of conversion from one CKD stage to the next when patients reached 35 years of age. The age-specific development of renal insufficiency in CRISP is not different from other cohorts in which volunteers were chosen at random (5).

This study confirmed a significant time lag between the increase in htTKV and the decline in GFR and an increasingly negative correlation between baseline htTKV and GFR measured in subsequent years (Figures 2 and 3). Significant changes in GFR from baseline were not identified until measurements were obtained in the sixth year of follow-up, yet htTKV increased significantly within 1 year with a continuous increase to >55% from baseline at 8 years of follow-up. Importantly, baseline htTKV predicted the subsequent development of stage 3 CKD with good sensitivity and specificity. The ROC analysis provides a specific htTKV of 600 cc/m that accurately predicts the development of stage 3 CKD within 8 years in this cohort (Figure 4).

Progressive nephron loss as a result of cyst formation and growth develops slowly over many decades before GFR actually decreases by clinically detectable measurement. Compensatory renal hypertrophy and glomerular hyperfiltration can mask the underlying destruction of renal parenchyma (33). The capacity of the kidneys to compensate for the loss of nephrons is best documented following donor nephrectomy for renal transplantation in which compensatory hyperfiltration is evident 1 month after uninephrectomy and 1 year later GFR remains within 10 ml/min per 1.73 m² (87.5%) of controls (34). Continued loss of nephrons in ADPKD provokes a decline in GFR when the combined effect in surviving glomeruli of compensatory hyperfiltration is maximized (33), whereupon the GFR declines more rapidly than in other progressive renal disorders (35).

This study was performed in a population heterogenous for sex, age, race, and place of residence, which may have affected the quantitative relationships among the variables of interest. It is conceivable that htTKV may be an even stronger biomarker of incipient renal insufficiency when associations are tested in more homogenous populations. TKV has taken on such an important role as a biomarker of

disease progression in current clinical trials that we elected to not include other renal symptoms and signs of injury in the analysis. Conceivably, in future analysis, the inclusion of the age of onset of hypertension, hematuria, and albuminuria with htTKV will strengthen the long-term forecasting of declining GFR.

This prospective longitudinal observational study demonstrates that a htTKV value of 600 cc/m in adults with ADPKD predicts the development of renal insufficiency with good sensitivity and specificity within 8 years. These findings provide a format for judging patients' prognosis with regard to the future development of renal insufficiency in clinical practice and for risk stratification in designing clinical trials for this disorder. Its utility as a surrogate marker of kidney volume is inarguable; a wider acceptance as a surrogate marker of renal disease progression may be on the horizon.

Disclosures

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