3DUS as an alternative to MRI for measuring renal volume in children with autosomal dominant polycystic kidney disease

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Abstract

Background Total kidney volume, measured by magnetic resonance imaging (MRI), is a validated disease progression marker in adults with autosomal dominant polycystic kidney disease (ADPKD). However, in childhood, MRI is burdensome, explaining the need for alternatives.

Methods Kidney volume (KV) was evaluated in 30 children with ADPKD, using three-dimensional ultrasound (3DUS), applying the ellipsoid method and manual contouring (KV_{3DUS-ellipsoid}, KV_{3DUS-contour} respectively); manual contouring on MRI (KV_{MRI}), and the ellipsoid method on two-dimensional ultrasound (2DUS, KV_{2DUS}). Correlations and differences were evaluated using Pearson's *r* and Wilcoxon signed-rank tests, and variability using Bland–Altman plots.

Results All ultrasound volumetry methods showed significantly lower mean ($\pm$ SD) KV (mL), compared with MRI—KV_{2DUS}: 159 ($\pm$ 101); KV_{3DUS-ellipsoid}: 169 ($\pm$ 105); KV_{3DUS-contour}: 185 ($\pm$ 110); KV_{MRI}: 206 ($\pm$ 130); all $p < 0.001$. All had a strong correlation with KV_{MRI}: 2DUS: $r = 0.96$; 3DUS-ellipsoid: $r = 0.89$ and 3DUS-contour: $r = 0.94$. Both before and after correction factor application, Bland–Altman plots showed lower variability and absolute error for KV_{3DUS-contour} vs KV_{2DUS} and KV_{3DUS-ellipsoid}.

Conclusions Compared with MRI, ultrasound volumetry was prone to underestimation. However, KV_{3DUS-contour} represents a valuable alternative for MRI in early ADPKD. Although more time-consuming, KV_{3DUS-contour} is recommended over KV_{2DUS} for estimation and follow-up of KV in ADPKD children, given its smaller error.

Keywords Autosomal dominant polycystic kidney disease · Pediatrics · Renal volumetry · Magnetic resonance imaging · 3D ultrasound

Abbreviations

2DUS Two-dimensional ultrasound
3DUS Three-dimensional ultrasound
ADPKD Autosomal dominant polycystic kidney disease

CKD Chronic kidney disease
(e)GFR (Estimated) glomerular filtration rate
(ht)TKV (Height-adjusted) total kidney volume
KV Kidney volume
MRI Magnetic resonance imaging

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic causes of kidney failure in humans, affecting 1 in 400 to 1,000 live births [1]. It is caused by a loss-of-function mutation in *PKD1* or *PKD2*. Recently, a third gene has been identified to cause ADPKD, namely *GANAB* [2]. The most prominent manifestation of this multi-organ disorder is renal cyst formation and growth, resulting in a progressive increase in total kidney volume (TKV) and end-stage renal disease (ESRD), the latter mainly

from the sixth decade of life [3]. As the glomerular filtration rate (GFR) remains normal for several decades, owing to hyperfiltration and hypertrophy of unaffected residual nephrons [4], it is not a valuable disease progression marker. From the Consortium for the Radiologic Imaging Study of PKD (CRISP) cohort, height-adjusted TKV (htTKV), measured by the stereology method on magnetic resonance imaging (MRI), was proven to be a strong and independent predictor for ESRD development [5, 6]. Recently, the Food and Drug Administration (FDA) approved TKV as an enrichment biomarker for ADPKD [7], meaning that it can be used as a parameter for patient selection for clinical trials and treatment [7–9], although, the recognition that TKV change is not a linear trait should always be kept in mind [10].

Given the debatable accuracy of TKV measurement by two-dimensional ultrasound (2DUS) via the ellipsoid formula in ADPKD adults [11–14], and the exposure to radiation and iodinated contrast medium that would result from (repetitive) CT scans [15], MRI is now the gold standard for TKV quantification [14–16]. Different techniques have been studied to measure TKV from MRI: whole kidney contouring method, stereology, mid-slice and ellipsoid method, in a manual or (semi-) automated manner, with the contouring method being the most accurate, but also the most time-consuming [14, 17–19].

Although 2DUS is now used worldwide to diagnose ADPKD [20], ultrasound TKV measurement via both ellipsoid formula and direct method, have been shown to be less accurate and less reproducible compared with MRI TKV, except for kidneys with a length less than 17 cm [12]. Importantly, ultrasound lacked the precision necessary to measure short-term (1-year) disease progression, required to assess the impact of therapy in adult ADPKD clinical trials [13]. However, over a longer period of follow-up (9.3 years), both ultrasound and MRI TKV and kidney length were demonstrated to be equal in predicting future stage 3 CKD [12].

Currently, disease progression predictors for ADPKD children are lacking. However, these need to be identified, given the growing interest in including children in registries and clinical trials [21], to assess early disease stages and to intervene before irreversible damage has occurred. Few studies, with small numbers, published kidney length via ultrasound or TKV via MRI in ADPKD children [22–25]. However, on the one hand, 2DUS has been reported to be less accurate than MRI in quantifying TKV, and on the other, MRI requires sedation or anesthesia in young children [26, 27], is generally more expensive, requiring skilled personnel, and is less readily available than ultrasound.

Although three-dimensional ultrasound (3DUS) TKV was shown to be accurate in non-ADPKD populations [28–31], to our knowledge, this alternative has never been studied in ADPKD patients.

The purpose of this study is to assess the value of 3DUS for kidney volume (KV) assessment in ADPKD children, in comparison with 2DUS- and MR-based KV measurements.

Materials and methods

Subjects

Children with ADPKD aged 6–18 years were eligible for inclusion in this cross-sectional monocentric study. ADPKD diagnosis was accepted if at least one renal cyst was visualized on ultrasound in a child from a known family with ADPKD [32] and/or in the case of a positive genetic analysis. Both kidneys were evaluated by the same senior pediatric radiologist with ultrasound, in both 2D and 3D modes, and MRI, to minimize inter-operator differences. The GFR was estimated according the adapted Schwartz formula [33].

Ultrasound acquisition and evaluation

For 2DUS, all patients were scanned in supine and prone position, with a broad spectrum curvilinear array transducer C9-2 or C5-1 MHz (EPIQ7, Philips Health Systems [Royal Philips], Best, The Netherlands), according to the patients' size. Measurement of the renal bipolar length and, perpendicular to this plane, renal width and height, at the level of the hilum were performed, with the patient in a prone position. 3DUS examination was performed using an X6-1 PureWave xMatrix Transducer (EPIQ7, Philips Healthcare, Best, The Netherlands). Ultrasound data were stored and sent to PACS and QLab software (Philips Healthcare, Best, The Netherlands) for calculation of the left and right KV separately. First, KV was calculated using the ellipsoid method ($\text{length} \times \text{transverse width} \times \text{height} \times \pi/6$) on the sagittal and axial 2DUS image ($\text{KV}_{2\text{DUS}}$), after which the same formula was applied to the reconstructed axial and sagittal 3DUS image in QLab ($\text{KV}_{3\text{DUS-ellipsoid}}$; Fig. 1). Third, renal contouring on up to nine segments (minimum of six, dependent on kidney length) of the axial 3DUS dataset was performed, also called “stacked contour volumetry” ($\text{KV}_{3\text{DUS-contour}}$; Fig. 2).

MRI image acquisition and evaluation

Kidney MRI images were acquired on a 1.5-T Philips Ingenia scanner (Philips Healthcare, Best, The Netherlands) within the first few months after ultrasound (median 38 days, range 0–76 days, with one 17-year-old outlier scanned on MRI 205 days before ultrasound, because of an unavailable 3DUS at first examination). The MRI protocol consisted of coronal and axial heavily T2-weighted (T2w) turbo spin-echo (TSE) images in addition to axial T2w-TSE and axial T1-weighted spoiled gradient echo images. KV measurements

Fig. 1 Representative **a, b** 2DUS and **c, d** 3DUS images of the left kidney in a 6-year-old autosomal dominant polycystic kidney disease (ADPKD) patient, as used for ellipsoid volumetric estimations. **a, c** Longitudinal images demonstrate the bipolar length (arrows, lines), **b, d** axial images show transverse width and height (arrows). Renal cysts can be seen in the upper and lower poles of the kidney (**a**, blue arrowheads). 3DUS images were reconstructed by the QLab software

were performed on the axial heavily T2w-TSE, with the following parameters: 45 slices; field of view of 400×350 mm; 4-mm slice thickness; 0.4-mm slice gap; repetition time (TR) of 768 ms; echo time (TE) of 340 ms; 288×220 image matrix; 1 average; 2 min 15 s acquisition time. Imaging was performed without administration of intravenous contrast

medium or anesthesia. We preferentially used the axial heavily T2w-TSE for renal volumetry, as with this sequence, cysts lighten up and sometimes small and extra renal bulging cysts can be detected more easily. It was recently demonstrated in adult ADPKD patients that KV measurement performs similarly when using T2- compared with T1-weighted images,

Fig. 2 Contour volumetry in a 6-year-old autosomal dominant polycystic kidney disease (ADPKD) patient. In the same patient as in Fig. 1, contour volumetry on a 3DUS-acquired image in QLab was reconstructed in the **a** sagittal, **b** axial, and **c** coronal planes. **d–f** Renal volume measurements by means of renal contouring on up to nine segments (minimum of six) of

the axial 3D ultrasound data set, also called stacked contour volumetry. On **d**, the sagittal image, the segments that need to be delineated are identified (in the case presented, 7 segments), each of which is then delineated on the **e** axial reconstructed 3DUS image

although T2 are more often of sufficient quality for volume measurement and result in slightly lower intra- and interreader variability [34].

Magnetic resonance images were evaluated using software developed in-house based on the MeVisLab framework (MeVis Medical Solutions, Bremen, Germany). Using this software, the renal contour was traced manually on all axial (short-axis) slices, including extra-renal bulging cysts and excluding the extra-renal pelvis, and KV (KV_{MRI}) was assessed by adding all the delineated areas and multiplying this by the distance between slice centers (Fig. 3).

Statistical analysis

As there was no significant difference in KV between the right and the left kidneys (data not shown), comparison of KV between ultrasound and MRI measurements was performed

using the left and right kidneys as independent entities. Therefore, we report KV instead of TKV. Moreover, we compared KV assessment from different techniques, performed simultaneously within the same patient, resulting in inherently paired data. As we focused on the delta (KV) between the techniques, dividing the different volumes by the same parameter, namely height, would not affect our results. Therefore, we report KV instead of htTKV.

First, differences and correlations among KV_{2DUS} , $KV_{3DUS-ellipsoid}$, $KV_{3DUS-contour}$, and KV_{MRI} were evaluated. Correlations between the volumetric datasets were assessed using Pearson's correlation coefficient (r), with their corresponding P values. The differences between the measurements were evaluated with the Wilcoxon signed rank test. Second, the level of agreement or variability between the KV_{US} and KV_{MRI} was determined using Bland–Altman plots. Third, the optimal linear regressions of the ultrasound KV measurements (KV_{US}) to KV_{MRI} were determined. Correction factors for converting the ultrasound measurements to MRI measurements were then extracted from these optimal regression formulas. After applying this factor, the error between KV_{US} and KV_{MRI} was determined and Bland–Altman plots were generated using the corrected data. All analyses were performed using Analyze-it for Microsoft Excel 4.60.1 (Analyze-it Software, Leeds, UK), with a P value below 0.05 indicating statistical significance.

Results

Thirty patients (18/12 males/females) with a median (range) age of 14 (8–18) years were included, leading to 60 kidneys for independent volumetric comparison. Patient characteristics are shown in Table 1. Mean (SD) KV (mL) were: 159

Fig. 3 Representative contour volumetry on magnetic resonance imaging (MRI) of the left kidney in a 30-year-old autosomal dominant polycystic kidney disease (ADPKD) patient. **a** Coronal and **b** axial heavily T2-weighted single-shot turbo spin-echo MRI of the left kidney. On the axial images, contours around the entire kidney are traced, including the extra-renal pelvis (**b**, contours). **c** 3D visualization of the entire kidney contours

Table 1 Study population characteristics

Characteristic	Data
Number of patients	30
Male, n (%)	18 (60)
Age (years)	14 (8–18)
Height (cm)	161 ($\pm$ 18)
Weight (kg)	52 ($\pm$ 20)
BMI (kg/m^2)	19 ($\pm$ 4)
Serum creatinine (mg/dL)	0.63 ($\pm$ 0.14)
eGFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$) ^a	109 ($\pm$ 17)

Values expressed with a “ $\pm$ ” sign are the mean $\pm$ standard deviation; the others represent median (minimum, maximum)

BMI body mass index, eGFR estimated glomerular filtration rate

^a eGFR was calculated using the Schwartz 2009 formula [33]

Fig. 4 Box-and-whisker plots for renal volume measured via the four approaches examined. *Box* indicates interquartile range, with the median indicated by the *horizontal line*, and the *whiskers* show range. All ultrasound measurements were significantly smaller than the contour magnetic resonance imaging (MRI) approach ($P < 0.001$)

(± 101) for KV_{2DUS} ; 169 (± 105) for $KV_{3DUS-ellipsoid}$; 185 (± 110) for $KV_{3DUS-contour}$; and 206 (± 130) for KV_{MRI} ; medians (minimum, maximum) were 133 (40, 566); 145 (39, 559); 152 (51, 577) and 167 (59, 822) respectively (Fig. 4). KV_{US} were consistently significantly smaller than KV_{MRI} ($p < 0.001$), with the largest underestimation on the 2DUS and ellipsoid 3DUS examinations of 47 and 37 mL respectively, whereas the contour 3DUS technique resulted in the smallest error, namely on average 21 mL, as shown in the Bland–Altman plots (Fig. 5).

Correlations between all ultrasound and MRI volumetric data were significant. The correlation was strongest between KV_{2DUS} and KV_{MRI} , followed by $KV_{3DUS-contour}$ vs KV_{MRI} and $KV_{3DUS-ellipsoid}$ vs KV_{MRI} , with Pearson's correlation coefficients of 0.96, 0.94, and 0.89 respectively ($P < 0.001$ for all; Fig. 6).

From the linear regression analysis, we extracted correction formulas, aiming at the approximation of ultrasound to MRI volumetric data. For 2DUS volumetry, the formula is: $KV_{MRI} = 8.60 + 1.24 \times KV_{2DUS}$. The formulas for ellipsoid and contour 3DUS volumetry are: $KV_{MRI} = 19.47 + 1.11 \times KV_{3DUS}$.

Fig. 5 Bland–Altman of the ultrasound measurements (before correction) via **a** 2DUS, **b** 3DUS-ellipsoid, **c** 3DUS-contour, all with regard to contour magnetic resonance imaging (MRI) volumes (on a logarithmic scale). For each evaluation method, the cumulative absolute error

compared with the MRI imaging measurements is shown in **d**. In each graph, **a–c**, the *filled circles* indicate the right kidneys, and the *empty circles* the left kidneys

Fig. 6 Linear regression analysis for **a** KV_{2DUS} , **b** $KV_{3DUS-ellipsoid}$, and **c** $KV_{3DUS-contour}$ in correlation with KV_{MRI} . The formula for the *black lines* represents the correction factors that can be applied to match the

ultrasound measurements with those on contour magnetic resonance imaging (MRI). On each graph, the *filled circles* indicate the right kidneys, and the *empty circles* the left kidneys. *KV* kidney volume

ellipsoid and $KV_{MRI} = 0.44 + 1.11 \times KV_{3DUS-contour}$ respectively. After applying the correction factors, the Bland–Altman plots again showed an overall lower variability and error for $KV_{3DUS-contour}$ compared with KV_{2DUS} , with the $KV_{3DUS-ellipsoid}$ measurement performing the worst (Fig. 7). However, the error is strongly dependent on kidney size, with better approximation of the corrected KV_{US} to KV_{MRI} in smaller KV (Fig. 7d). For instance, for $KV \leq 300$ mL, the cumulative average absolute error after applying the correction factor was 16 mL for $KV_{3DUS-contour}$ vs 18 mL for KV_{2DUS} and 22 mL for $KV_{3DUS-ellipsoid}$.

Only a few kidneys (3 out of the 60 included) were exceptionally large, with a 2DUS renal length of 18.1, 17.1, and 16.8 cm respectively. These understandably provided the largest error; however, as we found that their effect on the errors after correction was negligible, they were not excluded from the dataset.

Discussion

We report to our knowledge the first study to evaluate 3DUS in pediatric ADPKD and demonstrate that $KV_{3DUS-contour}$ represents a valuable alternative to KV_{MRI} in this population. This novel technique may be used for the follow-up of children with ADPKD, to avoid the burden and costs of MRI.

Overall in our cohort, ultrasound measurements underestimated KV in comparison to MRI. First, for the ellipsoid formula-based measurements, $KV_{3DUS-ellipsoid}$ and KV_{2DUS} , it is well known that volumetry based on applying this formula consistently and significantly underestimates the true KV [11, 35]. In a recently published study, performed in small ($N = 14$) adult ADPKD cohorts, this was confirmed and explained by the presence of exophytic cysts [14]. Although a study carried out in the CRISP cohort showed overestimation

Fig. 7 Bland–Altman plots detailing the error of the ultrasound measurements (after correction). **a** 2DUS, **b** 3DUS-ellipsoid, **c** 3DUS-contour, all with regard to contour magnetic resonance imaging (MRI) volumes (on a logarithmic scale). For each evaluation method, the cumulative absolute error after correction compared with the MRI

measurements is shown in **d**, i.e., the average absolute error (after correction) for all kidneys smaller than or equal to the size on MRI indicated on the X axis (logarithmic scale). On each graph **a–c**, the *filled circles* indicate the right kidneys, and the *empty circles* the left kidneys

of renal volumes by ultrasound measurement compared with MRI, this was a multicenter study, performed at different hospitals with different ultrasound devices and low-frequency probes. The error differed among centers, with 2 centers showing large mean overestimations and 2 centers showing slight underestimations [13]. Also, our data, all collected from a single center by a single observer, are in line with those of an *ex vivo* study, demonstrating an average of 24% underestimation when calculating the renal volume, applying the ellipsoid formula to both ultrasound and MRI images [36]. Moreover, we should keep in mind that ultrasound volumetry in adult ADPKD patients is different from that in children; in adults, the extremely enlarged kidneys exceed the sweep of the ultrasound probe [15].

Second, for KV_{3DUS-contour} the KV underestimation by this ultrasound technique compared with MRI is consistent with the literature in pediatric non-ADPKD populations [29, 30]. The reason for this observation is not well understood, but in our opinion, it might be explained by the lower resolution

generated by the X6-1 matrix 3DUS transducer compared with the commonly used 2D transducers, especially in larger volumes. In the latter, this is also because of the mechanically limited field of view of the 2D- and 3DUS probe, as seen in adult ADPKD patients [31, 37].

As our study demonstrated a significant correlation between the different ultrasound modalities and MRI volumetry, even higher than reported in the adult CRISP cohort [13], we were able to provide correction factors. As these are only applicable to this specific population, previous validation in a large sample cohort is required to obtain generalizable correction factors. Then, these offer the opportunity to convert KV from one method to another, which is important to longitudinally evaluate a pediatric cohort, of whom KV was followed based on 3DUS, into adolescence and adulthood, when their KV is assessed via MRI. However, as the current work shows remaining errors after correction, complete interchangeable use of ultrasound and MRI volumetric data cannot yet be established. The interplay between MRI volumetry reproducibility and ultrasound measurement robustness, in

addition to their effect on correction factors, needs to be examined in larger studies in the future.

Compared with MRI, we found that for both uncorrected and corrected data, the variability and error was slightly lower in corrected $KV_{3DUS-contour}$ vs corrected $KV_{3DUS-ellipsoid}$ and KV_{2DUS} data. The latter may be explained by the fact that a kidney, especially a polycystic one, is not a true ellipsoid organ, as the ellipsoid formula assumes [11]. Overall, $KV_{3DUS-ellipsoid}$ performed the worst and therefore should not be considered an alternative to KV_{MRI} , independent of the KV.

Specifically for smaller KV, ultrasound approximates MRI volumes better than for larger KV, with $KV_{3DUS-contour}$ performing the best (Figs. 5d and 7d). Although the difference with KV_{2DUS} is small, $KV_{3DUS-contour}$ tends to demonstrate less variability. Therefore, $KV_{3DUS-contour}$ may be the most appropriate method for assessing KV in ADPKD children, where small volume changes over time need to be identified. Despite the fact that TKV is not yet a validated disease progression marker in children, it represents an important parameter to monitor closely in ADPKD children, especially in the ongoing longitudinal follow-up registries. This is supported by the observation that hypertensive (blood pressure $\geq$ 95th percentile for age, height, and gender) children with ADPKD have significantly higher TKV compared with normotensive (blood pressure $<$ 95th percentile) subjects [22].

Our study is limited by the sample size. Moreover, the additional 3DUS examination and the post-processing study lengthen the procedure and analysis time. It is, however, an enormous advantage of 3DUS stacked contour volumetry that the incorporation of cysts bulging out of the renal contour is feasible, in contrast to 2DUS. Also, renal volumetry by means of 3DUS in ADPKD, and more specifically in a pediatric ADPKD cohort, with comparison of KV measurements on paired 2DUS, 3DUS, and MRI, has to our knowledge never been published. Importantly, the examinations and their analyses were performed by a single, senior pediatric radiologist to limit possible inter-observer variability. However, intra-observer variability and more importantly reproducibility of the ultrasound measurements could not be evaluated in the current study, and should be examined in a future larger scale study.

To conclude, this is the first report demonstrating that 3DUS represents a novel and valuable method for KV measurement in a young pediatric ADPKD cohort. Despite the observed KV underestimation of ultrasound compared with MRI, applying a correction factor may overcome this error. Moreover, the method tended to be more accurate in lower volumes, in accordance with the volumes of a young pediatric population. Also, in the longitudinal follow-up of children with ADPKD, small volume changes are to be expected. Therefore, this work provides evidence to have children with ADPKD followed-up with 3DUS instead of other KV-

measuring modalities. As a future perspective, the sequential performance of $KV_{3DUS-contour}$ measurement in children may reveal a critical threshold volume, identifying those children at a high risk for rapid disease progression. Based on our current observation, we expect this volume to be lower than that based on MRI.

Compliance with ethical standards The study was conducted according to the Declaration of Helsinki and the guidelines of Good Clinical Practice. Study approval was obtained from the local ethics committee (approval number S58230), and all patients and their parents gave written, informed consent.

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