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Original Investigation

Estimation of Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease

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Background: In autosomal dominant polycystic kidney disease (ADPKD), obtaining measured total kidney volume (mTKV) by magnetic resonance (MR) imaging and manual tracing is time consuming. Two alternative MR imaging methods have recently been proposed to estimate TKV ($eTKV_{ellipsoid}$ and $eTKV_{PANK}$), which require less time.

Study Design: Cross-sectional and longitudinal diagnostic test study.

Setting & Participants: Patients with ADPKD with a wide range of kidney function and an approved T2-weighted MR image obtained at the University Medical Centers of Groningen, Leiden, Nijmegen, and Rotterdam, the Netherlands, in 2007 to 2014. Test set for assessing reproducibility, n = 10; cohort for cross-sectional analyses, n = 220; and cohort for longitudinal analyses, n = 48.

Index Tests: Average times for $eTKV_{ellipsoid}$ and $eTKV_{PANK}$ were 5 and 15 minutes, respectively. Bias is defined as (mTKV − eTKV)/mTKV × 100%; precision, as one standard deviation of bias.

Reference Tests: mTKV using manual tracing to calculate the area within kidney boundaries times slice thickness. Average time for mTKV was 55 minutes.

Results: In the test set, intra- and intercoefficients of variation for mTKV, $eTKV_{ellipsoid}$, and $eTKV_{PANK}$ were 1.8% and 2.3%, 3.9% and 6.3%, and 3.0% and 3.4%, respectively. In cross-sectional analysis, baseline mTKV, $eTKV_{ellipsoid}$, and $eTKV_{PANK}$ were 1.96 (IQR, 1.28-2.82), 1.93 (IQR, 1.25-2.82), and 1.81 (IQR, 1.17-2.62) L, respectively. In cross-sectional analysis, bias was 0.02% ± 3.2%, 1.4% ± 9.2%, and 4.6% ± 7.6% for repeat mTKV, $eTKV_{ellipsoid}$, and $eTKV_{PANK}$, respectively. In longitudinal analysis, no significant differences were observed between percentage change in mTKV (16.7% ± 17.1%) and percentage change in $eTKV_{ellipsoid}$ (19.3% ± 16.1%) and $eTKV_{PANK}$ (17.8% ± 16.1%) over 3 years.

Limitations: Results for follow-up data should be interpreted with caution because of the limited number of patients.

Conclusions: Both methods for eTKV perform relatively well compared to mTKV and can detect change in TKV over time. Because $eTKV_{ellipsoid}$ requires less time than $eTKV_{PANK}$, we suggest that this method may be preferable in clinical care.

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INDEX WORDS: Autosomal dominant polycystic kidney disease (ADPKD); total kidney volume (TKV); magnetic resonance imaging (MRI); estimation methods; ellipsoid; PANK; validation.

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation and growth of numerous cysts in both kidneys, leading to an increase in kidney volume. These cysts compress healthy kidney tissue, causing progressive kidney function decline and, in most patients, ultimately a need for renal replacement therapy. In patients with ADPKD, total kidney volume (TKV) has been shown to be an early marker of disease severity and predictor of kidney function decline.[1] Measurement of TKV is therefore used to assess prognosis in clinical care and for selection of patients for randomized controlled

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trials.[2] In these trials that investigate potential treatments for patients with ADPKD, assessment of TKV is often used as the primary or secondary study end point.[3-5]

The true gold-standard method to assess TKV is the manual tracing method. Computer tomogram or magnetic resonance (MR) images are used, and in each slice, the kidney boundaries are traced manually using dedicated software. Measured TKV (mTKV) is calculated from a set of contiguous images by summing the products of the area measurements within the kidney boundaries and slice thickness.[6] This method is laborious, which limits its use in trial settings, but especially in clinical care.

If kidney volume could be estimated with sufficient accuracy and reliability, it would alleviate the time-consuming process of kidney volume measurement. Recently, 2 kidney volume estimation methods have been developed: the midslice method[7] by the Consortium for Radiologic Imaging Studies of ADPKD (CRISP) and the ellipsoid method[2] by the Mayo Clinic. For both methods, measured and estimated kidney volumes appeared to be well correlated, but other groups have not yet validated these methods. In addition, the midslice method was developed in a cohort that included only patients with creatinine clearance $>$ 70 mL/min. In general, such patients have relatively small kidneys, making manual tracing measurement of TKV relatively easy, which may have influenced the results that were obtained. This method should therefore also be validated in patients with lower kidney function. Estimation methods to assess TKV may also be used in clinical trials, but only when they can accurately and reliably detect changes in TKV over time. To our knowledge, these issues have not been investigated to date.

Given these considerations, the objective of the present study was to investigate cross-sectionally these methods to estimate TKV in a patient group with a wide range of kidney function. Furthermore, we investigated in a longitudinal study whether these estimation methods can accurately detect changes in TKV.

METHODS

Patients and Study Design

For this study, all MR images of patients with ADPKD that were available from 2007 through 2014 were used. These patients participated in 1 of 3 studies that were performed by the departments of nephrology at the University Medical Centers of Groningen, Leiden, Nijmegen, and Rotterdam (all in the Netherlands). Details of the study protocols have been published elsewhere[4,8,9]; see Figure S1 (available as online supplementary material) for a flow diagram showing the assembly of the cohort. All patients were included if an MR image was available. ADPKD was diagnosed based on the modified Ravine criteria.[10] The Medical Ethics Committee of the University Medical Center Groningen approved the protocols of the 3 studies that were conducted in accordance with the International Conference of Harmonization Good Clinical Practice Guidelines and in adherence to the ethics principles that have their origin in the Declaration of Helsinki. All patients gave written informed consent.

Measurement and Collections

All participants collected a 24-hour urine sample the day preceding the MR imaging (MRI), in which urinary albumin concentration was measured. At the outpatient clinic on the day of MRI, blood pressure was assessed at rest in a supine position with an automatic device (Dinamap; GE Medical Systems) for 15 minutes and weight and height were determined. Blood samples were drawn for determination of creatinine level with an enzymatic assay (isotope-dilution mass spectrometry traceable; Modular; Roche Diagnostics), which was used to estimate glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[11,12]

MR Imaging

All participants underwent a standardized abdominal MRI protocol without the use of intravenous contrast. For the specific MRI protocol, see Item S1.

Gold-Standard Method: mTKV

Kidney and liver volumes were measured on the coronal fat saturated T2-single shot fast spin-echo sequence if possible. If the T2-weighted images showed too low quality, the MR image was excluded. Kidney and liver volumes were measured using the manual tracing method. Kidney and liver boundaries were manually traced using the commercially available software Analyze Direct 11.0 (Analyze Direct Inc). Kidney and liver volumes were calculated from the set of contiguous images by summing the products of the area measurements within the kidney or liver boundaries and slice thickness.[6] Nonrenal parenchyma (eg, the renal hilus) was excluded from measurement.

Estimation Methods: Estimated TKV

The 2 formulas used to estimate kidney volume were derived from the literature.[2,7]

We first used the midslice method to estimate TKV ($eTKV_{PANK}$).[7] The midslices of the coronal MR images were selected for each kidney separately. The midslice was defined as the slice for which the slice number corresponds to half the sum of the numbers of the first and last slice that contained the kidney. If the sum was odd, the midslice number was rounded up. $eTKV_{PANK}$ was calculated in milliliters, with midslice area and slice thickness in millimeters squared and millimeters, respectively. $eTKV_{PANK}$ was calculated as the sum of the left eKV_{PANK} (ie, 0.624 $\times$ midslice area $\times$ number of slices covering the left kidney $\times$ slice thickness/1,000) and right eKV_{PANK} (ie, 0.637 $\times$ midslice area $\times$ number of slices covering the right kidney $\times$ slice thickness/1,000).

Second, we used the ellipsoid method to estimate TKV ($eTKV_{ellipsoid}$).[2] For each kidney, length was measured as the average maximal longitudinal diameter measured in the coronal and sagittal plane. Width was obtained from the transversal image at maximum transversal diameter, and depth was measured from the same image perpendicular to the width measurement. $eTKV_{ellipsoid}$ was calculated in milliliters, with length, width, and depth all in millimeters. $eTKV_{ellipsoid}$ was calculated as the sum of the left $KV_{ellipsoid}$ and right $KV_{ellipsoid}$, both derived by the equation $\pi/6 \times (length_{coronal} + length_{sagittal})/2 \times width \times depth/1{,}000$. Of note, to assess $eTKV_{ellipsoid}$, no specific software is necessary, in contrast to assessment of mTKV and $eTKV_{PANK}$.