Baseline total kidney volume and the rate of kidney growth are associated with chronic kidney disease progression in Autosomal Dominant Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by progressive enlargement of kidney cysts leading to chronic kidney disease (CKD) and end-stage renal disease (ESRD). Identification of an early biomarker that can predict progression of CKD is urgently needed. In an earlier Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study (a prospective, multicenter, observational analysis of 241 patients with ADPKD initiated in 2000), baseline height-adjusted total kidney volume (htTKV) was shown to be associated with development of CKD stage 3 after eight years of follow-up. Here we conducted an extended study and found that in a multivariable logistic regression model, baseline htTKV was shown to be a strong, independent predictor for the development of CKD after a median follow-up of 13 years. The odds ratio of reaching each CKD stage per 100 mL/m increment in htTKV was 1.38 (95% confidence interval 1.19-1.60) for stage 3, 1.42 (1.23-1.64) for stage 4, and 1.35 (1.18-1.55) for stage 5 or ESRD. Baseline htTKV was also associated with relative decreases in the glomerular filtration rate of 30%, and 57% or more. Moreover, the rate of change in htTKV was negatively correlated with the slope of the glomerular filtration rate. While ADPKD genotype was also associated with CKD outcomes, it was not an independent prognostic factor after adjusting for htTKV. Thus, baseline total kidney volume and the rate of kidney growth are strongly associated with the development of advanced stages of CKD. These findings support the use of total kidney volume as a prognostic and potentially monitoring biomarker in ADPKD.

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Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening genetic disease primarily affecting adults.[1,2] It is caused predominantly by mutations in 2 genes, *PKD1*, which accounts for ~80% of cases, and *PKD2*, which accounts for 15% of cases. In ADPKD, kidney cysts likely begin forming before birth[3] and grow exponentially throughout life.[4] During this time, cysts progressively compress and injure neighboring structures, including tubules and vasculature, and incite inflammation and eventually interstitial fibrosis. However, the glomerular filtration rate (GFR) is preserved for several decades, likely due to compensatory hyperfiltration of the remaining functional nephrons. Patients eventually reach end-stage renal disease (ESRD) at a median age of 54 years for *PKD1* and 74 years for *PKD2* mutations.[5] There is also considerable allelic heterogeneity in the *PKD1* mutations, with a poorer prognosis for patients with truncating mutations and nontruncating mutations that are predicted to be highly pathogenic.[6,7]

There is currently no therapy approved for the treatment of ADPKD in the United States. Drugs that slow cyst growth are likely to show greatest benefit in childhood or early adulthood when cyst growth has not yet caused irreparable damage.[8] Because of the long natural history of the disease, however, therapeutic trials conducted in early disease are unlikely to show improvement in endpoints considered to be

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clinically meaningful by regulatory agencies, such as doubling of the serum creatinine or ESRD. Conversely, trials of therapy at later stages of the disease when the GFR has begun to decline and irreversible kidney injury may already have supervened are less likely to show a benefit. For this reason, there is an urgent need for robust biomarkers of early ADPKD that are predictive of a later decline in GFR and progression to ESRD.[9] Biomarkers that are directly in the causal pathway for the disease have particular value as they can potentially serve as predictors of the efficacy of drug therapy.[10]

The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) is a prospective, longitudinal, observational cohort study of ADPKD that was conceived in 2000.[4] A cohort of young adults with a well-preserved GFR was selected with the goal of discovering biomarkers in early disease that could predict long-term renal outcomes. CRISP I showed that magnetic resonance imaging (MRI) could be used to accurately quantify total kidney volume (TKV),[11] that TKV increased exponentially with time, and that the increase in TKV was accounted for by the increase in total cyst volume, demonstrating that TKV is an informative marker of disease progression.[4,12] CRISP I provided the first indication that baseline TKV was weakly associated with a decline in GFR, after just 3 years of follow-up.[4] In CRISP II, with 8 years of follow-up available, baseline height-adjusted TKV (htTKV) was shown to be associated with development of CKD stage 3.[13]

However, it is unknown whether htTKV has prognostic value over longer durations of follow-up and whether it is prognostic of advanced, clinically significant CKD endpoints. Moreover, the relative value of ADPKD genotype compared with htTKV, as prognostic biomarkers, is unknown. The CRISP study is uniquely positioned to answer these important questions. We report here the outcomes of CRISP III, now with up to 14.5 years of follow-up, and test the association of baseline htTKV and ADPKD genotype with the development of advanced stages of CKD.

RESULTS

A total of 241 patients were originally enrolled in CRISP. Figure 1 shows the flow of participants and the number included in the current analysis. The baseline characteristics of the primary study cohort of 184 patients is shown in Table 1. The median follow-up duration was 13.0 years (mean, 11.3; maximum, 14.5). By the end of the follow-up period, 50.0% of subjects had reached CKD stage 3 or higher, as defined by measured GFR, with 25.7% reaching CKD stage 4 or higher and 18.6% reaching CKD stage 5 or ESRD (Table 2). Outcomes were similar when the CKD stages were classified according to estimated GFR (eGFR) calculated by either the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology (CKD-EPI) equations. The projected median age to reach each CKD stage, determined by Kaplan-Meier survival analysis, was 47.1 years for CKD stage 3, 53.7 years for CKD stage 4, and 56.2 years for CKD stage 5 or ESRD (Supplementary Figure S1).

To examine the relationship between htTKV at baseline and renal function at follow-up, baseline htTKV was plotted against the GFR values at each of the 8 visits over the course of the study (Figure 2). At baseline, there was a weak negative correlation between htTKV and GFR ($r = -0.40$). With increasing follow-up time, the correlation grew stronger, and the slope became steeper until year 8, after which increasing numbers of patients began to reach ESRD. This indicates that GFR declined faster in patients with a higher baseline htTKV.

To test the strength of the association of baseline htTKV with different categories of CKD, we used logistic regression models. Baseline htTKV was a strong independent predictor of the development of advanced stages of CKD both in an unadjusted model and after multivariable adjustment for baseline age, sex, race, body mass index, and GFR (Table 3).

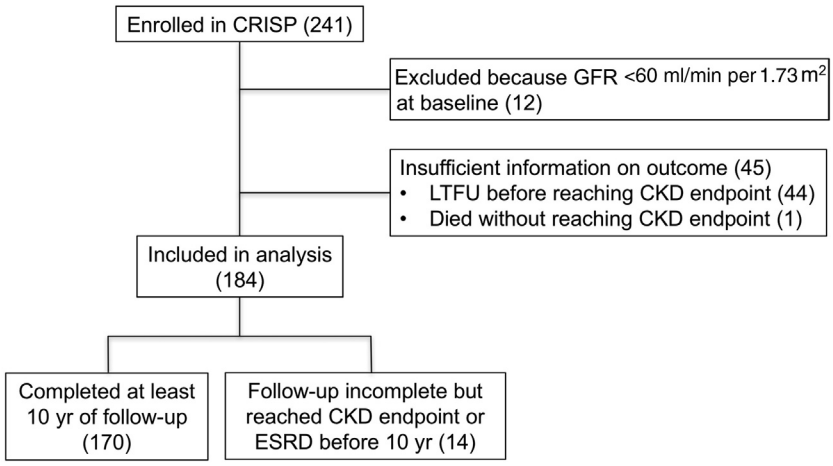

Figure 1 | Flow diagram showing the enrolled study participants who were included in the final analysis. Numbers shown are for analysis of the outcome of chronic kidney disease (CKD) stage 3, as determined from measured glomerular filtration rate (GFR). ESRD, end-stage renal disease; LTFU, lost to follow-up.