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Imaging Approaches to Patients with Polycystic Kidney Disease

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Abstract

Imaging is an important approach to diagnosis, monitoring and predicting outcomes for patients with Autosomal Dominant polycystic Kidney Disease (ADPKD). This paper reviews three common clinical imaging techniques, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and their role in management of ADPKD. Ultrasonographic criteria for diagnosis in children and adults are reviewed. Total kidney volume (TKV), as measured by MRI, is suggested as important potential marker to determine disease progression and overall prognosis. Renal blood flow (RBF) and a novel approach to interpreting non-cystic renal parenchymal by CT images are other innovative imaging approaches described.

Keywords

polycystic kidney disease; image; potential marker

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder occurring in 1:400–1:1,000 live births. ADPKD is a heterogenous disorder, caused by mutations in at least two known genes, *PKD1* and *PKD2*, and is characterized by gradual renal cyst development and expansion ultimately resulting in massive kidney enlargement and end stage renal disease (ESRD). ADPKD is a systemic disorder with cysts occurring in the liver, and less frequently in the pancreas, spleen, thyroid and the subarachnoid space. Other extra-renal manifestations in ADPKD include the development of intracranial aneurysms, diverticular disease and inguinal hernias ¹.

ADPKD is relatively oligosymptomatic during the first three decades of life and renal insufficiency usually does not develop until the 4th decade. However, significant disease progression due to renal cyst formation and expansion occurs during this time. Although cystic development and expansion occur, the majority of patients with ADPKD maintain normal kidney function during cyst enlargement. Once serum creatinine concentration has risen above the normal range, extensive irreversible replacement of renal parenchyma due to cysts and pericystic fibrosis has occurred. Importantly, utilizing accurate and reliable imaging techniques that monitor cyst growth is critical to predict the outcome of and associated complications of ADPKD. Therefore, renal imaging is important not only from a

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diagnostic standpoint, but also with regard to monitoring disease progression in ADPKD. We will now review the recommended diagnostic radiologic approaches as well as standardized and innovative imaging modalities used for monitoring disease progression and severity in ADPKD.

Imaging to Obtain a Diagnosis of ADPKD

Mutations on at least two genes are responsible for ADPKD. In 85% of individuals, mutations in the *PKD1* gene on chromosome 16 (16p13.3-p13.1) are causative; most of the rest are caused by mutations in the *PKD2* gene on chromosome 4 (4q21-q23)². The mutations in *PKD1* or *PKD2* set into motion a complex array of molecular processes due to abnormal polycystin 1–2 complex function that ultimately lead to the aberrant proliferation of tubular epithelia cells, the expansion of the tubular lumen and the formation of peritubular cysts³. Although the clinical presentations of *PKD1* and *PKD2* patients are similar, *PKD1* mutations cause more renal cysts and earlier-onset of hypertension, renal failure and death than *PKD2* mutations^{3,4}. Therefore diagnostic criteria utilizing radiological imaging differ for individuals who carry *PKD1* vs. *PKD2* mutations.

Although genetic testing can be performed in ADPKD, renal imaging remains the preferred method of diagnosis. The accuracy of sequence analysis of both *PKD1* and *PKD2* genes approaches 88% in specialized centers^{5,6}, which provide a significantly lower detection rate than ultrasonographic imaging. Importantly, in those individuals who are less than 15 years of age, the relative accuracy of genetic testing vs. ultrasonographic imaging is similar for screening *PKD1* individuals and better in *PKD2* individuals⁷. Therefore, if imaging studies are negative in at risk (either parent has known ADPKD) individuals in this age group further genetic testing could be considered to confirm a diagnosis.

The presence of multiple renal cysts is required for a diagnosis of ADPKD. The number of cysts required for a diagnosis is age-based and increases in an age dependent manner given that simple acquired renal cysts occur with increasing frequency with age in the general population⁴. Ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are all used to detect renal cysts; CT and MRI demonstrate greater resolution and increased sensitivity for detecting renal cysts less than one centimeter in diameter. However, due primarily to cost, level of radiation and contrast exposure, ultrasound is the initial imaging modality of choice for diagnosing ADPKD in the majority of patients. Disease penetrance of ADPKD is high and ultrasound provides an overall sensitivity and specificity of 99% and 95% by age 30 for *PKD1* individuals^{1,4,5}. Given that patients with *PKD2* mutations usually associate with less severe disease, they tend to be under-diagnosed when utilizing Ravine's criteria⁶. Recently Pei and co-workers modified ultrasound criteria for a diagnosis of ADPKD, which unify the criteria for *PKD1* and *PKD2* mutations and effectively reduces false negative rates for diagnosis⁶. Currently criteria require the presence of three or more renal cysts, either unilateral or bilateral, for establishing the diagnosis for at risk individuals 15 to 39 years; four (two or more cysts in each kidney) for individuals 40 to 59 years; and eight (four or more cysts in each) for individuals who are 60 years or older⁶. Conversely, fewer than two renal cysts in at-risk individuals 40 years or older is sufficient to exclude ADPKD⁶. In addition, the presence of liver cysts, which are present in over 85% of ADPKD patients by the age of 30, can provide diagnostic confirmation, particularly in those without a positive family history of ADPKD⁷. (Table 1) (Figure 1)

Ultrasound screening for a diagnosis of ADPKD in 106 PKD1 children diagnosed by gene linkage analysis demonstrated a 25% false positive screening rate and a 38% false negative rate in those less than 5 years of age⁸. Whether other imaging modalities can provide a more accurate detection rate in this age group remains to be determined. Both CT and MRI

methods have greater sensitivity compared to ultrasonography for detecting cysts less than one centimeter in diameter and most likely will have enhanced diagnostic capabilities in this age group^{7, 9}. However, if MRI or CT imaging is to be used to establish diagnostic criteria for ADPKD, separate and new criteria would be required⁹. T2-weighted MRI is specially suited for producing high resolution images of fluid filled renal cysts and is not associated with radiation exposure that accompanies CT examinations. In addition, simple and complex cysts (Figure 2) can be easily differentiated on T1-weighted and T2-weighted MRI images without gadolinium exposure¹.

Imaging to assess disease severity and progression in ADPKD

Although ultrasound is currently the imaging modality of choice for a diagnosis of ADPKD, its utilization for assessing disease progression is limited. Ultrasonography is highly operator-dependent and produces images that are less sensitive and reproducible than CT or MRI. In addition, ultrasound cannot reliably detect small but significant changes in kidney size or small cysts that are less than one centimeter in diameter. Ultrasound based measurements of kidney volume are calculated by utilizing parameters based on a modified ellipsoid formula. Formulas currently tested and published utilizing this approach include the following:

$$\text{Kidney volume} = \text{Length} \times \text{width} \times \text{thickness} \times \pi/610,11$$

$$\text{Kidney volume} = 4/3 \pi \times (1/4 \text{ anterior} - \text{posterior diameter} + 1/4 \text{ width})^2 \times 1/2 \text{ Length}^{12}$$

Problems related to the use of the ellipsoid formula include inter-operator variability when determining the maximal anterior-posterior diameter, the variability induced by patient respiration, and the lack of uniform cyst expansion throughout the kidney in ADPKD making the ellipsoid a less than perfect estimation of size. The contributions of these variables typically result in an overall underestimation of kidney volume. Importantly, if one applies the same ellipsoid formula utilizing MRI images to estimate kidney volume in ADPKD, a similar underestimation of kidney volumes occurs in comparison to volume measurements utilizing stereological methodology or voxel counting¹⁰. These findings suggest that the ellipsoid formula itself contributes significantly to the inaccuracy of the ultrasound method in estimating kidney volume in ADPKD¹⁰.

Kidney volume estimates using ellipsoid-based ultrasonographic methods vs. MRI using stereological methods in healthy volunteers demonstrated a 25% underestimation of total kidney volume¹⁰. Correlations of ultrasound and MRI estimates of kidney volume in ADPKD patients with relatively intact renal function are highly significant ($r=0.89$)¹³. However, reproducibility or the coefficient of variation differs greatly with 21%–35% for ultrasound vs. 2.1–2.5% for MRI. Kidney length was the most reproducible measurement using ultrasound¹³.

The earliest determinations of kidney volume in patients with ADPKD have been performed by CT¹⁴. In this method, kidney volume was measured by an integral method, completed by measuring the surface area of contiguous 13 mm CT slices followed by a summation volume estimate. Significant increases in kidney volume were found in ADPKD patients compared to unaffected controls regardless of renal function¹⁴ with more reproducible measurements of kidney volume obtained by CT vs. ultrasound¹⁵. CT imaging has similar accuracy and reliability coefficients to MRI and can be acquired relatively faster than MRI. CT is also better than ultrasound when evaluating complicated renal cysts and nephrolithiasis.

However, disadvantages of CT include ionizing radiation and exposure and the use of nephrotoxic contrast agents. Given these limitations CT has had a limited role in diagnostic or longitudinal imaging in ADPKD¹.

The Consortium of Radiologic Imaging Studies of PKD (CRISP) is a prospective, longitudinal study of kidney and cyst volume progression in patients with ADPKD using high-resolution magnetic resonance imaging (MRI)¹⁶. Qualified patients who had GFR ≥ 70 ml/min/1.73m² underwent standardized annual MRI kidney imaging, iothalamate clearance and comprehensive clinical evaluations. Total kidney volumes were measured from T1-weighted images and region-growing thresholds were used from T2-weighted images to determine cyst volume¹⁶. During the initial protocol development for image acquisition to determine kidney volume, ex-vivo phantoms for small and large kidneys were developed using materials that are close to the density of renal parenchyma and cyst fluid were created. These phantoms were then used to determine repeat scanning variability, inter and intra observer variability with regard to calculation of total kidney volume. Finally the phantoms and four individuals were tested on a repeat basis in MR scanners from different manufacturers. Importantly the error of measurement and coefficients of variation were extremely low in these studies indicating that MR could accurately and reliably measure total kidney volume in cystic kidneys.

Measuring cyst volume is more difficult compared to total kidney volume¹. Due to the irregular shape and enormous number of cysts, only CT/MRI methods using the integral or voxel counting method can accurately measure cyst volume. Reliability coefficients for MR renal and cyst volume measurements were 99.9% and 89.2%, respectively¹⁶. New techniques in the future may allow measuring cyst volume or observing intact renal parenchyma on an easy setting.

Because renal cysts form *in utero* and grow throughout life, kidney enlargement is suggested as a potential bio- or surrogate marker for disease progression and overall prognosis. Although ultrasonography is important for screening and diagnosing ADPKD, the variability of its measurement makes it a less preferred method to monitor disease progression¹. However, monitoring disease progression longitudinally in ADPKD using ultrasound longitudinally has been successful in large numbers of adults and children with ADPKD followed over a long period of time. In these studies, children were followed over a period of eight years and unilateral involvement was initially reported in 17%¹⁷ with a curvilinear growth of kidney size found in affected children¹⁸. The plotted exponential curves demonstrated that kidney volumes increased faster in affected children than in age matched unaffected children; and that disease progression tended to accelerate over time. For affected children with disease diagnosed in the first year of life or *in utero*, and hypertensive children, kidneys grew significantly faster than other affected children. Gender had no obvious effect on kidney growth in ADPKD children. In this and another study of adult PKD patients¹², it was noted that kidney volume of affected children (growth rate= $\sim 10.3\%$ per year)¹⁷ was faster than adults (growth rate= 8.2% per year)¹². Although these investigations were based on ultrasound images, the relative large population (pediatric study n=182, adults study n=229) and long interval between each measurements diminished major potential errors and allowed for insight from these studies.

CT has also been an effective tool to follow disease progression and change in kidney volume. Two early studies that employed serial CT demonstrated that kidney growth rate is highly variable (4.0% to 9.4% per year)^{12, 17} with a positive correlation between faster growth and the decline of eGFR^{15, 19}. In addition, interventional trials have utilized CT and kidney volume estimates reliably to determine the efficacy of octreotide²⁰.

The findings of CRISP reported that total kidney volume was modestly and inversely correlated with GFR²¹. Total kidney volume increased at a rate of 5.3% and total cyst volume by 12.0% per year. Cystic expansion occurred at a consistent rate within individuals with a high level of inter-individual variability. PKD1 patients demonstrated significantly larger kidney volumes, but with a similar rate of kidney growth between PKD1 and PKD2 (PKD1 5.68%/yr; PKD2 4.82%/yr)²¹. More cysts were detected in age matched PKD1 kidneys vs. PKD2 kidneys accounting for the differences seen in total kidney volume and patient outcomes. (Figure 3) The overall prevalence of hepatic cysts was 83% (85% female and 79% males) which directly correlated to renal and kidney volume²². Hepatic cysts increased in size and frequency with age, for instance, over 94% of patients 35 years and older demonstrating involvement. Importantly, hepatic cyst volume was significantly greater in women vs. men (Figure 4).

During the initial CRISP studies, gadolinium was used to enhance the visualization of renal parenchyma. Although no cases of nephrogenic systemic fibrosis have been reported in this cohort, given the investigational nature of these studies, subsequent imaging protocols have been refined and no longer include gadolinium²³.

Potential new imaging modalities in ADPKD

Activation of the renin-angiotensin aldosterone system and decreases in renal blood flow are thought to contribute to the pathogenesis of hypertension in ADPKD^{24, 25}. Classical measurements of renal blood flow (RBF) as measured by para-aminohippurate (PAH) clearance have been performed in ADPKD patients²⁶. These measures are accurate but still limited due to the logistical difficulties of continuous administration of PAH and inadequate estimation of PAH extraction by the renal tubules in cystic kidneys. Alternatively, RBF can be quantified utilizing breathheld magnetic resonance imaging. A blood flow validation study in phantoms and healthy controls demonstrated a high reliability of quantitative RBF measured by breath-held velocity encoded MRI²⁷. MRI measurements were compared with known measured flow rates in controlled-flow-loop phantoms using pulsatile flow and measurements with prospective and retrospective gating methods. Deviation from true flow was consistently below 13% for vessel diameters 3 mm and greater. Reproducibility in six healthy volunteers, comparing immediate rescan, repetition of the scan plane scouting, and week-to-week variation showed small levels of variability. The standard deviation of in vivo measurements of RBF in normal subjects was 59.7 mL/min or 10.5%. Comparison of RBF reproducibility with and without gadolinium contrast showed no significant differences in mean or standard deviation.

RBF measurements performed as part of the CRISP study indicated RBF can be accurately and reproducibly measured by MRI over a short period²⁸. The imaging protocols used in CRISP to determine RBF included a two dimensional cine phase-contrast breath-hold pulse sequence after obtaining renal artery diameters perpendicular to the renal arteries with flow rates²⁹. RBF was significantly associated with disease progression in the CRISP population³⁰. While renal and cystic volume increased over 3 years, RBF decreased and eGFR remained stable. Renal vascular resistance was negatively and RBF positively correlated with eGFR slopes. The RBF reduction found in CRISP paralleled total kidney volume increase, preceded eGFR decline and independently predicted disease progression. These findings suggest that RBF utilizing MR based methodologies may be a novel predictive marker for disease progression in ADPKD.

Although disease progression in ADPKD is characterized by enlargement of renal cysts and gradual loss of kidney function, all current observations demonstrate relatively weak correlation between renal/cystic volumes vs. eGFR change. In CRISP, age-adjusted renal (r

= -0.31, $P < 0.0001$), cyst ($r = -0.36$, $P < 0.0001$), and percentage cyst volume ($r = -0.35$, $P < 0.0001$) were inversely related to eGFR. Often there are individuals with extremely large exophytic cysts with completely normal kidney function or individuals with relatively small kidneys but with cysts throughout the medulla and parenchyma with progressive renal insufficiency. Especially when cysts tend to “hang” on the cortical edges of the kidney, grow outward and leave a major portion of the renal parenchyma intact, discordance between kidney structure and function appear. In 2006, a novel approach to interpret CT images from PKD patients indicated that potential novel morphological markers other than total kidney or cyst volume³¹.

Based on an interventional study³², CT scans of participants in the placebo arm were enhanced then analyzed by a histogram-based statistical approach known as otsu’s thresholding. In addition to differentiation between fluid-filled cysts and kidney tissue a third compartment among all patients, where the intensity was between cysts and renal parenchyma, approximately 100 Hounsfield, was referred as the “intermediated volume”. (Figure 5) Although renal and cystic volume failed to provide a strong correlation with change in kidney function, the “intermediate volume” demonstrated a significant association with change in GFR over a relatively short period of 6 months (duration of the study). The ratio between intermediate volume over parenchyma ($V_{int}/V_{par} \%$) plotted against baseline GFR ($r = -0.81$, $p < 0.001$) and 6 months later ($r = -0.80$, $p < 0.005$); the percentage changes of intermediate volume vs. percentage changes in GFR at the 6 months follow up ($r = -0.70$, $p < 0.01$); and the ratio between change in intermediate volume/baseline parenchyma ($\Delta V_{int}/V_{par} \%$) vs. change in GFR ($r = -0.75$, $p < 0.005$) were all highly significant.

Despite the small number of participants ($n = 13$) and short period of follow-up (6 months), intermediate volume may more accurately reflects change of kidney function, and be a potentially important marker that predicts disease progression in ADPKD. Intermediate volume may represent regions of impaired contrast uptake as a result of localized low blood flow or filtration. Alternatively atrophic or dilated tubules and fibrotic lesions may represent this component of renal parenchyma.

Summary

In summary, imaging plays a central role in the diagnosis, prognostic staging and management of patients with ADPKD. Currently ultrasound provides the most cost-effective and reliable approach to diagnosing at-risk individuals with ADPKD. However, for monitoring disease progression over short periods of time, more accurate and reliable measures of total kidney volume such as MRI play are more appropriate imaging approaches. Novel imaging assessments of reductions in RBF utilizing MRI or decreased enhancement of intermediate, non-cystic renal parenchyma utilizing CT may improve the identification of ADPKD individuals at greater risk for progression to ESRD.

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Figure 1.

Ultrasound images of ADPKD. Longitudinal view of right mid-kidney of an advanced case (A), with the poles extending well beyond the image. Innumerable cysts of varying size and shape are present with very little intervening parenchyma. Longitudinal images of right kidney of a child with early, mild changes (B). Several small cysts are present (arrows) and there is a reduction in sinus fat due to expansion of the cortex.

Figure 2.

Kidney with simple and complex cyst. Contrast material-enhanced-CT scan shows a poorly enhancing solid lesion (arrowhead) on the posterior aspect of the right kidney and a small simple cyst (long arrow) anteriorly. The large cystic mass (thick arrow) on the posterolateral surface of the left kidney has a thick wall and numerous septa and is therefore considered indeterminate. Fluid in the cystic compartment of the lesion remained at water density.³⁴

Figure 3. Coronal T2-weighted, single-shot fast spin echo magnetic resonance images from patients with PKD1 (a and b) and PKD2 (c and d) at 18 yr (a and c) and 41 yr (b and d). Renal cysts in PKD1 are more numerous, diffusely distributed, and heterogeneous in size than those in PKD2.²¹

Figure 4.

Coronal T2-weighted magnetic resonance imaging (MRI) from four different patients with variable severity of hepatic and renal cysts. Patient A is a 24-yr-old man with mild degree of hepatic cysts (a total volume of 6.3 ml) and renal cysts (15.4 ml). Patient B is a 46-yr-old man with mild hepatic cyst (9.3 ml) but severe renal cyst burden (1940 ml). Patient C is a 44-yr-old man has moderately severe degree of hepatic cysts (318.7 ml) but mild renal cyst burden (37.6 ml). Patient D is a 30-yr-old woman with severe degree of hepatic cysts (2368.8 ml) and renal cysts (1084.5 ml).²²

Figure 5. Representative computed tomography (CT) image before (A) and after (B) the application of anisotropic diffusion. (C) Image volume histogram and segmentation thresholds (F, fat; C, cysts; I, intermediate; P, parenchyma). (D) Segmented kidney tissue components.³¹

Table 1

Combined ultrasound diagnostic results for children and adults with ADPKD 4, 6, 8

Pediatric study	age range	subtype	False Negative (%)	False Positive (%)	sensitivity (%)	specificity (%)
(Gabow et al., 1997 ⁸⁾)	3 months–5yr	PKD1	38	11	62	89
	5yr–10yr	PKD1	19	0	82	100
	10yr–15yr	PKD1	23	0	86	100
	15yr–17.5yr	PKD1	22	0	67	100
	All children	PKD1	25	2	77	98

	Age range	subtype	Criteria	Sensitivity (%)	NPV (%)	PPV (%)
Adult ultrasound diagnostic criteria (Ravie et al., 1994 ⁴⁾)	15–29	PKD1	≥1 cyst	96.2	100	96.6
			≥2 cysts	96.2	100	96.6
			≥ 2 cyst in one kidney, ≥ 1 cyst in the other	88.5	100	90.5
			≥ 2, bilateral	84.6	100	87.7
			≥4 bilateral	80.8	100	85.1
	30–59	PKD1	≥1 cyst	100	97.7–45.5	100
Adult unified criteria for both PDK1 & 2 (Pei et al., 2008 ⁶⁾)	15–29	PKD1	≥2 cysts	100	99.2–61.2	100
			≥ 2 cyst in one kidney, ≥ 1 cyst in the other	100	99.2–85.2	100
			≥ 2, bilateral	100	100–90.7	100
			≥ 4 bilateral	100	100–96.9	89.9–100
		PKD1	≥1 cyst	99.1	99.1	97.5
	30–59	PKD2		79.1	83.5	95.6
		PKD1	≥ 2 cysts	98.1	98.3	98.7
		PKD2		71.9	79.7	100
		PKD1	≥ 3 cysts	94.3	94.8	100
		PKD2		69.5	78.0	100
	30–59	PKD1	≥ 2 cysts in each kidney	93.3–92.6	95.4–97.5	100
		PKD2		75.8–88.8	81.6–92.3	100
		PKD1	≥1 cyst	100	100	94.8–84.5
		PKD2		96.7–100	96.8–100	93.5–92.3

	Age range	subtype	Criteria	Sensitivity (%)	NPV (%)	PPV (%)
		PKD1	≥ 2 cysts	98.2–100	98.7–100	98.2–95.5
		PKD2		94.9–100	95.4–100	97.7–97.2
		PKD1	≥ 3 cysts	96.6–100	97.6–100	95.7–100
		PKD2		94.9–95.6	95.4–96.8	97–100

Ravine Criteria (1994)⁴ and unified Criteria (2008)⁶ were presented in boldface. For patients age 60+, both Ravine and unified criteria stated 4 cysts in each kidney is required for diagnosis. Unified criteria also stated <2 cysts in individuals aged 40+ is sufficient to excluded the diagnosis of ADPKD.