Kidney Medicine

Quest for the Cure: Testing the Old and New to Prevent Progression of Autosomal Dominant Polycystic Kidney Disease

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Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited disorder (lifetime risk of 1 in 1,000),[1] occurring in all races and ethnicities worldwide, with serious health consequences such as

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end-stage kidney disease (ESKD) requiring dialysis or kidney transplantation, heart disease, stroke, and premature death. Over a lifetime, thousands of cysts form and grow in the kidneys and liver, leading to massive enlargement of the kidneys and eventually resulting in kidney failure. Decades of research have unraveled the genetic basis of ADPKD, which is caused in >90% of cases by heterozygous mutations in 1 of 2 genes, *PKD1* and *PKD2* encoding the proteins polycystin 1 and 2. More recently, rare mutations in several other genes have been described, mostly responsible for milder and atypical forms of the disease.[1,2]

The exact molecular mechanisms of cyst initiation and progression to kidney failure remain unknown, but several aspects of the pathophysiology have been elucidated. Cyst growth requires increased proliferation of cyst-lining epithelial cells and continuous fluid secretion, as well as alterations in basement membrane and interstitial matrix properties to allow the cysts to expand.[3,4] Cyst fluids are rich in cytokines, promoting interstitial inflammation and fibrosis, which are prominent features in advanced disease.[3,4] Despite this progress, a cure is still elusive.

Early studies in ADPKD show that affected patients often have very large palpable kidneys before they develop ESKD, thus linking kidney growth to kidney failure.[5] More recent longitudinal observational studies have firmly established the link between cyst growth, increase in total kidney volume, and subsequent decline in kidney function.[6-8] Consequently, the idea that inhibiting cyst growth might preserve kidney function has led to new therapeutic approaches. Based on solid evidence that cyst epithelial cell proliferation and fluid secretion are stimulated by increased tissue levels of cyclic adenosine monophosphate (cAMP) in response to vasopressin, the vasopressin-antagonist tolvaptan was applied to the treatment of ADPKD.[4,9] In the pivotal TEMPO (Tolvaptan Efficacy and Safety in Management of ADPKD and Its Outcomes) 3:4 clinical trial among 1,445 patients, tolvaptan reduced the rate of kidney growth from 5.5% to 2.8% per year over 3 years compared to placebo, accompanied by a less steep (by 1 mL/min/1.73 m^2) decline in estimated glomerular filtration rate.[9] A recent outcomes modeling study predicts that tolvaptan treatment of patients with early-stage disease but evidence of rapid progression (large total kidney volume for age) will delay the onset of ESKD by 5 to 6.6 years.[10] In contrast, a smaller (n = 309) clinical trial using the somatostatin analogue lanreotide, which also inhibits cAMP generation, failed to show an improvement in kidney function despite slowing the increase in total kidney volume.[11] This negative result may have been due to the smaller effect of lanreotide on total kidney volume (4.2% growth per year with lanreotide vs 5.6% with placebo) than seen with tolvaptan. Both drugs can only moderately reduce the rate of total kidney volume enlargement. Therefore, if we could decrease total kidney volume more dramatically, could we achieve better preservation of kidney function? This question was addressed by Iliuta et al[12] in a prospective cohort study published in this issue of *Kidney Medicine*.

The authors selected 68 consecutive individuals from their large clinical center of more than 500 patients with ADPKD for sclerotherapy of large (>5 cm) nonexophytic kidney cysts, with the rationale that large intraparenchymal cysts are particularly deleterious to kidney function because of their potential to impede blood flow or obstruct urinary flow affecting a large kidney region.[3,12] Forty-one (62%) patients also sought relief from flank or back pain, abdominal pain, and abdominal distension caused by large cysts. Sclerotherapy was performed using a newer sclerosing agent than the traditional ethanol. Sodium tetradecyl sulfate (STS) is a sclerosing agent approved by the US Food and Drug Administration for varicose veins and has a better success rate and less pain complications than ethanol. In this study, STS was mixed with room air to form a foam and was instilled into target cysts by an interventional radiologist under ultrasound guidance. The foam was allowed to dwell for an hour and then was removed; for cysts > 7 cm, this treatment was repeated after 1 week. One to 2 cysts were treated per session; altogether, 77 treatment sessions were performed in 66 patients (2 dropped out due to intervening events). Most (74%) patients were treated unilaterally, so that of 132 kidneys, 95 were treated and 37 were not.

Magnetic resonance imaging performed before and at least 3 months after sclerotherapy confirmed that this treatment resulted in a lasting 22% volume reduction of the treated kidneys, whereas the volume of untreated kidneys increased by 3.4%. Despite successful total kidney volume reduction, kidney function as measured by

24-hour creatinine clearance (CL_{cr}) did not improve, remaining stable or continuing to decline in most patients. There was an inverse correlation between CL_{cr} 12 months after sclerotherapy and baseline total kidney volume, confirming the relationship between total kidney volume and kidney function decline, which was not altered by ablating 1 or 2 large cysts. The authors reported 4 patients having an improvement in CL_{cr} by >10 mL/min after sclerotherapy, but all 4 patients had high CL_{cr} values at baseline (83-193 mL/min, and estimated glomerular filtration rate was 115 mL/min/1.73 m^2 for the patient with CL_{cr} of 83 mL/min), raising doubts about the accuracy of measurements and clinical significance of the observed increase. Spontaneous periods of stability or increase in estimated glomerular filtration rate occur in a significant proportion of patients with ADPKD.[13]

Mechanical cyst reduction strategies, such as cyst aspiration and sclerosis with ethanol or laparoscopic cyst decortication, have been used for decades in an effort to relieve the pain associated with large cysts and/or large kidneys, with success rates for pain relief varying from 25% to 100% and follow-up ranging from 12 months to more than 10 years.[14-17] Similarly, among the 41 patients in the present study who reported symptoms due to mass effect of the large kidneys, ~70% experienced improvement in their symptoms. Adverse events occurred, comprising postprocedure pain in 9 patients (lasting for >1 month in 2), 1 potential and 2 definite procedure-related cyst infections, and asymptomatic intermittent hematuria for several days in 1 patient. Therefore, sclerotherapy of cysts is not without risk. All older studies, as well as the the present cohort study, were observational and underpowered to determine long-term effects on kidney function, but the general conclusion was that mechanical cyst reduction had no detrimental but also no beneficial effect on progression to ESKD.[14-17]

Why does reduction of total kidney volume by cyst aspiration not lead to improvement in kidney function in this and the older studies? One obvious reason is that only a few cysts among hundreds to thousands can be targeted by foam sclerotherapy. Although the largest cysts contribute most to total kidney volume, the smaller cysts certainly have an effect on the microenvironment around them, releasing cytokines and attracting macrophages that alter the integrity and function of the remaining healthy tubules.[18,19] Smaller cysts grow with time to become large cysts; therefore, sclerotherapy would have to be repeated over and over during a lifetime, with considerable accumulation of potential adverse events. Cyst sclerotherapy does not reverse interstitial inflammation and fibrosis that have already developed by the time this therapy is performed. In mouse models of ADPKD, infiltration of macrophages around the cysts is an early event,[18] likely triggered by the loss of polycystin 1 leading to secretion of monocyte chemoattractant protein 1 by the affected tubular epithelia, with injurious effects well established before a cyst can be aspirated.

Only a small proportion of patients with ADPKD may qualify for STS sclerotherapy. In the present study, only 68 patients from a population of more than 500 were identified as suitable. Interestingly, 41% of study participants had the *PKD2* genotype and 23% had no mutation detected, raising the possibility that individuals with these genotypes have the largest cysts most amenable for sclerotherapy. However, patients with these genotypes also have fewer cysts at any given age and late-onset ESKD compared with the more common *PKD1* genotype,[20] demonstrating that large cysts are not the main determinant of kidney function decline, although they may affect a large kidney region. Relatively few patients with the most severe genotype, that is, *PKD1* truncating mutations, were represented in this study (21%), presumably because they have innumerable cysts replacing the whole kidney, with fewer treatable large cysts.

In conclusion, sclerotherapy of large cysts with the new STS foam appears to be safe and effective as treatment for pain caused by large cysts and should be recommended as an option for relief of mass-effect symptoms. However, it remains unlikely that this treatment will prevent kidney function decline. Better understanding and targeting of the underlying molecular mechanisms of kidney function loss is needed to develop successful therapies to preserve kidney function.

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