Autosomal Dominant Polycystic Kidney Disease: Time for a Change?

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Diagnosis and treatment of autosomal dominant polycystic kidney disease (ADPKD) is rapidly changing. Cellular pathways that involve the polycystins are being mapped and involve the primary cilium, intracellular calcium and cAMP regulation, and the mammalian target of rapamycin (mTOR) pathway. With the use of new imaging approaches, earlier diagnosis of hepatic cystic disease is possible, and measurement of kidney and cystic growth as well as kidney blood flow is possible over relatively short periods. PKD gene type, gender, proteinuria, and the presence of hypertension relate to the rate of kidney growth in ADPKD. On the basis of risk factors for progression to ESRD and the pathogenic roles that intracellular cAMP and mTOR play in cystogenesis, novel therapies are now being tested, including maximal inhibition of the renin-angiotensin system, inhibition of renal intracellular cAMP using vasopressin V2 receptor antagonists, and somatostatin analogues, as well as inhibitors of mTOR. This review addresses the current understanding of the pathogenesis and the natural history of ADPKD; accuracy and reliability of diagnostic approaches in ADPKD, (2) the accuracy and the reliability of diagnostic approaches in ADPKD, (3) the availability of reliable measures of disease progression early in the course of ADPKD, and (4) potential new treatments that aim to slow kidney progression.

ADPKD is a dominantly inherited heterogenic, systemic disease that occurs in 1:700 to 1:1000 individuals and is characterized by the presence of multiple epithelial-lined kidney cysts, resulting in slow, gradual, and massive kidney enlargement that results in kidney failure in the majority of individuals by the fifth or sixth decade (1–3). Disease penetrance is 100%, and each offspring of an affected individual has a 50% chance of inheriting the disease. Mutations in the PKD1 (chromosome 16) or PKD2 (chromosome 4) genes are responsible for 85 and 15% of cases, respectively (4–6). Polycystin1 and polycystin2 are the protein products of PKD1 and PKD2, which interact and co-assemble (7,8). Although individuals with PKD1 are clinically indistinguishable from individuals with PKD2, patients with PKD2 have a less severe course of disease with a later mean age of diagnosis, hypertension, and ESRD (9,10).

The clinical features of ADPKD highlight its systemic nature (11). Extra-kidney cysts can be found most often in the liver, pancreas, spleen, thyroid, and arachnoid membranes. Cystic changes in the male reproductive system show a 39% frequency of seminal vesicle cysts without a significantly greater frequency of epididymal, prostatic, or testicular cysts (12). The presence of seminal vesicle cysts is a potential cause of infertility. Liver cystic disease was previously thought to develop approximately 10 yr later than kidney cystic disease by ultrasound (13); however, magnetic resonance (MR) studies (14) demonstrate liver cysts in 94% of individuals by 35 years of age. Liver cyst burden correlates with total kidney and cyst volume, and extreme hepatic cystic disease predominates in women (14,15). Intracranial aneurysms occur infrequently (5 to 7%) in a small number of families (1 to 3%), and family history is the most significant associated risk factor for this potentially lethal complication (16). Overt proteinuria is uncommon in ADPKD, with only 27% demonstrating >300 mg/d (17). Proteinuria ≥2 g/d is unusual and suggests the presence of another kidney disease. Importantly, the presence of both proteinuria and mi-
Pathogenesis of Cyst Formation in ADPKD

Since the initial cloning of PKD1 in 1994, an understanding of the PKD phenotype at a cellular level is emerging, as seen in other reviews in this issue and elsewhere (36). Central observations regarding pathogenesis and with therapeutic implications in ADPKD are briefly presented here. Before identification of the polycystins, three mechanisms were considered requisite for cyst formation and growth: Cellular proliferation, net-fluid secretion, and abnormal extracellular matrix and cell-cell interactions. Polycystins have been found to regulate each of these processes, working through multiple complex cellular pathways. Polycystin 1 and 2 can interact intracellularly through coiled-coiled domains, accounting for the similar clinical phenotypes of PKD1 and PKD2, and are found co-assembled or alone in a variety of cellular locations (8,37).

The polycystins are associated with primary ciliation in kidney tubular epithelial cells in the kidney. Although kidney epithelial cilia appear normal in ADPKD, alterations in mechano- and chemosensation are found (38). Polycystin 1 and 2, along with four other polycystic kidney disease proteins that are involved in cystic disorders, normally help regulate ciliary responses to mechanical stimulation to generate calcium fluxes (39,40). How the abnormalities in ciliary function that occur when PKD1 or PKD2 is mutated link to other components of cyst development (e.g., cAMP accumulation, CI-dependent cyst fluid secretion, regulation of mammalian target of rapamycin [mTOR]) are as of yet not completely understood.

Net transepithelial fluid secretion is required for the development of cysts. A strong body of evidence shows that intracellular cAMP concentration plays a major role by promoting cell proliferation and CI-dependent fluid secretion (41,42). Apical cAMP-dependent CI channels are ultimately responsible for cyst fluid secretion as well as extracellular signal-regulated kinase–dependent cellular proliferation. Animal models of cystic disease demonstrate increased kidney accumulation of cAMP (43,44), regulated through alterations in intracellular calcium concentration and/or alterations in G-protein–coupled receptor cell signaling. This alteration in intracellular cAMP concentration has become the focus for targeted interventions in ADPKD.

Increased cellular proliferation and apoptosis have been identified in human and murine models of PKD. Polycystin1 normally suppresses mTOR activity, and defects in polycystin1 consequently lead to abnormal mTOR activation. mTOR has essential roles in protein translation, cell growth, and proliferation. Tuberin, the TSC2 protein that is mutated in tuberous sclerosis, plays an important proximal role in mTOR function by regulating the kinase activity of mTOR through a small GTPase rheb (45). Importantly, the genes that regulate polycystin1 and tuberin (PKD1 and TSC2, respectively) lie adjacent on chromosome 16, and individuals with large deletions that involve both genes demonstrate a clinically severe form of ADPKD. In addition, the cytoplasmic tail of polycystin1 interacts with tuberin (46), and components of the mTOR pathway have been shown to be inappropriately activated in cyst-lining epithelial cells in human ADPKD.

Approaches to Diagnosis of ADPKD

The frequency of screening asymptomatic, at-risk individuals for ADPKD has increased during the past half century from 40 to >59% (47). Given the prognostic information that is available regarding PKD gene type, age-adjusted kidney volume (see Renal Volume), and potential treatments, indications for presymptomatic screening for ADPKD will most likely increase. Ultrasound remains the first approach for diagnosing ADPKD (48,49). Current diagnostic criteria for ultrasound in an at-risk individual (positive family history) for individuals between 30 and 60 yr is four cysts total, distributed bilaterally (48). Kidney cyst number (48) is the main criteria for a diagnosis of ADPKD (Table 1) in the context of the appropriate phenotype (family history, liver or pancreatic cysts). The number of kidney cysts required for a diagnosis varies on the basis of the age at the time of screening, whether a family history of ADPKD is present, and whether the patient is from a family with PKD1 or PKD2. Importantly, specific to ADPKD and uniformly present, increased kidney size or volume is a feature of this disorder (Figure 1).

Ultrasound screening provides important age-dependent diagnostic information (Table 1). The presence of cysts that are detected by ultrasound in an at-risk individual who has ADPKD and is younger than 30 yr is highly specific (close to 100%) in most series (48,50–53). Potential false-positive diagnoses are found with dense medullary pyramids (52). In individuals who are older than 60, simple cysts commonly occur and may result in a misdiagnosis, particularly in those without a family history, and more cysts (more than eight cysts present bilaterally) are required to make a diagnosis. A normal ultrasound in an individual who is older than 30 yr and from a family with PKD1 or PKD2 is highly sensitive (97 to 100%) (50,53,54). Age-specific information remains high in those who are between 15 and 30 yr and have a normal ultrasound conferring, a 95 to 97% likelihood of not inheriting ADPKD in individuals with PKD1 and 67% in individuals with PKD2 (55). If there is a clinical suspicion of PKD2 in an individual younger than 30 years and the ultrasound is normal, then further genetic testing should be.
Table 1. Sensitivity and use of genetic and ultrasonographic age-dependent diagnostic information when screening for the presence of ADPKD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fetal</th>
<th>Childhood (0 to 15 Yr)</th>
<th>Young Adulthood (15 to 30 Yr)</th>
<th>Adulthood &gt;30 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing</td>
<td>Linkage markers or mutation-specific screening</td>
<td>Full sequencing, DHPLC or mutation-specific screening (75% sensitivity)</td>
<td>Full sequencing, DHPLC (75% sensitivity) or mutation-based screen; less sensitive than ultrasound at age &gt;20 yr PKD1</td>
<td>Potential prognostic information based on genotypic prediction; less sensitive than ultrasound for diagnosis</td>
</tr>
<tr>
<td>Ultrasound findings</td>
<td>Enlarged, hyperechoic after gestational week 17, normal amniotic fluid levels usually present, renal cysts (11%)</td>
<td>Enlarged, discrete cysts, normal echogenicity, one cyst adequate to make a diagnosis in an at-risk individual (50% sensitivity); ultrasound less sensitive than genetic testing for PKD1 and PKD2</td>
<td>Enlarged, discrete cysts, normal echogenicity, PKD2 67% sensitivity, PKD1 95% sensitivity; ultrasound less sensitive than genetic testing for PKD2</td>
<td>97 to 100% sensitive PKD1 and PKD2, at least two cysts in each kidney needed for a diagnosis; kidney enlargement is uniformly present</td>
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*ADPKD, autosomal dominant polycystic kidney disease.

considered. Under 15 years of age, ultrasound provides less diagnostic information and has been found to be inconclusive in approximately half of at-risk individuals or 25% of those screened. False-negative rates are highest in children who are younger than 5 yr (38%).

Given that simple kidney cysts are rare under 20 yr of age (0.2%), the presence of a single kidney cyst in an at-risk individual who is younger than 20 years confers a diagnosis of ADPKD (Table 1). Although increased echogenicity is a common finding in ADPKD, it is not a typical feature in children with ADPKD. Cysts are more often present, and distribution is most often bilateral. The reason for the lack of increased echogenicity after birth is unclear but may represent a reduction in microcystic disease in association with developmental downregulation of polycystin expression. Increasing kidney enlargement to >4 SD above the mean will occur in a significant proportion (approximately 35%) of children with ADPKD, and cysts can often be larger than 3 cm, uncommon in other kidney cystic disorders. Importantly, in affected individuals who do not yet demonstrate kidney cysts by ultrasound, kidney enlargement is present relative to age- and gender-matched control subjects (52). In addition, when MR and computed tomography (CT)-based images of adults with ADPKD and normal kidney function are evaluated for cyst burden, increases in “noncystic parenchyma” volumes are found (56,57). These findings suggest that cystic expansion takes place below the level of detection by ultrasound, MR, or CT scan. Although accuracy of volumetric measurements using these three modalities differs (58), normal kidney volume in healthy control subjects is estimated to be between 120 and 160 ml per kidney (2).

Ultrasonographic identification of simple cysts are rare in utero (1:1100 pregnancies) and occur primarily in the first trimester, with complete resolution during pregnancy in approximately 90%. More than 80 fetal ultrasound reports of individuals with ADPKD are now available for review (59–61). Although cysts are required for the diagnosis of ADPKD in children, cystic changes occur seldom in utero (11%) and are found predominantly in the cortex. Increased echogenicity is the most common ultrasound finding and has been observed as early as 17 wk (61). Ultrastructural changes in affected fetuses demonstrate a range of changes that are uncharacteristic of adult ADPKD. Glomerular cystic changes occur in up to 30%, and more proximal as opposed to distal tubular dilations are present (62).

Although increased renal echogenicity is the hallmark of ADPKD in utero, it is also the most common fetal ultrasonographic feature of other kidney cystic diseases, including autosomal recessive polycystic kidney disease (ARPKD), Bardet-Biedl syndrome, Meckel-Gruver syndrome, and Ivemark II syndrome. Differentiating features from these disorders include the absence of malformations (central nervous system anomalies, polydactyly, spinal abnormalities, and hepatic fibrosis) and normal amniotic fluid levels. Both ARPKD and ADPKD demonstrate kidney enlargement in utero; however, individuals with ARPKD tend to have larger kidneys as compared to those with ADPKD (>5 versus >2 SD from the mean), and fetuses with ARPKD are more likely to demonstrate kidney cysts (39%). Kidney size and oligohydramnios provide the most prognostic information regarding survival for all the disorders. Earlier observational and retrospective series of ADPKD diagnosed in utero reported an increased (1) maternal affection.
status; (2) decreased fetal survival; (3) familial predisposition; and (4) more frequent adverse effects related to ADPKD, including proteinuria, hypertension, and kidney insufficiency (63). However, more recent, large, and prospective series indicated that transmission is equal from mother and father, in general affected individuals have normal kidney function and survive the perinatal period, and prognosis relates most to the presence of oligohydramnios and massive kidney enlargement seen on ultrasound (60,61,64–67). More recently, prenatal serum microglobulin and cystatin c levels have been shown to predict kidney function and survival accurately in fetuses with hypechoic kidneys (59).

Genetic testing in ADPKD has become more reliable and less expensive in recent years, and further details regarding genotype:phenotype relationships are reviewed elsewhere in this issue. Direct sequencing and DHPLC are used commercially to screen for the presence of mutations in PKD1 and PKD2. The success of identifying disease-causing mutations approaches 75% with both methods (68,69). Confirmation of the presence of a mutation in other affected family members is occasionally needed given the large number of missense mutations in PKD1 (approximately 35%). Genetic testing is used when a young family member (<30 yr) is considering kidney donation, when a clinical and radiologic diagnosis is uncertain, or during family planning. Although ultrasound is the initial approach for diagnosing at-risk individuals, with potentially efficacious therapies under consideration, genetic testing may take on a larger diagnostic role earlier in ADPKD, when kidney imaging is less reliable.

**Renal Volume: A Reliable Marker for Disease Progression Early in ADPKD**

Kidney enlargement as a result of cyst expansion is the hallmark of ADPKD. Dalgaard’s (70) classical series demonstrated that kidney enlargement identified on physical examination predicted kidney failure. Franz and Reubi (71) developed a model of a curvilinear relationship between kidney volume and function, indicating that significant renal enlargement takes place before loss of kidney function in ADPKD. Importantly, kidney function does not decline in individuals with ADPKD until kidney size is at least 5 times greater than normal (2). This model has been supported unanimously in studies in adults (2,18,51,56,72,73) and underscores the extent of kidney disease progression over decades that precedes loss of kidney function.
Before the loss of kidney function, MR imaging demonstrates that there is an exponential rate of kidney growth in ADPKD (74). Reliable and highly reproducible MR measures of kidney and cyst volume that were performed over 3 yr by the Consortium of Radiologic Imaging Study of PKD (CRISP) demonstrated an increased volume in most patients showed with an average increase of 204 ± 246 and 218 ± 263 ml in kidney and cyst volumes, respectively (74). The mean slope of the increase was 5.27 ± 3.92 and 12.2 ± 14.1%/yr for kidney and cyst volumes, respectively. In the group with the largest kidneys (>1500 ml, baseline), there was a significant decline in GFR during the 3 yr of study (−4.33 ± 8.07 ml/min per yr; P < 0.001), indicating that larger kidney volumes are associated with more advanced disease.

Although the annual volume change was greater in individuals with PKD1 versus PKD2 (74.9 versus 32.2 ml; P = 0.001), the annual rate of increase in kidney volume (5.68% in PKD1 and 4.82% in PKD2) was not significantly different (P = 0.24). For determination of whether the differences in kidney size are related to the number of cysts (≥4 mm), a count from a representative middle slice of the kidney was performed; PKD1 kidneys had significantly more cysts (31.5 versus 17.0; P < 0.0001) (75). It is interesting that both gender and the presence of hypertension had a significant influence on the rate of growth: Both absolute and relative rates of growth were faster for men and individuals with hypertension (76). This suggests that cysts appear later in individuals with PKD2 versus PKD1 and that both hormonal effects and elevations in BP play a role in disease progression, defined as change in kidney volume in ADPKD. Given this reproducible and accurate measurement of disease progression long before loss of kidney function, both understanding the causes of increased interfamilial variability using volumetric measures of cystic disease (Figure 2) and design of clinical trials to test interventions early in the course of ADPKD are now possible.

**Novel Therapies in ADPKD**

Although activation of the RAAS has been demonstrated in ADPKD and effective reduction in proteinuria and left ventricular hypertrophy has been demonstrated with blockade of the RAAS (28,29,31), studies have not demonstrated a renoprotective effect of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers in ADPKD. No benefit of ACE inhibitor therapy or BP control was found in 222 ADPKD individuals and participated in the Modification of Diet in Renal Disease (MDRD) study with a rate of decline of kidney function of 5.9 ml/min per yr (77). This study was not designed to randomly assign patients with regard to angiotensin blocking agents. Another study of ramipril versus placebo in 64 patients with ADPKD and chronic kidney insufficiency demonstrated no reduction of the rate of doubling of serum creatinine (78). In a 7-yr randomized trial of ACE inhibitors versus calcium channel blockers in 72 patients with ADPKD and hypertension, left ventricular hypertrophy and creatinine clearance >30 ml/min, no beneficial effect of ACE inhibitors on kidney function was found (79). Importantly, these studies evaluated relatively small numbers of patients for short periods of time once kidney insufficiency was established. To address more fully the question of value of inhibition of RAAS in ADPKD, a prospective, randomized, double-blind, placebo-controlled, clinical trial funded by the National Institutes of Health is under way and involves more than 1200 hypertensive individuals with ADPKD, both early (estimated GFR >60 ml) and late (estimated GFR <60 and >30 ml), to determine whether rigorous BP control or maximal blockade of RAAS using ACE inhibitors and angiotensin receptor blockers in combination is beneficial in comparison with ACE inhibitors alone (change in kidney volume measured by MR early in disease and kidney failure measured as a composite of frequency of doubling of serum creatinine, ESRD, and death in those with advanced disease).

Two approaches have been taken to reduce kidney cAMP levels in ADPKD. The vasopressin V2 receptor (VPV2R) antagonist OPC31260 has been effective in three models of PKD, including the PCK rat, the PKD2/-tm1som, and pcy model (43,44). A marked inhibition of kidney cAMP, prevention of kidney enlargement, cystogenesis, and protection of kidney function were found. These impressive animal studies have initiated clinical trials in patients with ADPKD. Phase IIB studies (80) determining response to escalating single-dose tolvaptan (15, 30, 60, and 120 mg, 3 d apart) in 11 patients with ADPKD and normal kidney function have been completed. Pharmacokinetic profiles were found to be similar to those of healthy control subjects. Urine output, frequency of nocturia, 24-h urine osmolality, and serum sodium concentrations changed in a dosage-dependent fashion. Twenty-seven individuals with ADPKD went on to determine the minimum dosage of tolvaptan required to inhibit urinary concentration yet prevent hyponatremia and frequent nocturia. Four dosage regimens over 5 d were investigated: 15 mg twice daily, 30 mg/d, 30 mg twice daily, and 30 mg every morning/15 mg every evening. Tolvaptan was well tolerated. After 5 d, patients were in fluid balance and demonstrated urine outputs of 6 L/d, frequency of nocturia was increased by 0.5 void per night, and urinary osmolality was suppressed over 24 h (Figure 3). A phase III clinical trial is being initiated to determine whether tolvaptan therapy can slow the rate of progression of ADPKD.

**Figure 2.** (Left) A 41-yr-old normotensive man with PKD2 intervening sequence splice mutation and serum creatinine 1.1 mg/dl. (Right) A 19-yr-old hypertensive woman with PKD2 ins/del exon 11 and serum creatinine 1.1 mg/dl.
early in the course of disease, defined as change in kidney volume by MR imaging.

Somatostatin, known to inhibit vasopressin-induced cAMP generation (57) and water permeability via G1-coupled somatostatin receptors 1 and 2, has also been tested in humans using a long-acting octreotide compound that is given intramuscularly every month for 6 mo. Substantial retardation in kidney growth defined as change in kidney volume measured by CT imaging was found during the period of octreotide therapy as compared with placebo (2.2 ± 3.7 versus 5.9 ± 5.4%/yr; P < 0.01).

Two preclinical studies that evaluated the efficacy of blocking mTOR using rapamycin in the Han:SPRD rat model of ADPKD demonstrated significant reduction in kidney cyst burden (81,82). In two independent mouse models of PKD (orpk and the bpk dominant and recessive PKD models respectively), rapamycin therapy was shown to significantly reduce kidney volume as measured by MR, kidney weight, and blood urea nitrogen levels. Although toxicities were noted (weight loss at higher levels of rapamycin), significant benefit was still seen when circulating rapamycin levels were appropriate for clinical use and not associated with significant weight loss. Importantly, in a retrospective review of kidney volume in transplant recipients with ADPKD, significant regression in kidney size (1.3%/mo; mean 24%) was seen in those who received rapamycin as compared with those who did not.

Conclusion

Although significant advances have been made and we are closer to slowing the progression of kidney disease in ADPKD, many unanswered questions remain. Will drugs work equally well in both PKD1 and PKD2 individuals? Should only high-risk individuals (with specific volume:age ratios) be targeted for therapy? Will therapies need to be life-long, or will short treatments provide long-term protection from cyst growth and expansion? How early should treatment be given? What will be the appropriate combination of therapies to treat the systemic manifestations of ADPKD (liver cystic disease, vascular abnormalities, and hypertension)? Further optimism is warranted as potential drug developments for the treatment of ADPKD aimed at preventing somatic mutations in the PKD genes in preclinical trials, altering intracellular calcium concentrations in preclinical trials, and inhibition of CI-dependent fluid secretion through epithelial sodium channels and the cystic fibrosis transmembrane conductance regulator channel are being tested.

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Disclosures

None.

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