Review Article

Update on the Application of Ultrasonography in Understanding Autosomal Dominant Polycystic Kidney Disease

CME Credits

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Abstract

With an estimated prevalence of 1 in 1000 individuals globally, autosomal dominant polycystic kidney disease (ADPKD) stands as the most prevalent inherited renal disorder. Ultrasonography (US) is the most widely used imaging modality in the diagnosis and monitoring of ADPKD. This review discusses the role of US in the evaluation of ADPKD, including its diagnostic accuracy, limitations, and recent advances. An overview of the pathophysiology and clinical manifestations of ADPKD has also been provided. Furthermore, the potential of US as a noninvasive tool for the assessment of disease progression and treatment response is examined. Overall, US remains an essential tool for the management of ADPKD, and ongoing research efforts are aimed at improving its diagnostic and prognostic capabilities.

Keywords: Autosomal dominant polycystic kidney disease, diagnosis, prognosis, ultrasonography

Introduction

Affecting an estimated frequency of 1 in 2500 to 1 in 400 individuals, autosomal dominant polycystic kidney disease (ADPKD) emerges as the prevailing hereditary kidney disorder.[1-3] ADPKD is characterized by the focal development and gradual enlargement of renal cysts, which commonly results in end-stage renal disease (ESRD) in over 75% of patients either during or after their sixth decade of life. Furthermore, ADPKD could be a systemic disorder because patients may have hepatic or pancreatic cysts, abdominal hernias, colonic diverticulosis, cardiac valvular lesions, or intracranial aneurysms.[4-6]

The main genetic abnormalities responsible for ADPKD are mutations in either the polycystic kidney disease-1 (*PKD1*) gene (found in 78% of disease pedigrees) or the polycystic kidney disease-2 (*PKD2*) gene (found in 15% of disease pedigrees).[7] *PKD1* encodes polycystin-1 (PC1) and *PKD2* encodes polycystin-2 (PC2).[8,9] PC1 and PC2 are located on the primary cilia of tubular epithelial cells, playing a crucial role in mechanotransduction and the regulation of cystogenesis.

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Increasing evidence substantiates that PC1 and PC2 suppress cystogenesis in a dose-dependent manner, and cyst formation transpires when the concentration of PC1 or PC2 drops below a specific threshold.[10,11] Mutations in other genes, including *DNAJB11, GANAB, PRKCSH*, and *SEC63*, cause milder forms of polycystic kidney disease (PKD) because proteins encoded by these genes are linked to maturation defects of PC1 or PC2.[12-14] The number and size of cysts, altered renal architecture, and renal function are largely determined by the mutations of these genes.

Ultrasonography as a Diagnostic Tool for Autosomal Dominant Polycystic Kidney Disease

Ultrasonography (US) has emerged as the preferred imaging method for diagnosing ADPKD because of its widespread availability, relatively low cost, lack of radiation exposure, and noninvasiveness.[15,16] It is also ideal for screening patients'

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family members. In addition to suggesting a diagnosis, US can be used to assess cyst complications. The ultrasonographic features of ADPKD, in general, include the presence of multiple cysts of varying sizes in both kidneys, usually starting at the age of 30–40 years, and an increased number and size over time. The cysts appear as round or oval, well-defined, anechoic structures with posterior enhancement (brighter area behind the cyst). Calcification may be observed in some cases. Cysts with hemorrhage or infection demonstrate echogenic material. The parenchymal echogenicity is increased. In the advanced stages of this disease, the kidneys are enlarged and lack corticomedullary differentiation. Other features observed on US include increased kidney size, loss of normal kidney architecture, and dilatation of the renal collecting system. Cysts may also be detected in the liver, spleen, and pancreas.[17]

Differences in the ultrasonographic features of dominant polycystic kidney disease caused by different genes

Although US is a common imaging technique used to diagnose and monitor ADPKD, no specific ultrasonographic features distinguish ADPKD caused by *PKD1* mutations from that caused by *PKD2* mutations. Both types of ADPKD are characterized by the presence of multiple cysts in the kidneys. *PKD1*-associated cysts are more commonly found in the renal cortex, while *PKD2*-associated cysts are often found in the medulla. Patients with *PKD1* mutations generally have larger cysts, faster disease progression, and higher risk of complications. Those afflicted with *PKD1*-related ADPKD typically possess kidneys of considerably larger size, containing a greater number of cysts compared to patients with *PKD2*-related ADPKD.[7] Nonetheless, the rates of cystic growth remained unchanged, suggesting that the increased severity of *PKD1*-related ADPKD stems from the earlier development of a greater number of cysts, rather than their accelerated growth.[18] However, the severity and number of cysts can vary from person to person regardless of the underlying genetic cause.

In rare cases of ADPKD caused by mutations in other genes, such as *GANAB, DNAJB11, PRKCSH, LRP5*, and *IFT140*, the ultrasonographic features may be slightly different. Individuals with ADPKD caused by mutations in the *GANAB* gene had a milder form of the disease, with fewer and smaller cysts than those with ADPKD caused by *PKD1* or *PKD2* mutations.[19] Mutations in *PRKCSH* or *LRP5* are associated with isolated polycystic liver disease; however, they have also been reported to contribute to ADPKD.[7,20,21] ADPKD caused by mutations in *PRKCSH* or *LRP5* was also in a milder form [Figure 1]. Interestingly, in a reported series[22] and our observations [Figure 2], patients with *IFT140* mutation-related ADPKD tended to exhibit large cysts on renal US. However, these differences are not always present, and more research is needed to fully understand the ultrasonographic features of ADPKD caused by different genes.

Diagnostic ultrasonography criteria of autosomal dominant polycystic kidney disease

Renal US is the gold standard for the radiological diagnosis of ADPKD.[23] However, the diagnosis of ADPKD using US is less sensitive in younger patients because the cysts can be smaller and less numerous. Specific criteria based on age have been developed for *PKD1*,[24] followed by PKD2 and adults with unknown genotypes who are at risk. Table 1 illustrates the performance of US-based unified criteria for the diagnosis or exclusion of ADPKD.[25,26]

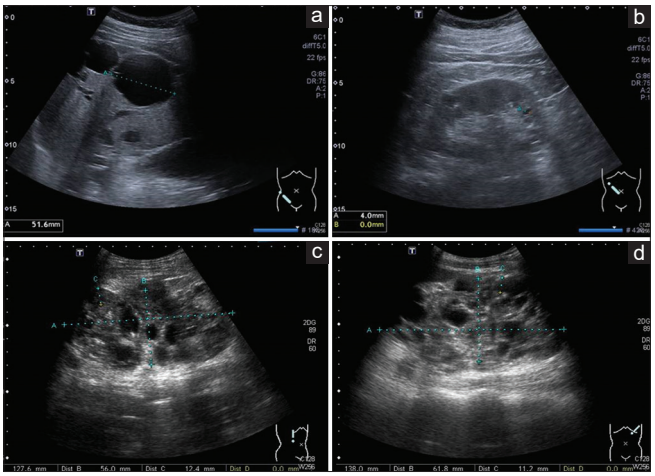

Figure 1: Ultrasonography (US) presentations of patients carrying *PRKCSH* or *LPR5* mutations. US in a 45-year-old man with *PRKCSH* mutations shows liver cysts (a) and few renal cysts (b). In a 42-year-old man carrying *LRP5* pathogenic mutations, US shows several small cysts in the right (c) and left (d) kidneys

Ultrasonography in evaluating renal manifestations of other diseases coexisting with autosomal dominant polycystic kidney disease

Horseshoe kidney or tuberous sclerosis complex (TSC) may coexist with PKD.[27,28] Horseshoe kidney is a congenital abnormality characterized by the fusion of both kidneys at the lower pole. It is frequently accompanied by other renal anomalies, such as ADPKD. In patients with horseshoe kidney and ADPKD, US can be employed to assess the structure and functionality of the kidneys.

TSC is a genetic disorder that results in the development of benign tumors in different organs, including the kidneys.[29] In patients with TSC, US can detect renal angiomyolipomas (AMLs), which are benign tumors comprising blood vessels, smooth muscle cells, and fat cells. Monitoring the size and growth of AMLs is crucial as they have the potential to cause bleeding or renal dysfunction if they reach a significant size. Notably, a subset of patients with TSC presented with characteristic features of ADPKD. Both the TSC type 2 and ADPKD type 1 genes are located within a limited portion of chromosome 16. In cases where deletions affect both of these genes, a condition called the TSC2/ADPKD1 contiguous gene syndrome arises, resulting in diverse manifestations of TSC and ADPKD phenotypes.[30] Over time, the renal US findings in TSC2/ADPKD1 contiguous gene syndrome evolve and exhibit a distinct pattern of renal disease, which differs from the usual presentation of TSC. At the initial stage, multiple cysts are

Table 1: Performance of ultrasound-based unified criteria for diagnosis or exclusion of autosomal dominant polycystic kidney disease

Age (years)	Number of cysts	*PKD1* (%)	*PKD2* (%)	Unknown genotype (%)
For diagnosis				
15–29	A total of ≥3 cysts	PPV=100; Sn=94.3	PPV=100; Sn=69.5	PPV=100; Sn=81.7
30–39	A total of ≥3 cysts	PPV=100; Sn=96.6	PPV=100; Sn=94.9	PPV=100; Sn=95.5
40–59	≥2 cysts in each kidney	PPV=100; Sn=92.6	PPV=100; Sn=88.8	PPV=100; Sn=90
For exclusion				
15–29	0	NPV=99.1; Sp=97.6	NPV=83.5; Sp=96.6	NPV=90.8; Sp=97.1
30–39	0	NPV=100; Sp=96	NPV=96.8; Sp=93.8	NPV=98.3; Sp=94.8
40–59	0	NPV=100; Sp=93.9	NPV=100; Sp=93.7	NPV=100; Sp=93.9

PKD: Polycystic kidney disease, ADPKD: Autosomal dominant PKD, NPV: Negative predictive value, PPV: Positive predictive value, Sn: Sensitivity, Sp: Specificity

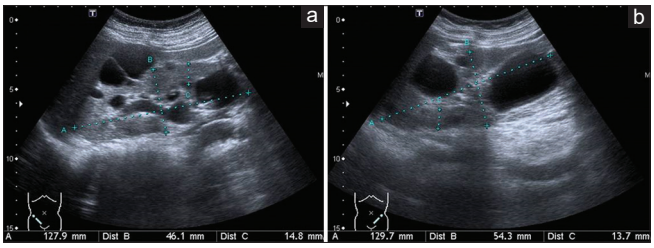

Figure 2: Characteristic ultrasonography (US) presentations of patients carrying *IFT140* mutations. US in a 54-year-old woman shows a few large cysts in the right (a) and left (b) kidneys

observed, and subsequently, there is a progressive increase in kidney size along with the growth of renal cysts.[31]

Ultrasonography as a Powerful Tool to Monitor Treatment Response

US is also useful in monitoring disease progression and treatment response in patients with ADPKD. Changes in cyst size and number observed on US can provide important information regarding disease activity and guide therapeutic decisions. Moreover, US can be used to assess the effectiveness of interventions, such as tolvaptan, a vasopressin V2 receptor antagonist that slows the rate of kidney function decline in patients with ADPKD.[32]

The assessment of total kidney volume (TKV) is of significant importance in evaluating the progression of ADPKD, as it enables the identification of individuals who are at a higher risk of rapidly developing ESRD[25,33] and allows for the evaluation of prognosis by predicting loss of renal function.[32,34,35] Clinical practice uses US to help prognostically stratify diseases. According to data from the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease and a position statement from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Working Groups of Inherited Kidney Disorders and European Renal Best Practice, in the absence of magnetic resonance imaging (MRI), patients below the age of 45 with kidneys measuring over 16.5 cm as determined by US are prone to experience rapid disease progression.[34,36-38] US is still currently the preferred imaging technique for diagnosing ADPKD although it has a number of drawbacks that can compromise the precision of TKV estimation and result in a wide range of variations when evaluating disease progression.[3]

Use ultrasonography to measure total kidney volume

The measurement of TKV using US involves imaging the kidneys in the transverse, longitudinal, and anteroposterior planes. To determine the TKV, the ellipsoid formula is employed, necessitating measurements of the length, width, and depth of each kidney. The measurements are recorded and used to calculate the volume of each kidney using the ellipsoid formula: TKV = $(\pi/6) \times$ length $\times$ width $\times$ depth. The volumes of both kidneys are added to obtain the TKV.[39] The imaging procedure is performed using a high-frequency transducer and can be performed in a relatively short time, making it convenient for use in clinical practice.

Comparison with computed tomography and magnetic resonance imaging in measuring total kidney volume

US, computed tomography (CT), and MRI are used to detect renal cysts and evaluate the TKV. While CT and MRI offer higher resolution and increased sensitivity in detecting renal cysts smaller than 1 cm in diameter, US is the preferred initial imaging method for diagnosing and monitoring ADPKD in most patients. This preference is mainly due to cost, radiation levels, and contrast exposure. Compared to CT or MRI, US provides images that are less sensitive and repeatable. Recently, in a prospective single-center study, the reproducibility of US measurements and the agreement between the calculated TKV using the ellipsoid formula by US and CT were examined. This study demonstrated good reproducibility of US measurements. In addition, it also showed that, using the maximum width in a transverse section, US-measured TKV was strongly correlated with the CT-measured TKV.[39] In addition, the early assessment of the efficacy of new therapies seems to be greatly enhanced by monitoring TKV. US for monitoring TKV proves advantageous due to its widespread availability, faster results, and dependable indications for the early evaluation of the effectiveness of current treatments. Table 2 summarizes the comparison of accuracy, advantages, and disadvantages in measuring kidney and cyst volumes using these three imaging modalities.

Recent Advances

Recent advances in US technology have improved the diagnostic capabilities for ADPKD. Three-dimensional (3D) US has been shown to improve the detection of small cysts and provide accurate measurements of cyst volumes.[45,46] Notably, Akbari *et al*. conducted a single-center prospective study revealing that TKV measurements in ADPKD using 3D US and US ellipsoid exhibit comparable bias and variability but are less accurate compared to MRI ellipsoid. In addition, all three methods demonstrate a high positive predictive value in predicting high-risk Mayo imaging classifications (MIC 1C–1E).[45] To address the challenges of using MRI and CT in pediatric patients, a new pediatric Leuven Imaging Classification based on 3D US has been suggested as a complementary approach to the MIC.[47] Promisingly, to optimize the performance of 3D US, Jagtap *et al*. developed an artificial intelligence (AI)-assisted system capable of

Table 2: Comparison of autosomal dominant polycystic kidney disease imaging modalities for measuring kidney and cyst volumes

Imaging modalities	US	CT	MRI
Accuracy	Can detect cysts >1 cm and 2–3 mm in diameter (new-generation scanners)[40] Coefficients of variation for TKV measurements: 18%–42%[36]	Can detect cysts ≥2 mm in diameter[41]	Can detect cysts ≥2 mm in diameter[41] Coefficients of variation for TKV measurements: 1.7%[36]
Advantages	No radiation or contrast medium Low cost Safety Widely available Established diagnostic criteria	Accurate assessments of TKV and cyst volume Highly correlated with US-derived results	No radiation, noniodinated contrast medium, high resolution, and tissue contrast 3D pictures Low bias, low inter- and intraoperator variability, accurately estimate TKV over short-time periods[42,43] Segmentation of individual cysts enables quantitative evaluation of disease severity in individuals with early or moderate ADPKD[43]
Disadvantages	Lacks precision and accuracy for detecting short-term changes in kidney volume	Ionizing radiation exposure and potentially nephrotoxic contrast agent	Patient-related factors (metallic medical implants, claustrophobia) Varying imaging results between scanners Lack of availability Cost Time needed for image acquisition[44]

TKV: Total kidney volume, MRI: Magnetic resonance imaging, ADPKD: Autosomal dominant polycystic kidney disease, CT: Computed tomography, US: Ultrasound, 3D: Three dimensional

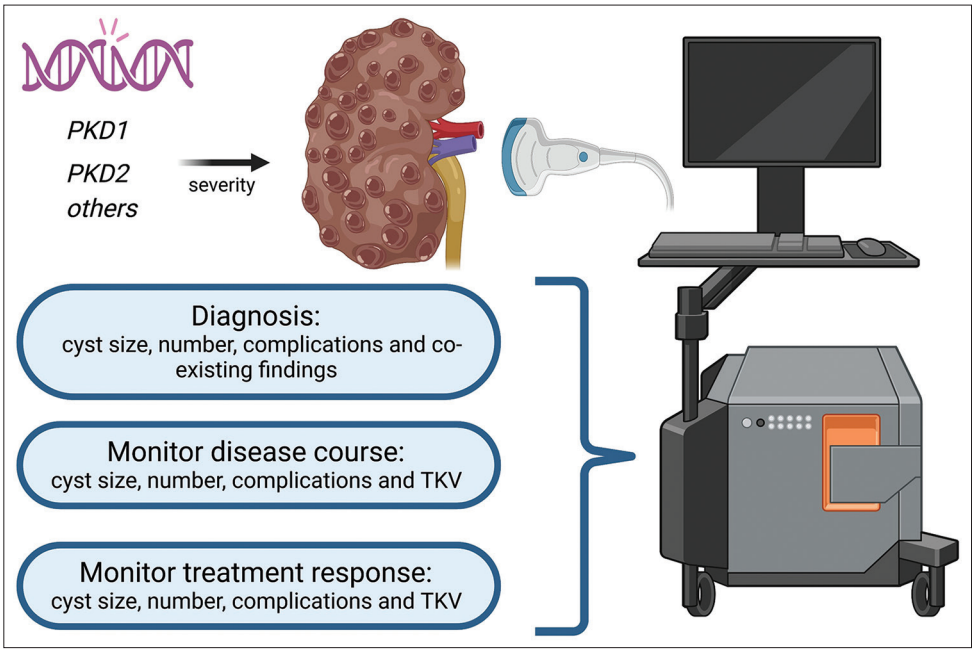

Figure 3: Application of ultrasonography (US) in the understanding of ADPKD. US is able to show features of ADPKD of various genetic backgrounds. It plays important roles in diagnosis, disease course monitoring, and treatment response assessment. The figure was created with BioRender.com. TKV: Total kidney volume

autosegmenting kidneys using 3D US to measure TKV. The performance of this AI-assisted system 3D US was similar to that of an MRI.[46] The clinical utility of these techniques in routine clinical practice is expected.

Conclusions and Perspectives

US remains an essential tool in the management of ADPKD, with its high diagnostic accuracy and the ability to monitor disease progression and treatment response [Figure 3]. Ongoing research efforts aim to further improve the diagnostic and prognostic capabilities of US in ADPKD and develop novel imaging systems that can provide additional information on disease activity and treatment efficacy.

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Conflicts of interest

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