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Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months

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Kidney volume growth is considered the best surrogate marker predicting the decline of renal function in autosomal dominant polycystic kidney disease. To assess the therapeutic benefit of new drugs more rapidly, changes in kidney volume need to be determined over a short time interval. Here we measured renal volume changes by manual segmentation volumetry applied to magnetic resonance imaging scans obtained with an optimized T1-weighted acquisition protocol without gadolinium-based contrast agents. One hundred young patients with autosomal dominant polycystic kidney disease and preserved renal function had a significant increase in total kidney volume by 2.71 ± 4.82% in 6 months. Volume measurements were highly reproducible and accurate, as indicated by correlation coefficients of 1.000 for intra-observer and 0.996 for inter-observer agreement, with acceptable within-subject standard deviations. The change in renal volume correlated with baseline total kidney volume in all age subgroups. Total kidney volume positively correlated with male gender, hypertension, albuminuria and a history of macrohematuria but negatively with creatinine clearance. Albuminuria was associated with accelerated volume progression. Our study shows that increases in kidney volume can be reliably measured over a 6 month period in early autosomal dominant polycystic kidney disease using unenhanced magnetic resonance imaging sequences.

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the development of innumerable cysts that originate from the tubular epithelium of the nephrons.[1] The disease affects all ethnic groups worldwide with an incidence of 1:500–1:1000.[2] The continuous growth of cysts leads to progressive kidney enlargement and subsequently to a loss of renal function.[3] Currently, specific treatment for ADPKD other than supportive care does not exist, but clinical trials have recently been initiated to examine the efficacy of various drugs in ADPKD, including the mTOR inhibitors sirolimus (rapamycin) and everolimus, the vasopressin V_2 receptor antagonist tolvaptan, the somatostatin analogue octreotide-acetate, and combined therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[4,5]

In patients with ADPKD, the glomerular filtration rate remains stable for decades because of compensatory mechanisms.[6] By the time renal function starts to decline, the kidneys are usually massively enlarged, and little normal renal parenchyma is recognizable on imaging studies. Thus, early intervention in ADPKD promises more therapeutic benefit than late treatment, as cysts have not yet replaced the bulk of intact renal parenchyma and renal function is still maintained.[4,6,7]

The analysis of sequential magnetic resonance imaging (MRI) or computed tomography scans can be used to monitor the rate of kidney volume enlargement in ADPKD.[8] To identify rapidly the potential therapeutic benefit of a future treatment, it is necessary to establish standardized imaging techniques and volumetric methods, which reliably detect kidney volume changes within a short time interval.

We have prospectively evaluated 100 young ADPKD patients with preserved renal function by two serial MRI volume determinations within an interval of 6 months. We hypothesized that a manual segmentation volumetry method applied to MRI scans which were obtained with an optimized T1-weighted acquisition protocol without administration of gadolinium-based MR contrast agents would be accurate and reliable to assess kidney volume change within 6 months.

RESULTS

Patient characteristics

A total of 100 Caucasian ADPKD patients were studied. A total of 97 patients had a positive family history for ADPKD. The demographic and clinical data of all patients are summarized in Table 1. The diagnosis of ADPKD was established in 89 patients before study inclusion at the age of 23.3 ± 7.9 years. Twenty-five percent of these patients had ADPKD-related symptoms at the time of diagnosis. In 11 patients, the diagnosis of ADPKD was established at screening for study inclusion. At study inclusion, 47 patients reported ADPKD-related symptoms, including recurrent flank pain, episodes of macrohematuria, and cyst infections. During follow up, 74 patients were asymptomatic, 25 experienced flank pain, 3 macrohematuria, and 1 patient had a cyst infection. Two-thirds of the patients had hypertension, mostly treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The baseline estimated creatinine clearance amounted to 109.8 ± 25.5 ml/min (98.2 ± 18.5 ml/min/1.73 m^2) and the urinary albumin/creatinine ratio was 3.86 ± 8.74 mg/mmol; both parameters remained unchanged during the 6-month follow up (108.4 ± 24.7 ml/min and 3.08 ± 3.59 mg/mmol at month 6; $P = 0.259$ and 0.497, respectively). Microalbuminuria was present in 25 patients and only 2 patients had macroalbuminuria.

Kidney and cyst volume changes within 6 months

MRI volumetry-based volumes of both kidneys of all 100 ADPKD patients were assessed twice within 192 ± 15 days. Figure 1a displays the total kidney volume (TKV) at baseline and at month 6 in all patients as a function of their age. The mean TKV amounted to 1003 ± 568 cm^3 at baseline and increased significantly to 1034 ± 602 cm^3 ($P < 0.001$). The mean TKV change was 31.8 ± 72.0 cm^3 (2.71 ± 4.82%). This measured kidney volume increase in 6 months corresponded to an extrapolated value of 62.2 ± 136.5 cm^3 (5.36 ± 9.47%) per year.

Figure 1b shows that TKV increased in most patients but decreased in some. A significant decrease of the renal volume (i.e. outside the 95% confidence interval (CI) for the volume measurements) was found in 13 single kidneys of 10 patients. Their MR images were reviewed in detail. In six patients (seven single kidneys), the volume decrease could be attributed to the rupture of one or few large cysts. These six patients were all male, had significantly higher TKV (1445 ± 435 vs 982 ± 568 cm^3; $P = 0.034$) and reported more symptoms at baseline (recurrent flank pain in 100 vs 32%, episodes of macrohematuria in 83 vs 16%, cyst or urinary tract infections in 33 vs 12%, and hypertension in 100 vs 65%), whereas the age was similar compared with the remainder of the cohort (33.4 ± 7.6 vs 31.1 ± 6.4 years; $P = 0.384$). Only two of these six patients reported flank pain and none had macrohematuria during follow up. Figure 2 shows an example for the rupture of a large cyst at the lower pole of the left kidney between baseline and follow-up.

The mean left kidney volume was higher than the right (530 ± 301 vs 480 ± 284 cm^3; $P < 0.001$), whereas the growth rate did not differ significantly (2.50 ± 5.48 vs 2.80 ± 5.14%; $P = 0.509$). Figure 3a shows that the baseline volumes of the

Table 1 | Demographic and clinical data at baseline in 100 ADPKD patients

Demographic characteristics	
Age (years)	31.2 ± 6.4
Sex (female; male)	37; 63
Family history of ADPKD	97
BMI (kg/m^2)	24.3 ± 3.8
SBP/DBD (mm Hg)	133.9 ± 16.5/84.8 ± 10.6
Current smoker	36
Symptoms and complications of ADPKD	
Hypertension	67
Antihypertensive treatment	41
ACEI and/or ARB therapy	39
Recurrent flank pain	36
History of macrohematuria	20
History of cyst infections	13
History of intracranial bleeding	2
Renal parameters	
Serum creatinine (μmol/l)	90.2 ± 19.1
Estimated creatinine clearance (C–G; ml/min)	109.8 ± 25.5

ACEI, angiotensin-converting enzyme inhibitor; ADPKD, autosomal-dominant polycystic kidney disease; ARB, angiotensin receptor blocker; BMI, body mass index; C–G, Cockcroft–Gault; DBP, diastolic blood pressure; SBP, systolic blood pressure. Data represent mean (s.d.) or the number of patients.

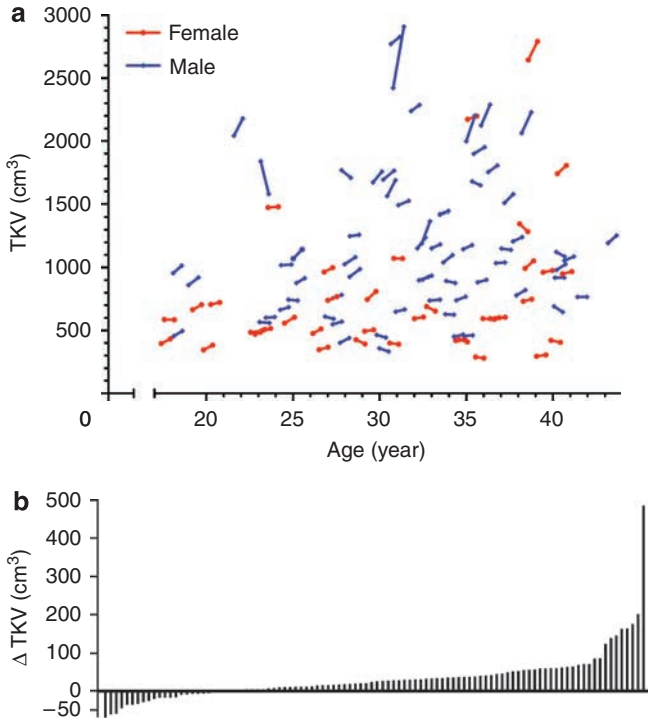

Figure 1 | Total kidney volume progression within 6 months. (**a**) Total kidney volume (TKV) in relation to age in 100 individual ADPKD patients (female in red, male in blue). (**b**) TKV change (ΔTKV) of individual patients lined up in ascending order.

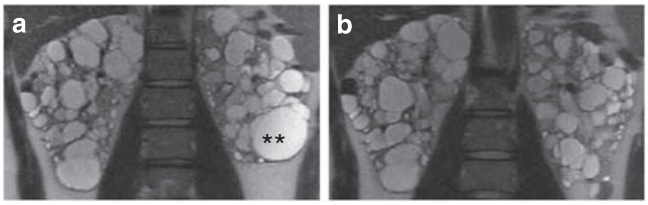

Figure 2 | Coronal T2-weighted MRI sections reveal the rupture of a large cyst. (**a**) At month 0, a large cyst (**) at the lower pole of the left kidney is seen. (**b**) The large lower left pole cyst has disappeared at month 6. In the 6-month observation period, the right kidney volume increased by 44 cm^3 whereas the left kidney volume decreased by 59 cm^3 and hence total kidney volume was reduced by 15 cm^3 within 6 months.

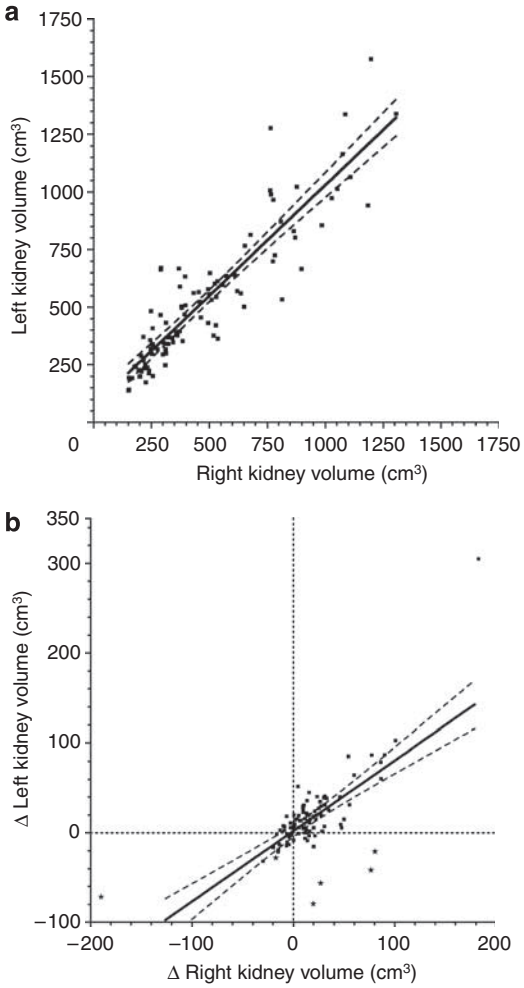

Figure 3 | Comparison between left and right kidney volumes and their changes. (**a**) A high correlation was found between left and right kidney volumes at baseline ($r = 0.905$, $P < 0.001$) and (**b**) between single kidney volume changes (ΔSKV) of the left and right kidney over 6 months in 100 patients ($r = 0.702$, $P < 0.001$). The correlation between ΔSKV of the right and left kidney increased after the exclusion of patients with documented cyst rupture ($r = 0.818$, $P < 0.001$). Squares represent individual patients, stars represent patients with documented cyst rupture ($n = 6$). Lines of linear regression with 95% confidence interval are shown.

right and left kidney were highly correlated in individual patients ($r = 0.905$, $P < 0.001$). Furthermore, Figure 3b reveals that their growth rates were also correlated ($r = 0.702$, $P < 0.001$). When six patients with documented cyst rupture were excluded, the correlation of the growth rates of the right and left kidney increased ($r = 0.818$, $P < 0.001$).

Using T2-weighted MRI volumetry, we also determined total cyst volume. Total cyst volume was $476 \pm 440\ cm^3$ at baseline and increased by $32.8 \pm 92.5\ cm^3$ ($5.45 \pm 14.28\%$) to $509 \pm 490\ cm^3$ ($P < 0.001$). The change in total cyst volume was directly correlated with the change in TKV ($r = 0.780$, $P < 0.001$). The mean noncystic renal volume (i.e. TKV minus total cystic volume) at baseline was $527 \pm 183\ cm^3$ and did not change during follow up ($526 \pm 187\ cm^3$, $P = 0.867$).

To assess the association between growth rate and kidney volume, the patients were stratified into three subgroups according to their kidney volume and the volume subgroups were further stratified by age (Table 2). Six patients who exhibited a significant volume loss due to a cyst rupture and two patients with unilateral renal agenesis were excluded from this analysis. The proportion of young patients declines with increasing TKV, reflecting that TKV increased with age. There was a positive correlation between TKV and TKV change in both age subgroups ($r = 0.588$, $P < 0.001$ and $r = 0.612$, $P < 0.001$ for age < 30 and > 30 years, respectively) and in the subgroups of higher age also the percentage TKV change correlated with TKV ($r = 0.080$, $P = 0.639$ for age < 30 years and $r = 0.485$, $P < 0.001$ for age > 30 years). The TKV change was inversely correlated with age in most TKV subgroups. For the correlation of absolute and percentage TKV change with age, the coefficients are $r = -0.379$, $P = 0.013$ and $r = -0.418$, $P = 0.006$ in patients with TKV 750 ml; $r = -0.308$, $P = 0.076$ and $r = -0.360$, $P = 0.036$ in patients with TKV 750–1500 ml; $r = -0.143$, $P = 0.597$ and $r = -0.165$, $P = 0.541$ in patients with TKV > 1500 ml. The percentage but not absolute kidney volume progression was also inversely correlated with age in the whole cohort ($r = -0.242$, $P = 0.020$ and $r = 0.015$, $P = 0.891$, respectively).

Reproducibility of MRI kidney volumetry

The comparison of single kidney volume (SKV) measurements for observer 1 (D.P.) and 2 (F.K.) are shown as Lin's concordance correlation plot in Figure 4. The concordance correlation coefficients (95% CI) were 1.000 (0.999–1.000) for intraobserver and 0.996 (0.995–0.999) for interobserver correlations, representing excellent agreement. The coefficient increases in value as a function of the nearness of the data to the line of perfect concordance (accuracy) and the tightness of the data around this axis (precision). Accuracy and precision was high over the entire range of measured kidney volumes, indicating that there is similar reliability in measuring lower and higher SKV.

Table 3 shows the measurement error, expressed as the within-subject standard deviation (s_w) for intraobserver and interobserver duplicate measurements. The measurement error was similar over the entire range of kidney volumes ($\tau = 0.139$, $P = 0.163$ and $\tau = 0.142$, $P = 0.155$ for intraobserver and interobserver measurement error, respectively).

Table 2 | Relationship between age, total kidney volume, volume progression, and creatinine clearance

Total kidney volume and age group	N	Total kidney volume			Estimated creatinine clearance	
		At baseline (ml)	Change (ml)	Change (%)	At baseline (ml/min)	Change (ml/min)
<750 ml and <30 years	23	544 ± 126	18.5 ± 24.8	2.79 ± 4.81	120 ± 27	−0.9 ± 15.1
<750 ml and ⩾30 years	18	530 ± 149	1.2 ± 17.0	0.06 ± 4.06	100 ± 22	−0.4 ± 10.1
750–1500 ml and <30 years	11	1016 ± 198	39.2 ± 24.6	4.60 ± 2.60	126 ± 26	−2.6 ± 8.7
750–1500 ml and ⩾30 years	23	1054 ± 156	24.9 ± 46.0	2.52 ± 4.31	109 ± 26	−2.7 ± 14.1
>1500 ml and <30 years	2	1857 ± 261	112.6 ± 38.1	6.16 ± 1.30	116 ± 2	13.3 ± 21.3[a]
>1500 ml and ⩾30 years	14	2043 ± 386	123.7 ± 118.2	5.94 ± 4.06	100 ± 16	−3.2 ± 9.4

Data represent mean (s.d.).
[a]The apparent improvement of creatinine clearance is due to a 15 kg weight gain during follow up of one of these two patients affecting the estimate of creatinine clearance according to the Cockcroft-Gault formula.

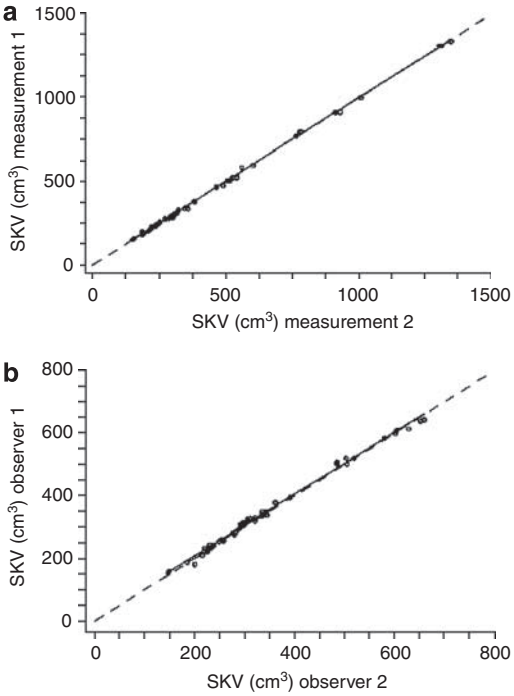

Figure 4 | Intraobserver and interobserver agreement of kidney volume measurements. Lin's concordance correlation plots demonstrating high degree of agreement between repeated measurements of observer 1 ($n = 48$; **a**) and between measurements of observers 1 and 2 ($n = 48$; **b**). All measurements are in cm^3. SKV, single kidney volume.

Table 3 | Intraobserver and interobserver agreement of kidney volumetry measurements

Comparison N=48	Lin's concordance correlation coefficient, ρ_c (95% CI)	Within-subject standard deviation, s_w (cm^3)
Kidney volume		
Observer 1 vs 1	1.000 (0.999–1.000) *P<0.001*	6.130
Observer 1 vs 2	0.996 (0.995–0.999) *P<0.001*	8.003
Cyst volume		
Observer 1 vs 1	0.993 (0.989–0.997) *P<0.001*	9.8387
Observer 1 vs 2	0.943 (0.918–0.969) *P<0.001*	25.500

Comparison of single kidney volume and cyst volume of single kidney measurements by two observers.

The difference between an observer's measurement and the true kidney volume would be expected to be less than $1.96 s_w$ for 95% of measurements. Thus, the 95% CI for SKV measurements as calculated based on the interobserver s_w is ± 15.687 cm^3 and therefore lower than the mean positive or negative SKV change of ± 25.3 cm^3 during follow up.

For single kidney cyst volume measurements, the concordance correlation coefficients and the within subjects standard deviations for duplicate measurements (s_w) are shown in Table 3.

Correlation between renal volume and clinical variables

Male patients had larger renal volumes than female patients (TKV 1158 ± 555 vs 738 ± 493 cm^3; $P<0.001$). TKV was also higher in patients with arterial hypertension compared with normotensives (1190 ± 581 vs 622 ± 277 cm^3; $P<0.001$) and in patients who reported previous episodes of hematuria (1399 ± 581 vs 904 ± 522 cm^3; $P<0.001$) and it was positively associated with albuminuria ($r = 0.424$, $P<0.001$) and negatively associated with creatinine clearance ($r = -0.348$, $P<0.001$). These associations remained significant after normalization of TKV for body surface area and adjustment for age (for the association of TKV with gender $P = 0.004$, hypertension $P<0.001$, hematuria $P<0.001$, creatinine clearance $P = 0.002$, and albuminuria $P<0.001$).

To identify risk factors for accelerated progression, the percentage kidney volume change was correlated with clinical and demographical variables. Patients with documented cyst rupture or unilateral renal agenesis were excluded from this analysis. Male patients tended to have higher growth rates than female patients, but this difference was not statistically significant (3.24 ± 5.07 vs 2.25 ± 4.43%, $P = 0.339$). Albuminuria was positively associated with volume growth rate ($r = 0.298$, $P = 0.005$). This association remained significant after adjusting for sex, age, diagnosis of hypertension, use of angiotensin converting enzyme inhibitor/angiotensin receptor blockers, systolic blood pressure, creatinine clearance, TKV at baseline, and the interval between the two MRI acquisitions ($P = 0.041$).

DISCUSSION

The results of the present study demonstrate that an unenhanced MRI technique combined with manual segmentation volumetry can provide reproducible measures of renal volumes useful for monitoring changes that occur in early ADPKD within a short time interval.

Various imaging modalities have been used to monitor volume progression in ADPKD, including sonography,[9] MRI[8], and computed tomography.[10–13] Sonography is highly operator dependent and lacks accuracy to detect small changes in renal volume.[14] For safety reasons, MRI is favorable compared with computed tomography technique, as it avoids the radiation exposure and administration of iodinated contrast media. Previously, gadolinium-enhanced MRI has been used for renal volume determination in ADPKD patients.[8] We used unenhanced MR image sequences only because gadolinium-based MR contrast agents have been associated with nephrogenic systemic fibrosis in patients with renal disease.[15,16] Although nephrogenic systemic fibrosis occurred predominantly in patients with glomerular filtration rate <60 ml/min, the avoidance of gadolinium-based MR contrast agents is desirable for further studies in patients with ADPKD and impaired kidney function. As the US Food and Drug Administration (FDA) has raised concerns over using gadolinium in ADPKD patients, also the Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) has migrated to an unenhanced MRI protocol for further studies.

Volume determination from MRI data requires a segmentation of MR images. An automated method would be desirable but is not easily applicable to polycystic kidneys because of their inhomogeneous structure. Semiautomated segmentation methods include region-based thresholding and stereology. In region-based thresholding, an intensity threshold is set by a trained analyst for every image slice to differentiate the area of interest from surrounding tissue. This method is limited by the intrinsic spatial intensity fluctuation of MR images. The human visual system has the ability to overcome spatial intensity fluctuations and resolve small contrast differences and is probably most feasible for MR image segmentation. The stereological technique depends on the capability of an analyst to differentiate adjacent tissues and makes use of a grid superimposed on the image data, which facilitates volume determination but does not utilize the full resolution of image data.[17,18] We used a manual contour tracing method, which is more time consuming than semiautomated approaches but allows a very precise definition of organ boundaries utilizing the full resolution of MR data. Manual segmentation is not applicable to cyst volume determination due to the large number of cysts. Thus, we used a region-based thresholding method to determine cyst volumes.

The question, if renal volume changes can be measured within a 6-month interval, depends on the magnitude of the measurement imprecision compared with the actual kidney volume change. The accuracy and reliability of renal volume measurements was mirrored by excellent concordance among all measurements as continuous variables, based on Lin's concordance correlation coefficients of 1.000 and 0.996 for intra- and interobserver correlations. The 95% CI for kidney volume measurements as calculated based on the interobserver variability was considerably lower than the true volume change. This applies for the entire range of measured kidney volumes as the measurement error was independent of the kidney volume. The high accuracy and reproducibility of our method thus allows monitoring changes that occur in early ADPKD within a short time interval. Cyst volume measurements were also reliable but the measurement error was larger compared with kidney volume measurements owing to the use of a region-based thresholding method instead of manual segmentation.

The CRISP analyzed annual contrast-enhanced MRI over 3 years in 241 American ADPKD patients.[8] The renal volume was measured in T1-weighted gadolinium-enhanced images with the use of a stereologic method. At baseline, TKV amounted to 1076 cm^3 and increased by 63.4 cm^3 or 5.27% per year. Using a manual segmentation technique, we studied 100 European ADPKD patients with similar baseline characteristics as the CRISP cohort. TKV increased by 31.8 cm^3 within 6 months corresponding to a growth rate of 2.71%. Assuming an exponential growth kinetic with a constant growth rate, the calculated annual growth rate was 5.36% in our cohort and hence very similar to the CRISP results. In further analogy to the CRISP data, we could confirm the high degree of correlation between right and left renal volumes and their growth rates. Thus, we were able to confirm the CRISP results in an European ADPKD population.

In seven kidneys, we identified the asymptomatic spontaneous rupture of large cysts, causing a significant reduction of the kidney volume. Cyst loss has been judged not to contribute appreciably to the renal growth kinetic over the long term.[19] In the short term however, we could demonstrate that cyst ruptures can cause considerable reduction of renal volume. Thus, if volumetry data are used to monitor disease progression over a short time interval, complemented detailed image analysis can be helpful.

The kidney volume enlargement in ADPKD has been suggested to follow an exponential characteristic with a growth rate that is patient-specific and relatively constant over time.[19] On the basis of two measurements per patient, the growth characteristic cannot be defined exactly. However, the correlation between TKV and TKV growth found in both age subgroups of our cohort supports the hypothesis of a patient-specific growth rate. The percentage TKV change correlated with TKV only in patients >30 years and the correlation between TKV and TKV growth gained strength with increasing patient age. It is clear that the enlargement of the polycystic kidney is due to the growth of the cysts. With increasing age, cyst volume contributes proportionally more and more to TKV. Hence, the rate of cyst growth will influence total renal volume more pronouncedly in advanced

disease. As a consequence, TKV in relation to age might serve as a prognostic marker in patients >30 years but it seems to be less reliable in young patients.

We found the percentage renal volume growth rate to be higher in young patients. Rather than reflecting an accelerated progression in these patients, this finding might be due to selection bias: young patients with mild disease were probably underrepresented in our cohort because the diagnosis was not yet established or they were not motivated for study participation by lack of symptoms.

Renal volume in ADPKD has previously been correlated with other markers of advanced disease, such as hypertension, albuminuria, and reduced glomerular filtration rate.[20,21] Previously identified risk factors for accelerated disease include male sex, gross hematuria, early onset of hypertension, and proteinuria.[9,21–23] Our results are in line with these previous studies as TKV at baseline was positively correlated with hypertension, hematuria, and albuminuria and albuminuria was associated with accelerated volume progression.

Taken together, the high reproducibility and accuracy of the measurements, the correlation of the volumetry results with clinically known progression markers and the accordance of our results with the CRISP data underscore the validity of our method to monitor changes in early ADPKD within an interval of 6 months. The method we describe here can be easily implemented into clinical practice as we relied on a standardized MRI acquisition protocol and commercially available US Food and Drug Administration-approved volumetry software. These data may have implications for designing future interventional trials and are important for examining the therapeutic benefit of ongoing clinical trials for this devastating disease.

MATERIALS AND METHODS

Patient population

The subjects for this study were 100 participants of an ADPKD registry. The diagnosis of ADPKD was based on ultrasonographic diagnostic criteria in patients with a family history of ADPKD.[24] In patients with a negative family history, proof of a disease-causing mutation in the *PKD1* gene was obtained by genetic testing (sequencing analysis by Athena Diagnostics Inc., Worcester, MA, USA). As we also aimed to screen patients for a clinical trial, they generally fulfilled the inclusion criteria of that trial,[25] most importantly age 18–40 years and estimated creatinine clearance ⩾70 ml/min. Patients were studied at the University Hospital of Zürich, Switzerland, between April 2005 and March 2008. The study was conducted according to the guidelines on Good Clinical Practice and the Declaration of Helsinki Principles. Study approval was obtained from the local ethics committee, and all patients gave written, informed consent.

Clinical evaluation and laboratory analyses

After screening and enrolment, a detailed medical history was obtained, including ADPKD-related symptoms, previous hospitalization, and medication. Blood pressures were measured twice in each arm at every study visit in sitting position after a rest of 5 min, using an oscillometric blood pressure monitor (Boso-Medicus, Jungingen, Germany). The lower of the two consecutive measurements in the arm with the higher blood pressure was used for analysis. Arterial hypertension was defined as systolic blood pressure ⩾140 mm Hg or diastolic blood pressure ⩾90 mm Hg at all three study visits (screening, baseline and month 6), or treatment with an antihypertensive drug. Blood samples were obtained at month 0 and 6 for the determination of serum creatinine (IDMS traceable modified Jaffé method). Creatinine clearance was estimated according to the Cockcroft–Gault formula. The spot urine was analyzed for the ratio of albumin to creatinine (mg/mmol).

Magnetic resonance imaging

All subjects underwent a standardized MRI protocol at month 0 and 6 using an 1.5 T scanner (Signa EchoSpeed EXCITE HD or HDx; GE Healthcare, Waukesha, WI, USA), as described elsewhere.[25] Briefly, for signal reception in all examinations, an eight-channel anteroposterior-phased array surface coil was placed around the patient covering the entire kidneys. The imaging protocol included unenhanced sequences only. After obtaining a localizer sequence, a coronal single shot fast spin echo sequence (TR ms/TE ms 1349/90.1; field of view, 48 × 48 cm; acquisition matrix, 384 × 224; section thickness, 4 mm; no interslice gap) was acquired in breathhold technique to obtain an overview of the extent of the cystic disease of the patient. On the basis of this coronal sequence, the transaxial sequences were planned. The transaxial sequences consisted of two breathhold T1-weighted fast-spoiled gradient echo sequences (TR ms/TE ms = 85/1.4, flip angle, 70°) with 3 and 4 mm slice thicknesses and no interslice gap. Sequences with 4 mm slice thickness were only assessed if 3 mm sequences were not analyzable due to artefacts or insufficient coverage of the volume of interest. In addition, a transaxial T2-weighted fast spin echo sequence with respiratory triggering was performed (TR ms/TE ms = 17,143/102.8) with 3 mm slice thickness and no interslice gap.

Renal volume measurements

Kidney volumes were measured by manually tracing the kidney contours using volume analysis software implemented on an Advantage Windows workstation (4.4, GE Healthcare, Buc, France). The renal volume was calculated for each kidney by multiplying all outlined areas by the section thickness and summing the volume of each section. Non-kidney parenchyma, for example renal hilus, was identified by checking adjacent slides if needed and excluded from the measurement. For measurements of the TKVs, the T1-weighted fast-spoiled gradient echo sequences were used.

For the determination of cyst volumes, a region-based thresholding technique was applied to the axial T2-weighted fast spin echo sequences. In this sequence, the cysts appear brighter than the renal parenchyma. An intensity threshold was selected on every image slice by an analyst. The volume of all cysts was calculated for each kidney by multiplying cyst areas by the section thickness and summing the volume of each section. These measurements were also performed using the Advantage Windows workstation.

Individual kidneys were measured in cm^3 and the values of the right and left kidney were added to calculate the TKV and the total cyst volume for each patient. The annual change in kidney volume was determined for each patient assuming an exponential growth.[19]

The measurements of total kidney and cyst volumes were performed by two observers (D.P. and F.K.), which have been trained by a radiologist and have performed their first measurements under

supervision. Depending on the kidney size, analysis time was 15–45 min for one single kidney volume determination, whereas cyst volume measurement required 10–25 min per kidney. For the assessment of the intraobserver agreement of kidney volume determination, one of the observers (D.P.) repeated 48 SKV measurements at a different occasion. To further validate the measurements, a second independent observer (F.K.) repeated the measurements and interobserver agreement was determined. Repeated measurements were performed without knowledge of the results of earlier measurements or each other's results.

Statistical analysis

Results are expressed as means ± s.d. Means of continuous data were compared by Student's *t*-test. All *P*-values were two sided for the comparison with the baseline values, and those less than 0.05 were considered statistically significant. The Pearson correlation coefficient was used to test for associations between continuous variables. TKV and albumin/creatinine ratio variables were log-transformed to achieve a normal distribution for parametric tests. Multivariate linear regression was used to determine independent predictors of growth rate and to adjust TKV for age in the comparison among patients with different clinical characteristics.

Intra- and interobserver agreement of the kidney volumetry was evaluated by computing Lin's concordance correlation coefficient (ρ_c) for each comparison.[26] In addition, the within-subject standard deviation was calculated to assess the reproducibility of kidney and cyst volume measurement.[27] The Kendall τ rank correlation coefficient between the standard deviation and the mean of replicate measurements was used to test whether the measurement error was proportional to the volume measured.

DISCLOSURE

The authors declared no competing interests.

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