Polycystic Kidney Disease—Strategies to Prevent Kidney Function Decline

a report by

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Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease, with an estimated prevalence of 1:400 to 1:1,000 individuals. It is also the most common genetic cause of end-stage KD (ESKD) in both pediatric and adult settings.[1] Understanding of the pathogenesis of ADPKD has significantly improved since the mid-1990s, with the identification and characterization of two disease-associated genes: *PKD1*, localized to chromosome 16p13.3, and *PKD2*, on chromosome 4q21.[2,3] *PKD1* encodes the polycystin-1 protein while *PKD2* encodes polycystin-2. Both of these gene products are transmembrane proteins that localize to the primary cilium of the tubular epithelial cells, where they act as mechanosensors to regulate the inflow of calcium ions (Ca^{2+}) into the cell. Polycystin-2 is also present in the endoplasmic reticulum, where it mediates the release of Ca^{2+} from intracellular stores. In cultured cells derived from individuals or animal models of PKD, the decreased intracellular levels of Ca^{2+} likely lead to increased cyclic adenosine monophosphate (cAMP) activity. Increased cAMP levels also result from stimulation or upregulation of the vasopressin V2-receptor, and cAMP-dependent intracellular signaling acts to stimulate mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and other downstream signaling molecules. Eventually, nuclear signaling is modulated and an alteration in cell cycle G1/S phase transition occurs. This abnormal cell proliferation manifests as renal tubular dilatation and initiation of cyst growth. With continuing growth of cysts, separation from the parent nephron occurs with ongoing cyst expansion, resulting from both cell proliferation and fluid secretion into the lumen of the cyst.

Monitoring Progression of Disease

Patients with ADPKD typically progress to ESKD over a period of decades, and usually not until the fourth or fifth decade of life. Interventional trials targeting patients at the early stages of the disease face the obstacle of requiring a prolonged study period to attain the end-point of ESKD or dialysis. The Consortium of Radiologic Imaging Studies of PKD (CRISP) has provided useful information on disease progression as it relates to the rate of kidney and cyst volume expansion. Using magnetic resonance imaging (MRI), they demonstrated that kidney volume was the strongest predictor of the rate of kidney function decline.[4] Only in individuals with total kidney volume exceeding 1,500cc did glomerular filtration rate (GFR) decline (by 4.3ml/min/year) during the study period of three years. The end-point of kidney volume expansion has rapidly been adopted by the majority of ongoing studies on PKD progression. Other findings from CRISP revealed that the *PKD1* genotype results in earlier cyst development, rather than a more rapid rate of cyst growth. It has been postulated that the *PKD1* gene may play a more prominent role in cyst initiation rather than cyst expansion, accounting for clinical differences in disease severity.[5]

Protein Restriction

Low dietary protein intake has been examined as a method of slowing progression of chronic KD (CKD) through lowering of renal ammoniagenesis and a reduction in glomerular capillary pressure, which was shown to influence cyst growth in rats.[6] The Modification of Diet in Renal Disease (MDRD) Study was a multicenter trial that examined the effect of targeted protein restriction and blood-pressure lowering on CKD progression.[7] The study included 200 individuals with ADPKD and failed to demonstrate that low dietary protein intake was effective in slowing the progression of kidney disease. In this subpopulation of subjects with ADPKD, there was a suggestion of slower progression (4 versus 4.9ml/min per year) noted in those randomized to a low-protein diet (0.28 protein with 4–9mg/kg phosphorus, supplemented with a keto acid–amino acid mixture) compared with the low-protein diet group (0.6g/kg protein with 5–10mg/kg of phosphorus per day), but this did not affect the proportion or time to reach kidney failure or death.[8] Subsequent follow-up of the overall MDRD cohort also failed to conclude that dietary protein restriction during the trial period was beneficial for long-term progression of kidney disease, regardless of the etiology.[9]

The most recent meta-analysis of low-protein diets in non-diabetic adult CKD was performed by the Cochrane Collaboration. Their analysis included eight studies comprising 763 patients on low-protein diets (three studies targeting 0.6g/kg/d and five targeting 0.3–0.6g/kg/d) and 761 patients on higher protein intake. A significant reduction in renal death (defined as death from any cause, need for renal dialysis, or kidney transplantation) was found in favor of low-protein diets, with a relative risk of 0.69 (95% confidence interval (CI) 0.56–0.86). The proportion of ADPKD patients in these eight studies ranged from 6 to 30%.[10] It is worthwhile considering a restricted protein intake in this population, in addition to conventional renoprotective approaches. Guidelines from the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), however, recommend dietary protein be restricted to 0.6–0.8g/kg per day for all non-dialysis patients with a GFR <60ml/min/1.73m^2.[11]

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Blood-pressure Lowering

Several studies have examined blood-pressure lowering in ADPKD, but no specific antihypertensive agent has emerged as the drug of choice. The MDRD Study also showed no benefit of lower than usual blood-pressure reduction in any of the treatment groups throughout the duration of the study.[8] A long-term follow-up of the MDRD cohort revealed a dialysis-free survival benefit with the lower blood-pressure goal when follow-up of up to 10 years after initiating the study was accomplished.[12] Of course, blood-pressure management extends beyond its impact on preventing kidney disease progression. A seven-year follow-up of 79 patients with ADPKD showed a beneficial impact on left ventricular mass in those treated to a more rigorous blood pressure target (<120/80 versus 135–140/85–90mmHg), but no difference in kidney function was found.[13] Recommended blood-pressure targets in patients with ADPKD are similar to other CKD populations to minimize the risk of cardiovascular disease.

Renin–Angiotensin System Interruption

Cyst expansion in ADPKD was thought to cause local compression and ischemia of the renal microvasculature, resulting in activation of the renin–angiotensin system.[14] Subsequently, this classic understanding has been questioned by further evidence. It has been demonstrated that systemic renin–angiotensin activation is similar in matched hypertensive subjects with or without ADPKD, despite reduced sodium intake or angiotensin-converting enzyme inhibitor (ACE-I) therapy.[15] There does remain substantial evidence to support intra-renal activation of renin–angiotensin, but it is unclear whether angiotensin blockade—independent of blood-pressure lowering—would be effective in slowing the progression of ADPKD. A randomized trial of enalapril treatment in both normotensive and hypertensive patients with ADPKD and preserved kidney function failed to show any renoprotective benefit in terms of slowing deterioration of the GFR.[16]

If the renin–angiotensin system is integral in the progression of ADPKD, it would be reasonable to assume that ACE gene alterations would also be associated with outcomes. Several studies have examined the role of the ACE insertion/deletion (I/D) gene polymorphism on progression to ESKD. A meta-analysis of such gene association studies consisting of a total of 1,420 individuals showed no significant influence of ACE I/D polymorphisms on the risk of ESKD or age at onset of kidney failure.[17]

Two multicenter randomized controlled trials are ongoing to further elucidate the role of renin–angiotensin system interruption in patients with ADPKD. The HALT Progression of Polycystic Kidney Disease (HALT-PKD) Trial (ClinicalTrials.gov identifier NCT00283686) randomizes patients to ACE-I monotherapy (lisinopril) or combined therapy with an ACE-I and an angiotensin receptor blocker (telmisartan). The primary outcome of total kidney volume expansion will be measured over a four- to five-year period in those with an earlier state of disease (GFR >60ml/min), whereas in moderately advanced kidney disease (GFR 30–60ml/min) the primary outcome will be a composite of 50% reduction in estimated GFR, development of end-stage renal disease, or death. This study will also determine whether a low blood-pressure target of 110/75mmHg is better than standard blood-pressure management (<130/80mmHg).

Beta-hydroxy-beta-methylglutaryl-CoA Reductase Inhibitors

A short-term evaluation of the beta-hydroxy-beta-methylglutaryl-CoA (HMG-CoA) reductase inhibitor simvastatin demonstrated an improvement in inulin-measured GFR following four weeks of treatment in normotensive ADPKD patients with relatively preserved kidney function (creatinine clearance >50ml/min). This beneficial effect was attributed to measurable improvements in renal plasma flow, possibly related to improved endothelial function.[18] A randomized, double-blind, placebo-controlled trial is ongoing to examine the efficacy of pravastatin on progression of kidney cysts and kidney volume in children and adolescents with ADPKD (ClinicalTrials.gov identifier NCT00456365).

Mammalian Target of Rapamycin Inhibitor

The *PKD1* gene lies adjacent to the *TSC2* gene, one of the two genes responsible for tuberous sclerosis. *TSC1* and *TSC2* encode for the proteins tuberin and hamartin, which—when complexed—act as a guanosine triphosphate (GTP)-ase to maintain Ras homologue enriched in the brain (Rheb) in an inactive state. Increases in Rheb activate mammalian target of rapamycin (mTOR), a serine-threonine protein kinase that regulates cell growth. Some ADPKD patients with contiguous deletions of both *PKD1* and *TSC2* exhibit a more severe form of kidney cyst disease.[19] In ADPKD patients, tuberin is phosphorylated by ERK activation, resulting in the dissociation of the tuberin–hamartin complex, the release of Rheb from its inactive state, and the triggering of mTOR.[20] Rodent models of PKD treated with mTOR inhibitors have shown convincing evidence of retarded cyst growth and preserved kidney function.[21–23] Clinical studies in patients are ongoing with the mTOR inhibitors rapamycin and everolimus to prevent progression of kidney disease as measured by radiographic increases in kidney size (ClinicalTrials.gov identifiers NCT00346918 and NCT00414440).

Vasopressin V2-Receptor Antagonist

As stimulation of the vasopressin V2-receptor is associated with increased cAMP production, antagonizing this process may be beneficial in reducing cyst growth. In a polycystic kidney (PCK) rat model of PKD, antagonism of vasopressin levels by high water intake was associated with reduced renal expression of vasopressin V2 receptors, reduction in kidney- and body-weight ratios, and improved kidney function.[24] Pre-clinical trials of a vasopressin inhibitor, OPC-31260, in animal models of PKD successfully showed reductions in both cAMP and cystogenesis.[25,26] This prompted human testing, and a phase II clinical study has been completed with the highly selective and potent vasopressin V2-receptor antagonist tolvaptan. The Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and Its Outcomes (TEMPO) phase III/IV Trial (ClinicalTrials.gov identifier NCT00428948) will attempt to recruit 1,200–1,500 subjects as part of a multinational, randomized, placebo-controlled trial examining tolvaptan and its long-term effect on kidney volume increase as the primary outcome.

Somatostatin Analogs

The renal cysts in PKD progressively fill with fluid via secondary chloride transport. Somatostatin may play a role in slowing cyst growth by inhibiting this process. A small (n=12) six-month cross-over, placebo-controlled, randomized clinical trial examined the efficacy of a long-acting somatostatin in patients with ADPKD by measuring kidney size using computed tomography (CT) and GFR by an iohexol-based clearance method. They found that somatostatin was well tolerated and led to a slower increase in kidney volume (2.2±3.7% versus 5.9±5.4%; $p<0.05$), but there was no change in GFR during the treatment period.[27]

This group is now examining the longer-term effect of somatostatin in ADPKD using MRI to measure kidney volume (ClinicalTrials.gov identifier NCT00309283).

Potential Therapies

Although we have focused on therapies that have reached the phase of clinical testing in humans, additional potential therapies directed at different targets are being developed. The compound roscovitine (R) is a cancer chemotherapeutic agent that preferentially inhibits cyclin-dependent kinases (CDKs).[28] Currently, it is undergoing phase I and II testing trials, but its potential in PKD has been proposed. In two mouse models of PKD, the jck (NEK8) and the cpk (cystin) mouse, roscovitine prevented cell proliferation and subsequently slowed cyst progression. Although it was administered for only three weeks, it offered prolonged benefits with a favorable tolerability profile.[29,30]

Several experimental agents (EKI-785, EKB-569, HKI-272, AG825, PD184352, and WY-606) have been used to target the epidermal growth factor (EGF) receptor (ErbB) family or its effector molecules, which are important for cell proliferation and differentiation, particularly during development. Upon binding of one of its ligands—i.e. EGF, transforming growth factor alpha (TGFα), amphiregulin, or heparin-binding EGF receptor—autophosphorylation occurs, leading to intracellular signaling via the Ras/MAPK pathway and promoting tubular epithelial cell proliferation.[31,32] Several *in vitro* and *in vivo* studies have examined the relationship of increased EGF activity with cyst growth, but the inhibition of EGF in animal models has not been uniform in its inhibition of cystic disease.[33–35]

A recent study examined the use of triptolide—a potent diterpine found in *Tripterygium wilfordii* Hook F, sometimes known as Thunder God Vine, in PKD. Using murine kidney epithelial cells, the investigators demonstrated that triptolide induces intracellular Ca^{2+} release via a polycystin-2-dependent pathway. Triptolide has been recognized for its apoptotic effects, and may offer a therapeutic strategy to restore calcium signaling and attenuate cyst progression in PKD.[36] Dietary interventions such as soy consumption or flax seed diets may have beneficial effects in that they reduce arachidonic acid and prostaglandin E2 synthesis, but there are no validated trials to justify their use in patients with ADPKD.

Conclusion

Currently, there is no cure for ADPKD; however, novel interventions are attempting to slow progression of the disease in order to prevent ESKD. Some of these therapies are not specific to PKD and may apply to any CKD. Other strategies have been translated from our recent advances in the molecular pathogenesis of the disease. From the multitude of potential targets, several therapeutic strategies have not only emerged, but have advanced to phases of clinical testing in patients. Future results from ongoing trials should help to determine which strategies will be efficacious in slowing progression of PKD and affecting the lives of the people with the disease. ■

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