CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will understand the causes, symptoms, and possible treatment of autosomal dominant polycystic kidney disease

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Advances in autosomal dominant polycystic kidney disease—2014 and beyond

ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD), which frequently leads to end-stage renal disease, currently has no specific drug therapies. Better understanding of its pathogenesis and recent clinical trials have led to more accurate diagnosis of the disease and its manifestations, as well as to promising new approaches to treatment.

KEY POINTS

For at-risk patients in the previously difficult diagnostic group from 30 to 39 years of age, newer ultrasonographic criteria for diagnosing PKD1 and PKD2 now require a minimum total of three renal cysts.

An intracranial aneurysm occurs in approximately 16% of ADPKD patients who have a family member with ADPKD plus an intracranial aneurysm or subarachnoid hemorrhage. Appropriate screening is warranted.

Combined positron-emission and computed tomography helps identify infected renal or liver cysts and may uncover other unsuspected abdominal or pelvic infections.

Cyst expansion and increasing total kidney volume might be slowed by increasing water intake to 2,500 to 3,000 mL per day, although formal documentation of this is not published. However, this must be done under a physician's supervision because of possible adverse effects.

Tolvaptan, a promising new drug for treating ADPKD, failed to receive US approval. Rapamycin is another potentially effective agent but has had mixed results in clinical trials.

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AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) is the most common inherited renal disease, has an estimated prevalence of 1:400 to 1:1,000 live births in the United States, and occurs worldwide.[1,2] There are about 700,000 people living with it in the United States, and about 6,000 new cases arise annually. It accounts for nearly 5% of all patients with end-stage renal disease in the United States.[3]

This paper will offer an overview of the pathogenesis of renal cysts, review some of the clinical aspects of ADPKD including diagnosis and management of complications, and discuss recent drug trials and current management.

TWO TYPES—PKD1 IS MORE COMMON AND PROGRESSES MORE RAPIDLY

Two major forms of ADPKD are recognized and can usually be determined by genetic testing: PKD1, accounting for about 85% of cases, and PKD2, accounting for 15%.

The gene locus for PKD1 is on the short arm of the 16th chromosome (16p13.3), and its glycoprotein gene product is polycystin 1 (PC1), a large molecule with 4,303 amino acids.[2] PC1 has a long N-terminal extracellular tail that can function as a mechanosensor. Disease progression is much faster with PKD1, and end-stage renal disease usually occurs before age 56.[4]

In PKD2, the gene locus is on the long arm of the fourth chromosome (4q21-23), and has a smaller glycoprotein gene product, polycystin 2 (PC2), that plays a role in calcium transport. The disease course of PKD2 tends to be slower. End-stage renal disease might not develop in the patient's lifetime, since it typically develops when the patient is more than 70 years old.[4]

TABLE 1

Unified ultrasonographic criteria for diagnosis of ADPKD with positive family history

Age and number of cysts	PKD1	PKD2	Unknown gene type
15–29 years—a total of 3 cysts in both kidneys			
Positive predictive value	100%	100%	100%
Sensitivity	94.3%	69.5%	81.7%
30–39 years—a total of 3 cysts in both kidneys			
Positive predictive value	100%	100%	100%
Sensitivity	96.6%	94.9%	95.5%
49–59 years—2 or more cysts in each kidney			
Positive predictive value	100%	100%	100%
Sensitivity	92.6%	88.8%	90%

PEI Y. IMAGING IN PKD: ROLE OF ULTRASOUND. PRESENTED AT THE AMERICAN SOCIETY OF NEPHROLOGY KIDNEY WEEK 2013, ATLANTA, GA, NOVEMBER 6, 2013; DATA FROM: PEI Y, OBAJI J, DUPUIS A, ET AL. UNIFIED CRITERIA FOR ULTRASONOGRAPHIC DIAGNOSIS OF ADPKD. J AM SOC NEPHROL 2009; 20:205–212.

Although the growth rate of renal cysts is similar between the two types, patients with PKD1 develop about twice as many cysts as those with PDK2, and their cyst development starts at a younger age.[5]

Typically, patients have a clear phenotype and a positive family history, but in about 10% of possible ADPKD cases, there is no family history of ADPKD. Genetic variations such as incompletely penetrant PKD1 alleles,[6] hypomorphic alleles,[7] and trans-heterozygous mutations[8] account for at least some of these cases.

Because renal cysts in ADPKD are noncommunicating, bleeding into or infection in a cyst may not always be apparent in the urinalysis

IMAGING CRITERIA HAVE BROADENED

Ultrasonographic criteria for the diagnosis of ADPKD that were published in 1994 were based on patients who had a family history of PKD1.[9] The criteria have since been modified (the "unified criteria") to include patients with a family history of PKD2 who begin cyst development at a later age and with lower numbers.[10] For patients ages 30 to 39, a previously difficult diagnostic group, the criterion for the minimum number of cysts visible on ultrasonography changed from four to three, improving the sensitivity of detecting disease from approximately 76% to approximately 95% (TABLE 1).[9,10] It is important to note that these criteria apply only to patients "at risk," ie, with a positive family history of ADPKD.

Computed tomography (CT) and magnetic resonance imaging (MRI) classically show bilaterally enlarged multicystic kidneys, though variations can be seen.

DISEASE CAN PRESENT IN MYRIAD WAYS

Although cystic kidney disease is the basic underlying problem, undiagnosed patients may present with a variety of symptoms caused by other manifestations of ADPKD (TABLE 2).

Hypertension is the most common presentation, occurring in about 50% of patients ages 20 to 34, and essentially 100% of those with end-stage renal disease.[11] It is associated with up-regulation of the renin-angiotensin-aldosterone system.

Pain is typically located in the abdomen, flank, or back and can occur in a localized or diffuse manner. Early abdominal distress is often simply described as "fullness." Localized pain is usually caused by bleeding into or rupture of a cyst, renal stones, or infection.[12] Because renal cysts are noncommunicating, bleeding can occur into a cyst and cause pain without gross hematuria. Compression by greatly enlarged kidneys, liver, or both can cause a variety of gastrointestinal symptoms such as reflux esophagitis and varying degrees of constipation. Diffuse pain is often musculoskeletal and related to exaggerated lordosis from increasing

abdominal size due to enlarging cystic kidneys and sometimes liver.[12] In carefully selected cases, cyst aspiration may be helpful.[11]

Although renal carcinomas are rare and not more frequent than in the general population, they can occur at an earlier age and with constitutional symptoms.[11]

Urinary tract infections are increased in frequency. A patient may have a simple urinary tract infection that is cured with the appropriate antibiotic. However, a urinary tract infection repeatedly recurring with the same organism is a strong clue that an infected cyst is the source and requires more intensive treatment with the appropriate cyst-penetrating antibiotic. On the other hand, because cysts are noncommunicating, an infected cyst might be present despite a negative urine culture.

Identifying infected cysts can be a challenge with conventional imaging techniques, but combined positron emission tomography and CT (PET/CT) can be a valuable though expensive diagnostic tool to identify an infected kidney or liver cyst, or to identify an unsuspected source of the pain and infection.[13]

Jouret et al[13] evaluated 27 PET/CT scans performed in 24 patients with ADPKD and suspicion of an abdominal infection. Patients were deemed to have *probable* cyst infection if they met all of the following criteria: temperature more than 38°C for longer than 3 days, loin or liver tenderness, plasma C-reactive protein level greater than 5 mg/dL, and no evidence of intracystic bleeding on CT. Patients with only two or three of these criteria were classified as having fever of unknown origin. Diagnosis of cyst infection was confirmed by cyst fluid analysis.

PET/CT identified a kidney or liver cyst infection in 85% of 13 infectious events in 11 patients who met all the criteria for *probable* cyst infection; CT alone contributed to the diagnosis in only one patient.[13] In those with fever of unknown origin, PET/CT identified a source of infection in 64% of 14 events in 13 patients: two infected renal cysts, as well as one patient each with other infections that would be difficult to diagnose clinically, ie, small bowel diverticulitis, psoas abscess, diverticulitis of the right colon, pyelonephritis in a transplanted kidney, infected abdominal aortic aneurysm, prostatitis, colitis, and *Helicobacter pylori* gastritis. Results of PET/CT were negative in five patients with intracystic bleeding.

TABLE 2

Cystic and noncystic complications of ADPKD

CYSTIC COMPLICATIONS

Renal cysts

Hypertension
Pain
Bleeding
Urinary tract infection
Infected cyst
Renal stones
Urinary tract obstruction
Progressive enlargement of the kidneys and liver
Decline in renal function (glomerular filtration rate)

Nonrenal cysts

Liver (cystic enlargement more pronounced in women)
Pancreas (cysts uncommon and typically do not affect function)
Seminal vesicles (might affect fertility)
Arachnoid membrane (usually asymptomatic but need monitoring for atypical course)

NONCYSTIC COMPLICATIONS

Intracranial aneurysm
Cardiac valve abnormalities (mostly mitral and aortic valves)
Aortic root dilatation or aneurysm
Abdominal aortic aneurysm
Thromboembolic events (before and after renal transplantation)
Hernia
Diverticulosis

Kidney stones occur in 20% to 36% of patients.[11,14] Uric acid stones occur at almost the same frequency as calcium oxalate stones.

Chronic kidney disease not previously diagnosed may be the presenting condition in a small percentage of patients, sometimes those in whom much earlier hypertension was not fully evaluated. ADPKD is typically not associated with significant proteinuria (eg, nephrotic range), and the presence of heavy proteinuria usually indicates the presence of a superimposed primary glomerulopathy.[15]

Cysts in other locations. By MRI, liver cysts are present in 58% of patients ages 15 to 24, rising to 94% in those ages 35 to 46.[11] Because liver cysts are estrogen-dependent, they are more prominent in women. A small percentage of patients develop cysts in the

pancreas (5%), arachnoid membranes (8%), and seminal vesicles (40% of men with ADPKD).[11]

Cardiovascular abnormalities occur in almost one-third of patients with ADPKD, usually as mitral and aortic valve abnormalities.[16] Aneurysms of the aortic root and abdominal aorta can also occur, in addition to intracranial aneurysms (see below).[17]

Intracranial aneurysms are not uncommon, and size usually determines their risk.

Intracranial aneurysms are strongly influenced by family history: 16% of ADPKD patients with a family history of intracranial aneurysm also develop them, compared with 5% to 6% of patients with no family history.[11] The anterior cerebral circulation is involved in about 80% of cases. A sentinel or sudden "thunderclap" headache is a classic presentation that may precede full-blown rupture in about 17% of cases.[18] Patients who rupture an intracranial aneurysm have a mean age of 39, usually have normal renal function, and can be normotensive.[11]

For patients with no history of subarachnoid hemorrhage, the 5-year cumulative rupture rates for patients with aneurysms located in the internal carotid artery, anterior communicating or anterior cerebral artery, or middle cerebral artery were 0% for aneurysms less than 7 mm, 2.6% for those 7 to 12 mm, 14.5% for those 13 to 24 mm, and 40% for those 25 mm or larger, with higher rates for the same sizes in the posterior circulation.[11]

The occurrence of intracranial aneurysms is strongly influenced by family history, and size is a major determinant of their risk

In patients without symptoms, size is correlated with risk of rupture: less than 4 mm is usually associated with very low risk, 4 to less than 7 mm with moderate risk, and 7 mm or more with increasing risk. An aneurysm larger than 10 mm is associated with roughly a 1% risk of rupture per year.[19]

Irazabal et al[20] retrospectively studied 407 patients with ADPKD who were screened for intracranial aneurysm. Saccular aneurysms were detected in 45 patients; most were small (median diameter 3.5 mm). During cumulative imaging follow-up of 243 years, only one new intracranial aneurysm was detected (increasing from 2 to 4.4 mm over 144 months) and two previously identified aneurysms grew (one increasing 4.5 to 5.9 mm over 69 months and the other 4.7 to 6.2 mm over 184 months). No change occurred in 28 patients. Seven patients were lost to follow-up, however. During cumulative clinical follow-up of 316 years, no aneurysm ruptured. Two patients were lost to follow-up, three had surgical clipping, and five died of unrelated causes. The authors concluded that presymptomatic intracranial aneurysms are usually small, and that growth and rupture risks are no higher than for unruptured intracranial aneurysms in the general population. A 2014 study also suggests a conservative approach for managing intracranial aneurysm in the general population.[21]

In asymptomatic ADPKD patients, it is reasonable to reserve screening for those with a positive family history of intracranial aneurysm or subarachnoid hemorrhage, those with a previous ruptured aneurysm, those in high-risk professions (eg, pilots), and for patients prior to anticoagulant therapy or major surgery possibly associated with hemodynamic instability.[11,22] Certain extremely anxious patients might also need to be studied. Screening can be performed with magnetic resonance angiography without gadolinium contrast. It is prudent to have patients with an intracranial aneurysm thoroughly evaluated by an experienced neurosurgeon with continued follow-up.

PROGRESSION OF ADPKD

The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study[23] evaluated 241 patients with ADPKD (ages 15 to 46) by measuring the annual rate of change in total kidney volume, total cyst volume, and iothalamate glomerular filtration rate (GFR) over 3 years. The annual increase in total kidney volume averaged 5.3%,[23] though the reported range with various imaging techniques is from 4% to 12.8% in adults.[24] This study focused on macrocystic disease, ie, cysts that are visible by MRI and measurably increase total kidney volume. Although larger total kidney volume at baseline generally predicted a more rapid decline in GFR, there were wide and overlapping variations in yearly GFR declines within and among different total-kidney-volume groups.[23]

SPECIAL CLINICAL PROBLEMS IN ADPKD

Case 1: A man with ADPKD develops new and increasing proteinuria

A 55-year-old man with ADPKD and stage 3 chronic kidney disease developed new and

increasing proteinuria, rising to 5,500 mg per 24 hours. What is the most likely explanation?

- ☐ Rapidly progressive renal failure with increasing proteinuria in ADPKD
- ☐ Bilateral renal vein thromboses because of cyst compression
- ☐ Malignant hypertension with bilateral renal artery compression
- ☐ Superimposed primary glomerulopathy
- ☐ Multiple infected renal cysts with pyonephrosis

Answer: Superimposed primary glomerulopathy.

ADPKD (similar to uncomplicated obstructive uropathy, pyelonephritis, main renal artery disease, and often cases of interstitial nephritis without secondary glomerular changes) typically does not result in nephrotic-range proteinuria. A superimposed primary glomerulopathy, focal segmental glomerulosclerosis, was the biopsy-proved diagnosis.

At least 21 cases have been reported of ADPKD with nephrotic-range proteinuria and a renal biopsy showing a primary glomerulopathy, including focal segmental glomerulosclerosis (5 cases), minimal-change disease (5), membranous nephropathy (3), IgA nephropathy (2), and one each of crescentic glomerulonephropathy, diabetic nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephropathy, amyloid glomerulopathy, and mesangioproliferative glomerulopathy.[15] Treatment was directed at the primary glomerulopathy, and the outcomes corresponded to the primary diagnosis (eg, with appropriate treatment, three of the five patients with focal segmental glomerulosclerosis progressed to end-stage renal disease, all of the patients with minimal-change disease went into remission, and one of the two cases with IgA nephropathy improved).[15]

Case 2: A woman with ADPKD and advanced renal failure develops shortness of breath

A 47-year-old woman with very large polycystic kidneys (total kidney volume 7,500 mL; normal range for a single kidney approximately 136–295 mL, mean 196)[25] and estimated GFR of 25 mL/min developed new-onset shortness of breath while climbing steps and later even when making a bed. She had no chest pain, cough, or edema. She was sent directly to the emergency department and was admitted and treated; her condition improved, and she was discharged after 6 days. What did she have?

- ☐ Presentation of rare cystic pulmonary disease in ADPKD
- ☐ Onset of pneumonia with early bacteremia
- ☐ Progressive reduction in ventilatory capacity from massive polycystic kidneys and liver elevating both sides of the diaphragm
- ☐ Pulmonary emboli from an iliac vein or inferior vena cava source
- ☐ Progressive anemia accompanying rapidly worsening stage 4 chronic kidney disease

Answer: She had pulmonary emboli from an iliac vein (right) or inferior vena cava source.

Pulmonary emboli in ADPKD can be caused by thrombi in the inferior vena cava or the iliac or femoral vein because of compression by a massive right polycystic kidney. Four cases were reported at Mayo Clinic,[26] three diagnosed by MRI and one with CT. One additional case occurred at Cleveland Clinic. All patients survived after treatment with anticoagulation therapy; early nephrectomy was required in two cases.

Interestingly, following kidney transplantation, the patients at greatest risk for pulmonary emboli are those with ADPKD as their original disease.[27]

Typically, ADPKD by itself does not cause nephrotic-range proteinuria

RENAL CYSTS RESULT FROM COMBINED MUTATIONS, INJURY

The germline ADPKD mutation that occurs in one allele of all renal tubular epithelial cells is necessary but not sufficient for cystogenesis.[28] One or more additional somatic mutations of the normal allele—the "second hit"—also develop within individual tubular epithelial cells.[28,29] These epithelial cells undergo clonal proliferation, resulting in tubular dilatation and cyst formation. Monoclonality of cells in cysts has been documented.

Ischemia-reperfusion injury can be viewed as a "third hit."[30] In PKD1 knockout mice, which at 5 weeks of age normally develop only

mild cystic kidney disease, the superimposition of unilateral ischemia-reperfusion injury at 8 weeks caused widespread and rapid cyst formation. It is believed that acute renal injury reactivates developmental signaling pathways within 48 hours that trigger epithelial cell proliferation and then cyst development detectable by MRI 2 weeks later. Although this phenomenon has not been documented in humans, it is a cautionary tale.

CYSTOGENESIS INVOLVES MULTIPLE PATHWAYS

A comprehensive description of pathways leading to renal cyst formation is beyond the scope of this article, and the reader is referred to much more detailed and extensive reviews.[2,31] Disturbances in at least three major interconnected pathways promote cystogenesis in renal tubular epithelial cells:

- Normal calcium transport into the endoplasmic reticulum is disrupted by abnormal polycystins on the surface of the primary cilium
- Vasopressin and other stimuli increase the production of cyclic adenosine monophosphate (cAMP)
- The mammalian target of rapamycin (mTOR) proliferative pathway is up-regulated.

DISRUPTION OF CALCIUM TRANSPORT IN THE PRIMARY CILIUM

Primary cilia have been identified in numerous species, from green algae to humans, and genetic defects in them are the cause of diseases known as 'ciliopathies'

Primary cilia are nonmotile cellular organelles of varying size, from about 0.25 µm up to about 1 µm.[32] Each primary cilium has nine peripheral pairs of microtubules but lacks a centrally located pair that is present in motile cilia. Primary cilia are ubiquitous and have been highly conserved throughout evolution. A single cilium is present on almost all vertebral cells.[33]

Cilial defects have been identified in autosomal dominant as well as recessive diseases and are known as ciliopathies.[33] Although rare in humans, they can affect a broad spectrum of organs other than the kidney, including the eye, liver, and brain.[33]

Urine flow in a renal tubule is believed to exert mechanical stimulation on the extracellular flagellum-like N-terminal tail of PC1 that extends from a primary cilium into the urinary space. PC1 in concert with PC2 opens PC2 calcium channels, allowing calcium ions to flow down the microtubules to ryanodine receptors and the basal body.[32,33] This leads to local release of calcium ions that regulate cell proliferation.[32,34] However, in ADPKD kidneys, PC1 and PC2 molecules are sparse or mutated, resulting in defective calcium transport, increased and unregulated tubular epithelial cell proliferation, and cyst formation.

In a totally different clinical setting, biopsies of human renal transplants that sustained acute tubular necrosis during transplantation reveal that a cilium dramatically elongates in response to injury,[35] possibly as a compensatory mechanism to maintain calcium transport in the presence of meager urine flow and to restore the proliferation of tubular epithelial cells in a regulated repair process.

THE ROLE OF VASOPRESSIN AND ACTIVATION OF cAMP

In classic experiments, Wang et al[36] cross-bred rats having genetically inherited polycystic kidney disease (actually, autosomal recessive polycystic kidney disease) with Brattleboro rats that completely lack vasopressin. At 10 and 20 weeks of age, the offspring had virtually complete inhibition of cystogenesis because of the absence of vasopressin. However, when vasopressin was restored by exogenous administration continuously for 8 weeks, the animals formed massive renal cysts.

Vasopressin activates cAMP, which then functions as a second messenger in cell signaling. cAMP increases the activation of the protein kinase A (PKA) pathway, which in turn increases downstream activity of the B-raf/ERK pathway. Up-regulation of cAMP and PKA appears to perpetuate activation of canonical Wnt signaling, down-regulate noncanonical Wnt/planar cell polarity signaling, and lead to loss of tubular diameter control, resulting in cyst formation.[31] Normally, cAMP is degraded by phosphodiesterase. However, because of the primary cilium calcium transport defect in ADPKD, phosphodiesterase is reduced and cAMP persists.[37] In conjunction with the defective primary cilial calcium transport, cAMP exerts a proliferative effect

on renal tubular epithelial cells that is opposite to its effect in normal kidneys.[31,32] cAMP also up-regulates the cystic fibrosis transmembrane conductance regulator (CFTR) that promotes chloride ion transport. Sodium ions follow the chloride ions, leading to fluid accumulation and cyst enlargement.[31]

Inhibiting vasopressin by increasing water intake

A simple key mechanism for limiting vasopressin secretion is by sufficient water ingestion. Nagao et al[38] found that rats with polycystic kidney disease given water with 5% glucose (resulting in 3.5-fold increased fluid intake compared with rats given tap water) had a 68% reduction in urinary vasopressin and a urine osmolality less than 290 mOsm/kg. The high-water-intake rats had dramatically reduced cystic areas in the kidney and a 28% reduction of kidney-to-body weight ratio vs controls.

In an obvious oversimplification, these findings raised the question of whether a sufficient increase in water intake could be an effective therapy for polycystic kidney disease.[39] A pilot clinical study evaluated changes in urine osmolality in eight patients with ADPKD who had normal renal function.[40] At baseline, 24-hour urine osmolality was typically elevated to approximately 753 mOsm/kg compared to the plasma at 285 mOsm/kg, indicating that antidiuresis is the usual state. During the 2-week study, urine volume and osmolality were measured, and additional water intake was adjusted in order to achieve a urine osmolality goal of 285 ± 45 mOsm/kg. These adjustments resulted in water intake that appeared to be in the range of 2,400 to 3,000 mL per 24 hours. The major limitations of the study were that it was very short term, and there was no opportunity to measure changes in total kidney volume or estimated GFR.

In a recent preliminary report from Japan, high water intake (2,500–3,000 mL daily) in 18 ADPKD patients was compared over 12 months with ad libitum water intake in 14 ADPKD controls (clinicaltrials.gov NCT 01348505). There was no statistically significant change in total kidney volume or cystatin-estimated GFR in those on high water intake, but serious defects in study design (patients in the high water intake group were allowed to decrease their intake if it was causing them difficulty, and patients in the ad libitum water intake group had no measurement of their actual water intake) prevent any conclusions because there was no evidence that the groups were different from one another with respect to the key element of the study, namely, water intake.

Blocking the vasopressin receptor slows disease progression

Using another approach, Gattone et al[41] inhibited the effect of vasopressin by blocking the vasopressin 2 receptor (V2R) in mouse and rat models of polycystic kidney disease, using an experimental drug, OPC31260. The drug halted disease progression and, in one situation, appeared to cause regression of established disease. As noted by Torres and Harris,[31] even though both increased water intake and V2R antagonists decrease cAMP in the distal tubules and collecting ducts, circulating levels of vasopressin are decreased by increased water intake but increased by V2R antagonists.

After these remarkable results in animal models, clinical trials of the V2R antagonist tolvaptan were conducted in patients with ADPKD. In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes 3:4 study,[42] 1,445 adults (ages 18 to 50) with ADPKD in 133 centers worldwide were randomized to receive either tolvaptan or placebo for 3 years. Key inclusion criteria included good renal function (estimated GFR ≥ 60 mL/min) and total kidney volume of at least 750 mL (mean 1,700 mL) as measured by MRI. Tolvaptan was titrated to the highest tolerated twice-daily dose (average total of 95 mg/day). All patients were advised to maintain good hydration and to avoid thirst by drinking a glass of water after each urination. Unfortunately, neither water intake nor urine output was measured.

The primary end point was the annual rate of change in total kidney volume, with secondary end points of clinical progression (worsening kidney function, pain, hypertension, albuminuria), and rate of decline in kidney function as measured by the slope of the reciprocal of serum creatinine.[42]

Tolvaptan, in a major clinical trial, led to a smaller yearly increase in total kidney volume and slower decline in renal function, but had significant side effects

Patients in the tolvaptan arm had a slower annual increase in total kidney volume than controls (2.8% vs 5.5%, respectively, $P < .001$) and a slower annual decline in renal function (–2.61 vs –3.81 mg/mL^{-1}, respectively, $P < .001$).[42] More participants in the treatment group withdrew than in the placebo group (23% vs 14%, respectively).

Adverse events occurred more frequently with tolvaptan.[42] Liver enzyme elevations of greater than three times the upper limit of normal occurred in 4.4% of patients in the treatment group, leading to a drug warning issued in January 2013. As expected, side effects related to diuresis (urinary frequency, nocturia, polyuria, and thirst) were more frequent in the treatment group, occurring in up to 55% of participants.

The authors noted, "Although maintaining hydration helped ensure that the blinding in the study was maintained, the suppression of vasopressin release in the placebo group may have led to an underestimation of the beneficial effect of tolvaptan and may account for the lower rates of kidney growth observed in the placebo group."[42]

In 2013, the US Food and Drug Administration (FDA) denied a new drug application for tolvaptan as a treatment for ADPKD.

New cellular pathways and new histologic findings are being identified in ADPKD

THE mTOR PATHWAY IS UP-REGULATED

The mTOR pathway that plays a major role in cell growth and proliferation includes interaction of the cytoplasmic tail of polycystin 1 with tuberin.[43] Activation products of mTOR, including phospho-S6K, have been found in tubular epithelial cells lining cysts of ADPKD kidneys but not in normal kidneys.[43] Mutant mice with polycystic disease had phospho-S6K in tubular epithelial cells of cysts, whereas those treated with the mTOR inhibitor rapamycin did not.[43] But subsequent studies have shown that only a low level of mTOR activation is present in 65% to 70% of ADPKD cysts.[44]

Two major studies of the treatment of ADPKD with rapamycin that were published contemporaneously in 2010 failed to demonstrate any significant benefit with mTOR inhibitor treatment.[45,46]

Serra et al[45] conducted an 18-month, open-label trial of 100 ADPKD patients ages 18 to 40 with an estimated GFR (eGFR) of at least 70 mL/min. Patients were randomized to receive rapamycin, given as sirolimus 2 mg per day, or standard care. The primary end point was the reduction in the growth rate of total kidney volume, measured by MRI. Secondary end points were eGFR and protein excretion (albumin-creatinine ratio). No significant difference was found in total kidney volume, but a nonsignificant stabilization of eGFR was noted.

Walz et al[46] in a 2-year, multicenter, double-blind trial, randomized 433 patients (mean age 44; mean eGFR 54.5 mL/min) to treatment with either the short-acting mTOR inhibitor everolimus (2.5 mg twice daily) or placebo. Although patients in the treatment group had less of an increase in total kidney volume (significant at 1 year but not at 2 years), they tended to show a decline in eGFR. But further analysis showed that the only patients who had a reduction in eGFR were males who already had impaired kidney function at baseline.[47]

In a pilot study, 30 patients with ADPKD (mean age 49) were randomized to one of three therapies:

- Low-dose rapamycin (trough blood level 2–5 ng/mL)
- Standard-dose rapamycin (trough blood level > 5–8 ng/mL)
- Standard care without rapamycin.[48]

In contrast to other studies, the primary end point was the change in iothalamate GFR at 12 months, with change in total kidney volume being a secondary end point.

At 12 months, with 26 patients completing the study, the low-dose rapamycin group (n = 9) had a significant increase in iothalamate GFR of 7.7 ± 12.5 mL/min/1.73 m^2, whereas the standard-dose rapamycin group (n = 8) had a nonsignificant increase of 1.6 ± 12.1 mL/min/1.73 m^2, and the no-rapamycin group (n = 9) had a fall in iothalamate GFR of 11.2 ± 9.1 mL/min/1.73 m^2 ($P = .005$ for low-dose vs no rapamycin; $P = .07$ for standard-dose vs no rapamycin; $P = .52$ for low-dose vs standard-dose rapamycin; and $P = .002$ for combined low-dose and standard-dose rapamycin vs no rapamycin.).[48] These differences were observed despite there being no significant change in total kidney volume in any of the groups. Patients on low-dose ra-

pamycin had fewer adverse effects than those on standard dose and were more often able to continue therapy for the entire study. This, and the use of iothalamate GFR rather than eGFR to measure GFR, are believed to be the main reasons that low-dose effects were more pronounced than those with standard doses. One may speculate that rapamycin may have its effect on microcysts and cystogenic cells, resulting in stabilization of or improvement in renal function without detectable slowing in total kidney volume enlargement. Mechanisms for this possibility involve new concepts, as discussed below.

NEW CONCEPTS

Specialized cells also promote renal cyst formation

Specialized cells that promote cyst formation have been identified by Karihaloo et al[49] in a mouse model of polycystic kidney disease. In this model, alternatively activated macrophages homed to cystic areas and promoted cyst growth. These findings suggested that interrupting the homing and proliferative signals of macrophages could be a therapeutic target for ADPKD. Although rapamycin can suppress macrophage proliferation by macrophage colony-stimulating factor and inhibit macrophage function,[50] alternatively activated macrophages have not been specifically studied for rapamycin responsiveness.

More promising is evidence that CD133+ progenitor cells from human ADPKD kidneys —but not from normal human kidneys—form cysts in vitro and in severe combined immunodeficient mouse models.[51] Treatment with rapamycin decreased proliferation of the dedifferentiated CD133+ cells from ADPKD patients and reduced cystogenesis.[51]

Visible cysts are the tip of the iceberg

Using ADPKD nephrectomy specimens from eight patients, Grantham et al[52] compared cyst counts by MRI and by histology and found that for every renal cyst detected by MRI, about 62 smaller cysts (< 0.9 mm) are present in the kidney. For a typical patient having an average of 587 cysts in both kidneys that are detectable by MRI, this means that more than 36,000 cysts are actually present, and MRI detects less than 2% of the total cysts present.

Although microcysts are too small to contribute much to total kidney volume, they can interfere with kidney function. Microcysts can reduce GFR in two major ways: by compressing microvasculature, tubules, and glomeruli in the cortex; or by blocking the drainage of multiple upstream nephrons when they form in or block medullary collecting ducts.[52] Although the growth rates of microcysts less than 1 mm in size have not yet been measured, the adult combined growth rates of the renal cyst component is approximately 12% per year, with yearly individual cyst growth rates up to 71%, and with fetal cyst growth rates even higher for cysts larger than 7.0 mm.[53] Before and during an accelerated growth period, microcysts may be susceptible to certain therapies that could first improve GFR and only later change measurable total kidney volume by slowing microcyst progression to macrocysts either directly or through specialized cells that may be sensitive to rapamycin.

CURRENT MANAGEMENT OF ADPKD

Blood pressure control is essential—but too low is not good. For adult patients with hypertension caused by ADPKD, an acceptable blood pressure range is 120–130/70–80 mm Hg. However, further information from recently published blood pressure guidelines[54] and the results of the Halt Progression of Polycystic Kidney Disease (HALT-PKD) study to be reported in late 2014[55] may provide more precise ranges for blood pressure control in ADPKD.

Although substantial experimental evidence exists for the benefits of inhibiting the up-regulation of the renin-angiotensin-aldosterone system in ADPKD, clinical proof is not yet available to confirm that angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are preferred therapy.[55] This may be determined by results of the HALT-PKD study, due for release in late 2014.[55]

Controlling blood pressure should be done with caution. Patients with low GFRs whose blood pressure is too low tend to have a more rapid decline of GFR, as suggested in the Modification of Diet in Renal Disease (MDRD) study in 1995.[56]

Increased water intake, which decreases serum osmolality and thereby inhibits vasopressin secretion, should be done with physician supervision because of possible complications, particularly hyponatremia

Experimental evidence suggests that avoiding calcium channel blockers may be advisable. Yamaguchi et al[34] found that calcium channel blockers worsen the calcium transport defect and convert tubular epithelial cells to a proliferative phenotype.[34]

High fluid intake (2,500–3,000 mL/day), because it suppresses vasopressin, may be useful if permitted by several factors such as the patient's cardiopulmonary and renal and electrolyte status, other medications, and diet.[31] The reader is referred to a detailed description of the precautions necessary when prescribing high water intake.[31] Patients should have their fluid intake managed by a physician and their renal function and serum sodium and electrolytes monitored regularly in order to avoid hyponatremia. Severe hyponatremia has occurred in patients with ADPKD and impaired kidney function who drank excessive quantities of water. Cardiac and pulmonary complications from excessive fluid intake are also possible, especially with a low GFR and compromised cardiac function.

A low-sodium diet, if not a contributing factor in hyponatremia, can be used under physician direction in the management of hypertension as well as in the prevention of calcium oxalate kidney stones.

Caffeine should be avoided because it may interfere with the activity of the phosphodiesterase that is necessary for the catabolism of cAMP to 5´AMP.

A low-protein diet is of unproven benefit,[56] but it is prudent to avoid high protein intake.[57]

Complications such as bleeding (into or from cysts), infection (urinary tract, kidney cysts, and liver cysts), kidney stones, and urinary tract obstruction should be treated promptly and may require hospitalization.

Regular symptom reviews and physical examinations need to be performed with nonrenal concerns also in mind, such as intracranial aneurysms and cardiac valve lesions.[11,58]

Formal genetic counseling and molecular testing are becoming more frequently indicated as more complex inheritance patterns arise.[6–8,59]

Renal replacement therapy in the form of dialysis or transplantation is usually available for the patient when end-stage renal disease occurs. In the largest study thus far, ADPKD patient survival with a kidney transplant was similar to that of patients without ADPKD (about 93% at 5 years), and from 5 years to 15 years death-censored graft survival was actually better.[60] Thromboembolic events are more frequent after transplantation,[27,60] but they may also occur before transplantation from a massive right kidney compressing the iliac vein or the inferior vena cava, or both, leading to thrombus formation.[26]

Investigational as well as standard drug studies have intensified. Results from a large randomized study in approximately 1,000 adult ADPKD patients that evaluated over 6 to 8 years the effects of ACE inhibition with or without ARB treatment of hypertension, at both usual and lower blood pressure ranges in those with good renal function, are expected in late 2014.[55] Outcomes from a few small clinical studies, eg, one with long-acting somatostatin[31,61] and one using low-dose rapamycin[48] in adults with ADPKD, will require confirmation in large randomized placebo-controlled clinical studies. In a new 3-year randomized placebo-controlled study of 91 children and young adults (ages 8 to 22) with ADPKD and essentially normal renal function who continued treatment with lisinopril, the addition of pravastatin (20 mg or 40 mg daily based on age) resulted in a significant reduction in the number of patients (46% vs 68%, respectively, $P = .03$) experiencing a greater than 20% change (increase) in height-adjusted total kidney volume.[62] Change in GFR was not reported,[62] but an earlier 4-week study in 10 patients treated with simvastatin did show an increase in renal blood flow and GFR.[63] Numerous other agents that lack human studies include some described in older experimental work (eg, amiloride,[31,64] citrate[31,65]) and many others from a growing list of potential therapeutic targets.[31,66–73] It must be emphasized that there is no FDA-approved medication specifically for the treatment of ADPKD.

Future specific treatments of ADPKD may also involve minimally toxic doses of combination or sequential therapy directed at precystic and then both micro- and macrocystic/cystic fluid expansion aspects of ADPKD.[48,74] Unfortunately, at the present time there is no specific FDA-approved therapy for ADPKD. ■

The Polycystic Kidney Disease Foundation currently lists 15 studies, ranging from observational to interventional trials, that are actively recruiting ADPKD patients

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