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ULTRASOUND

Autosomal dominant polycystic kidney disease: new role for ultrasound

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Abstract

Objectives To evaluate the accuracy of US in calculating renal volumes and renal resistive index (RRI) that was obtained using a new method in patients with autosomal dominant polycystic kidney disease (ADPKD).

Methods In this prospective study, US and MRI were performed in 57 patients with ADPKD (31 female and 26 male; age range, 19–79 years) between August 2017 and May 2018. The volumes determined using US and MRI were compared. The ellipsoid formula was re-evaluated using different multipliers. RRI was obtained 1.5–2 cm distal to the outlet of main renal arteries. The relationship between mean RRI, renal function tests, and kidney volumes and difference between mean RRI of ADPKD patients with and without renal failure were investigated using a two-sided independent samples *t* test and Pearson correlation test. Interobserver agreements for volume assessments and RRI measurements were determined.

Results By changing the ellipsoid formula, a very good agreement was found (ICC 0.970 for the right kidney and ICC 0.973 for the left kidney). The mean RRI in the right renal artery was 0.61 ± 0.07 and in the left renal artery 0.63 ± 0.06. The mean RRI of ADPKD patients with renal failure was significantly higher than that of patients without renal failure ($p = 0.005$). There was a significant correlation between mean RRI and renal function tests.

Conclusion The accuracy of the US in calculating renal volumes increases by adapting the ellipsoid formula. RRI may be used for the management of ADPKD independently of volumes.

Key Points

- *The accuracy of ultrasonography for renal volume measurement increases by changing the classical ellipsoid formula.*
- *Renal resistive index measured by color Doppler ultrasonography is helpful for the management of autosomal dominant polycystic kidney disease.*
- *The role of Doppler US in autosomal dominant polycystic kidney disease should increase as a result of our findings.*

Keywords Polycystic kidney, autosomal dominant · Renal artery · Kidney · Renal insufficiency · Ultrasonography, Doppler

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Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
AP	Maximum anteroposterior distance
BUN	Blood urea nitrogen
CCC	Concordance correlation coefficient
eGFR	Estimated glomerular filtration rate
H	Maximum renal height
ICC	Intraclass correlation coefficient
ML	Maximum mediolateral distance
MRI	Magnetic resonance imaging
RRI	Renal resistive index
TKV	Total kidney volume
US	Ultrasound

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease. It is a result of mutation in the PKD1 or PKD2 genes and can lead to end-stage renal failure. ADPKD is characterized by cyst formation and growth. The prevalence of ADPKD is 1/400 and 1/1000 with autopsy and without autopsy, respectively [1].

Imaging is often used for the diagnosis and management of ADPKD. US is important for these purposes [2] due to high sensitivity, availability, non-invasiveness, and low cost [3–5].

Standard serum-based parameters are used for evaluating progression of ADPKD in routine clinical management, but are usually normal in the early phase of the disease [6]. Recently, total kidney volume (TKV) was approved as a proper imaging parameter for clinical trials by both the U.S. Food and Drug Administration and the European Medicines Agency [7, 8]. MRI is the preferred imaging tool for TKV measurement in clinical trials, but the use of MRI in routine clinical management is limited by cost, availability, and scanning and processing (TKV) time.

Renal function can be evaluated with color Doppler US in acute and chronic renal failure [9–11]. Renal resistive index (RRI) ((peak systolic velocity − end diastolic velocity) peak systolic velocity) is one of the semi-quantitative indices measured by color Doppler US. Decreased renal blood flow exists in early stages of disease and is an important factor in the progression of ADPKD [12]. Thus, disease progression can be assessed by using color Doppler US [13].

The purpose of this study was to evaluate the accuracy of US in both calculating renal volumes in comparison with MRI as the reference standard and RRI obtained using a new method in ADPKD for functional evaluation.

Materials and methods

Ethics

This prospective single center study was approved by the local Ethics Committee (case number: 2017/345). Informed consent was obtained from all patients.

Patient selection

US and MRI were performed in 57 patients with ADPKD (31 female and 26 male; age range, 19–79 years) between August 2017 and May 2018. Obese patients were excluded because of the limitation of gantry opening and table weight limits for MRI and insufficient image quality for US. Patients with cardiac

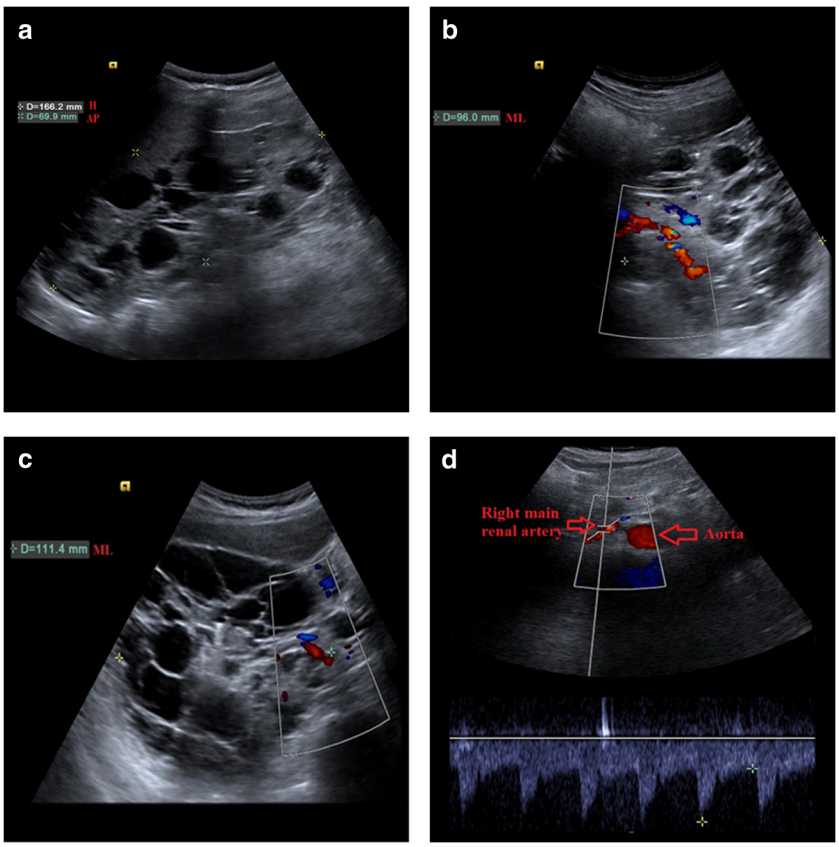

Fig. 1 Ultrasonography (US) and Doppler measurements. **a** B-mode US in a 50-year-old woman shows maximum renal height (*H*) and maximum anteroposterior distance (AP) on the right. **b** Color Doppler US in a 60-year-old man shows maximum mediolateral distance (ML) on the left. The left renal vasculature in the hilum is as parallel as possible to the axial plane. **c** Color Doppler US in a 43-year-old woman shows maximum mediolateral distance (ML) on the right. The right renal vasculature in the hilum is as parallel as possible to the axial plane. **d** Color Doppler US in a 55-year-old man shows where RRI was measured on the right. The exact location is 1.5–2 cm distal to the outlet

pacemaker, aneurysm clips, nerve stimulators, cochlear implants, and prostheses that are not suitable for MRI were excluded due to contraindication of MRI. Patients with claustrophobia who did not wish to perform MRI were excluded from the study. The median time between US and MRI was 5 days (range 1–14 days). US was performed after the blood tests such as blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), and creatinine were routinely performed.

Ultrasonography and Doppler measurements

Examinations were performed in the supine position for color Doppler US and supine, lateral, and posterolateral positions for B-mode to provide the optimal images. Fasting and bladder evacuation were recommended to the patients before examination. Measurements were done during breath hold using an Acuson S3000, Helx Evolution ultrasound system (Siemens) with a 6C1HD convex probe.

A single experienced radiologist (HI, with over 18 years of experience in renal US) first determined maximum renal height (*H*) in the sagittal plane, and then measured maximum anteroposterior distance (AP) in the same plane, perpendicular to the plane used to measure H (Fig. 1a). Maximum mediolateral distance (ML) was determined in the axial plane. For the purpose of measuring ML, the renal hilus was determined with color Doppler US. Measurement plane was performed in which the renal vasculature in the hilum was as parallel as possible to the axial plane (Fig. 1b, c). All measurements were obtained three times, and the mean value was noted. The ellipsoid formula was used for sonographic volume measurement (Volume: $H \times \mathrm{AP} \times \mathrm{ML} \times \pi\ 6$).

Main renal artery was detected at the outlet from the aorta with color Doppler US, and flow spectra were obtained 1.5–2 cm distal to the outlet (Fig. 1d). The flow spectra, which contained at least three consecutive waveforms, were defined as proper for measurements. To identify the main renal arteries, the superior mesenteric artery and left renal vein were used as landmarks for the right and left renal arteries, respectively. The right renal artery originates from the aorta, below the origin of the superior mesenteric artery, and the left renal artery lies posterior of the left renal vein, near the aorta (Fig. 2a, b).

RRI was measured automatically by the software that exists in the US system in 1.5–2 cm distal to the outlet of main renal arteries. All RRI measurements were obtained three times and the mean value was noted.

MRI protocol and kidney volume measurement

MR imaging was performed without gadolinium contrast with a 1.5-T system (MAGNETOM Aera; Siemens Healthineers) using the following sequences and parameters: breath-hold T1-weighted ultrafast gradient echo (VIBE) without fat saturation (coronal plane; FOV 350 mm, slice thickness 3 mm, TR 3.95 ms, TE 1.88 ms, averages 1, bandwidth 540 Hz/px, flip angle 5, voxel size 0.9 × 0.9 × 3 mm), T2-weighted turbo spin echo without fat saturation (coronal plane; FOV 300 mm, slice thickness 5 mm, TR 2340 ms, TE 105 ms, averages 2, bandwidth 221 Hz/px, voxel size 0.8 × 0.8 × 5 mm), T2-weighted ultrafast spin echo (HASTE) with fat saturation (coronal plane; FOV 350 mm, slice thickness 3 mm, TR 1200 ms, TE 94 ms, averages 1, bandwidth 710 Hz/px, voxel size 1.1 × 1.1 × 3 mm). Mid-slice technique [14] was performed for kidney volume measurement by using post-processing Workstation (VitreaWorkstation, Version 4.1.51, Canon Medical Systems Corporation) on breath-hold T1-weighted ultrafast gradient echo MRI sequences.

Statistical analysis

To compare US and MRI in measuring kidney volume of ADPKD patients, Passing-Bablok regression analysis was performed and Bland-Altman plots were generated. Passing-

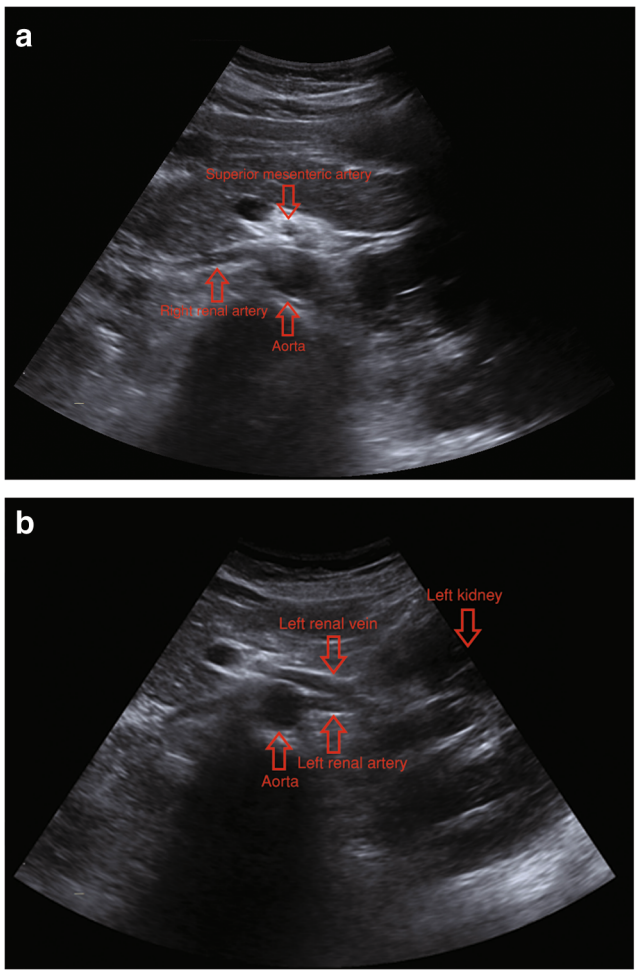

Fig. 2 Landmarks using to identify main renal arteries. **a** The right renal artery originates from the aorta, below the origin of the superior mesenteric artery, and (**b**) left renal artery lies posterior of the left renal vein, near the aorta

Table 1 Distribution of US and MRI measurements

Measurement	Left		Right	
	Median	25p–75p	Median	25p–75p
US ellipsoid volume (cm^3)	523.08	263.09–818.16	385.90	203.56–725.02
US length (cm)	16	12.95–18.50	14.30	12–17.45
US anteroposterior (cm)	7	5.30–8.20	6.30	4.95–7.90
US mediolateral (cm)	8.80	7.05–10.80	7.90	6.55–10.45
MRI volume (cm^3)	440	270.50–861	479	239–759.50

US ultrasound, *MRI* magnetic resonance imaging, *SD* standard deviation, *p* percentile

Bablok regression results are interpreted as follows: (i) constant error is assumed to be present when the 95% confidence interval of the model intercept excludes 0, (ii) proportional error is assumed to be present when the 95% confidence interval of the model slope excludes 1. Moreover, method agreements were assessed with intraclass and concordance correlation coefficients. Intraclass correlation coefficients were calculated by the average absolute differences of measurements.

All coefficient estimates are expressed with 95% confidence intervals. Agreement statistics are interpreted as follows: 0–0.20: poor agreement, 0.21–0.40: fair agreement, 0.41–0.60: moderate agreement, 0.61–0.80: good agreement, 0.81–1.00: very good agreement. The ellipsoid formula was re-evaluated using different multipliers between 0.40 and 0.92 in steps of 0.01. Intraclass correlation coefficients (ICC) were calculated in order to determine the optimal multiplier. Statistical difference was investigated between the mean RRI of the right and left renal arteries and the mean RRI of ADPKD patients with and without renal failure using a two-sided independent samples *t* test.

The Pearson test was used to assess the correlation between mean RRI, renal function tests, and kidney volumes (volumes measured by MRI). Interobserver agreements for volume assessments and RRI measurements were evaluated by ICC analysis between two radiologists (HI, SD) in a small group of patients (*n* 15). All analyses were done using TURCOSA

Table 2 Comparison and agreement of US and MRI methods in measuring kidney volumes of ADPKD patients

Measurement	Passing-Bablok regression		Agreement statistics	
	Intercept	Slope	ICC	CCC
Left				
Ellipsoid formula (multiplier = 0.52)				
Coefficient estimate	− 0.250	1.006	0.972	0.946
95% CI	(− 42.885/61.580)	(0.860/1.114)	(0.954/0.984)	(0.911/0.968)
Interpretation	No constant error	No proportional error	Very good agreement	Very good agreement
Ellipsoid formula (multiplier = 0.55)				
Coefficient estimate	− 1.035	1.067	0.973	0.947
95% CI	(− 45.441/63.644)	(0.912/1.178)	(0.954/0.984)	(0.912/0.969)
Interpretation	No constant error	No proportional error	Very good agreement	Very good agreement
Right				
Ellipsoid formula (multiplier = 0.52)				
Coefficient estimate	14.684	0.823	0.933	0.872
95% CI	(− 27.357/41.396)	(0.724/0.993)	(0.873/0.963)	(0.819/0.910)
Interpretation	No constant error	Proportional error is present	Very good agreement	Very good agreement
Ellipsoid formula (multiplier = 0.74)				
Coefficient estimate	18.574	1.190	0.970	0.927
95% CI	(− 46.139/51.544)	(1.044/1.437)	(0.907/0.992)	(0.880/0.956)
Interpretation	No constant error	Proportional error is present	Very good agreement	Very good agreement

US ultrasound, *MRI* magnetic resonance imaging, *ADPKD* autosomal dominant polycystic kidney disease, *ICC* intraclass correlation coefficient, *CCC* concordance correlation coefficient, *CI* confidence interval

(www.turcosa.com.tr, Turcosa Analytics Solutions Ltd Co) and R 3.2.0 (www.r-project.org) software. A p value less than 5% was considered statistically significant.

Results

Distribution of US and MRI measurements is shown in Table 1. A very good agreement was found between volumes measured by MRI and US (ICC 0.933, CCC 0.872 for the right kidney and ICC 0.972, CCC 0.946 for the left kidney). If the multiplier (π 6) in the classical formula of the ellipsoid was changed to 0.74 and 0.55 for the right and left kidneys respectively, a better agreement was found, especially for the right kidney (ICC 0.970, CCC 0.927 for the right kidney and ICC 0.973, CCC 0.947 for the left kidney) (Table 2 and Figs. 3 and 4).

The mean RRI in the right renal artery was 0.61 ± 0.07 and in the left renal artery 0.63 ± 0.06. Statistical significance was observed between the right and left RRI values ($p < 0.001$). The mean RRI in the presence of renal failure ($n = 18$) was significantly higher than in its absence ($n = 39$) (0.67 ± 0.06 vs. 0.61 ± 0.06 respectively; $p = 0.005$).

There was a significant positive correlation of mean RRI with both BUN and creatinine (r 0.311, p 0.033 for BUN and r 0.321, p 0.028 for creatinine). There was a significant negative correlation between mean RRI and eGFR (r − 0.324, p 0.026). No significant correlation was found between mean RRI and volume measured on MRI (r 0.064, p 0.670). Interobserver agreements for RRI measurements and measured renal volumes with US were as follows: ICC, 0.773 (0.470–0.902) and 0.740 (0.413–0.884) respectively.

Discussion

By changing the multiplier in classical ellipsoid formula from π 6 to a specific multiplier for each kidney (0.55 left kidney, 0.74 right kidney), a better agreement was found between US and MRI. This is especially true for the right kidney as the specific multiplier (0.74) is quite different from the conventional π 6. RRI that was obtained 1.5–2 cm distal to the outlet of main renal arteries was associated with BUN, creatinine, and eGFR independent of renal volumes and was a statistically significant indicator of renal failure (p 0.005). The reference standard for TKV measurement is MRI. One of the reasons has been the low accuracy of US. Because the shape of the kidney is not exactly ellipsoid, the classical ellipsoid formula is probably not reliable [15–17]. Our findings support the literature, especially for the right kidney. Right and left kidney growth in ADPKD may be different in shape because of their anatomic relationships with other organs, and the most likely explanation for our findings is the preservation of the ellipsoid shape in the left kidney. Another reason for the low accuracy is the different planes that are used for measurement of ML and AP [16, 17]. Hammoud et al [18] investigated the correct plane for measurements and found that ML in the axial plane is the best for volume measurements with US. However, obtaining the actual axial plane is problematic. For this purpose, we recommend the use of color Doppler US. We measured ML in the plane that includes as much as possible the renal vasculature in the hilum. Other suggested reasons for the low accuracy are poor imaging access due to gas distension, body habitus, ribs, and respiratory artifacts [19]. This was solved in this study by varying patient's position, especially in the case of large kidney. Recent studies have shown that newer US imaging techniques like three-dimensional sonography can increase the accuracy [20–24], but three-dimensional US is not an appropriate imaging technique for routine management of ADPKD as it requires advanced training and experience and is not widely available.

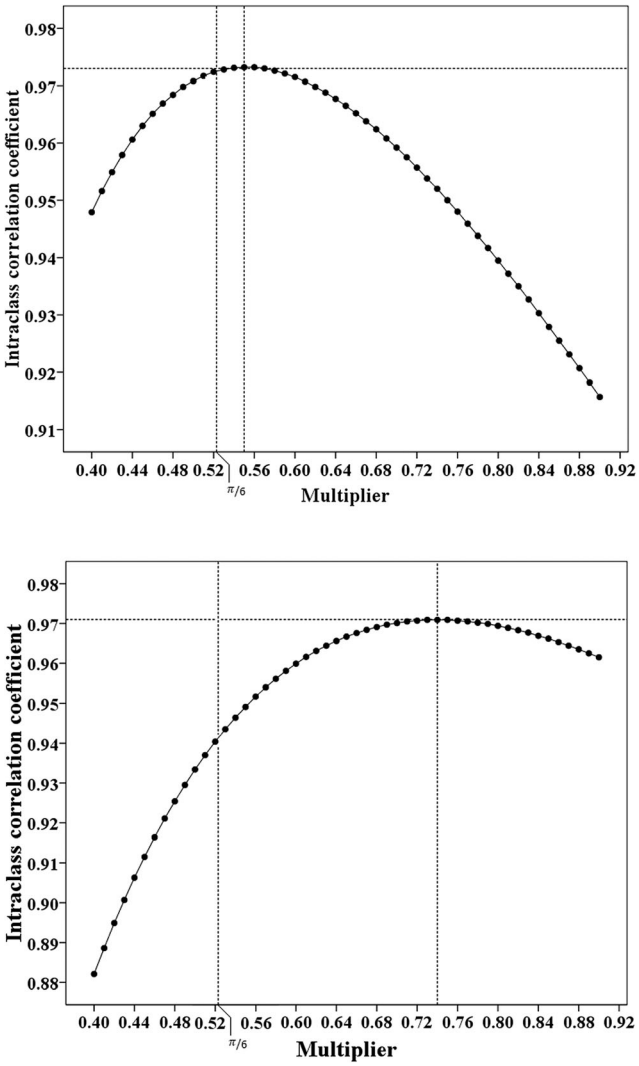

Fig. 3 Identifying the optimal multiplier of the ellipsoid formula in measuring the (**a**) left and (**b**) right kidney volumes of ADPKD patients

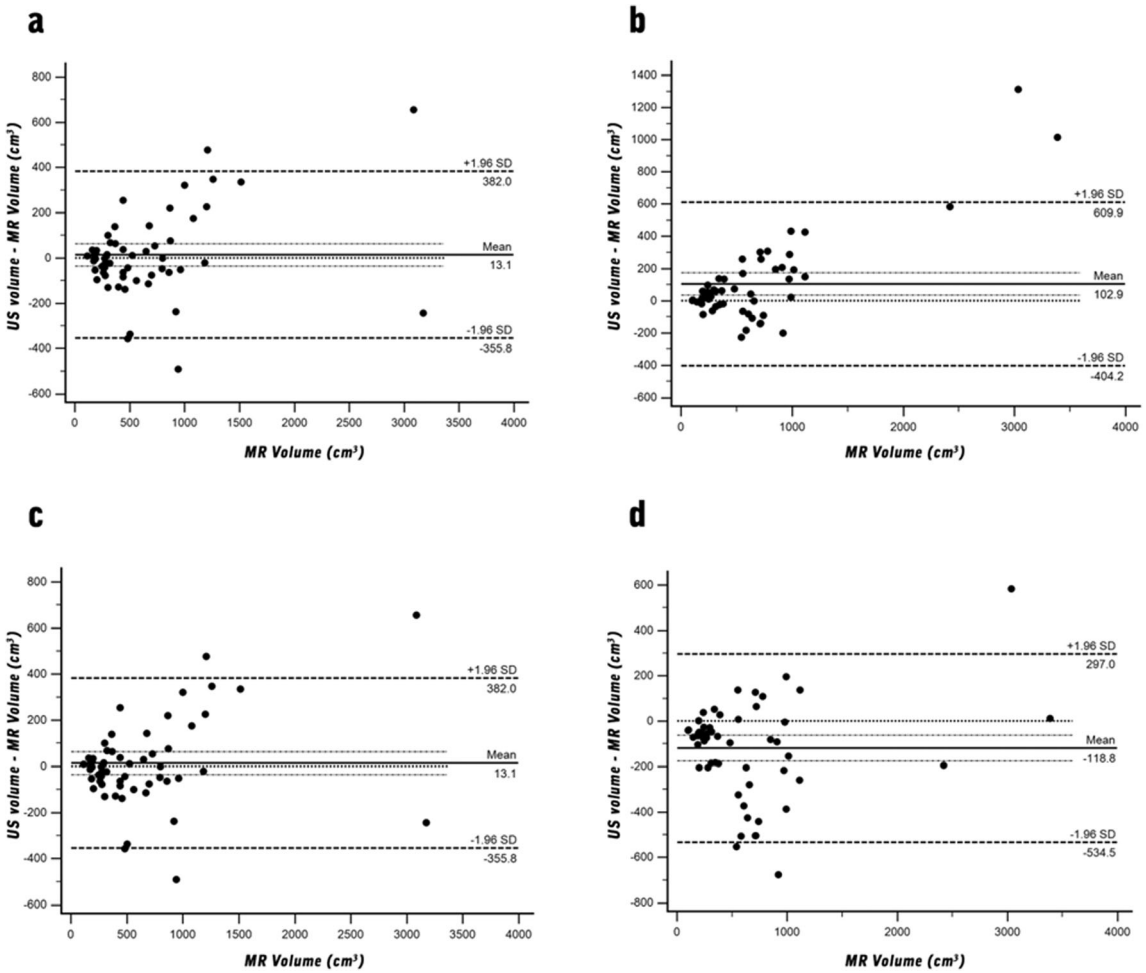

Fig. 4 **a** Bland-Altman plots demonstrating the agreement of MR volumes and US volumes of left kidneys calculated via ellipsoid formula (multiplier = 0.52). **b** Bland-Altman plots demonstrating the agreement of MR volumes and US volumes of right kidneys calculated via ellipsoid formula (multiplier = 0.52). **c** Bland-Altman plots demonstrating the agreement of MR volumes and US volumes of left kidneys calculated via adjusted ellipsoid formula (multiplier = 0.55). **d** Bland-Altman plots demonstrating the agreement of MR volumes and US volumes of right kidneys calculated via ellipsoid formula (multiplier = 0.74)

While Doppler US has a premium role in renal diseases in general [25–29], its use is limited in ADPKD, mainly because identification of intrarenal arteries is difficult.

The intrarenal arteries were assessed in the upper, medium, and lower parts of the kidneys in previous studies [13, 30, 31] but this assessment is indistinct in ADPKD due to the large size of the kidneys. In this study, the measurements were not performed at the level of intrarenal arteries, and the exact location was 1.5–2 cm distal to the outlet of the main renal artery. We found good interobserver agreement using this approach. This approach may standardize identification and monitoring of RRI, enabling dynamic assessment of the renal blood flow as a semi-quantitative index. This is important for the management of ADPKD patients because progression varies across patients and even within family members [32, 33]. Although dynamic assessment of renal blood flow is feasible with MRI [34], it is not done in daily practice. No correlation was found between mean RRI and the volume measured on MRI. This finding shows that RRI may reflect progression independently of renal volumes.

In terms of RRI measurements, there was a statistically significant difference between the right and left main renal arteries ($p < 0.001$). It is thought that both kidneys are equally affected in ADPKD but renal function may deteriorate in one of them due to local complications like urolithiasis and urinary tract infection. This may lead to different RRI values between the right and left main renal arteries. The mean RRI in this study was lower in patients with or without renal failure than that in other studies that measured mean RRI in intrarenal arteries [13, 30]. Compression and displacement of intrarenal arteries by numerous cysts may explain this difference.

There are several limitations to this study. First, this is a single-center study and the number of patients is relatively low. Second, cardiac dysfunction, age, and use of

antihypertensive medications, all of which potentially affecting the RRI, were not taken into account.

In conclusion, the classical ellipsoid formula is inadequate for renal volume measurement; the accuracy of US can be increased by changing the formula. RRI may be used for the management of ADPKD independent of volumes by using a standardized approach.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Hakan İmamoğlu.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry Two of the authors have significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- diagnostic or prognostic study
- performed at one institution

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