Volume Progression in Autosomal Dominant Polycystic Kidney Disease: The Major Factor Determining Clinical Outcomes

Jared J. Grantham,* Arlene B. Chapman,† and Vicente E. Torres‡

Kansas University Medical Center, Kansas City, Kansas; †Emory University, Atlanta, Georgia; and ‡Mayo Clinic College of Medicine, Rochester, Minnesota

Autosomal dominant polycystic kidney disease (PKD) is a hereditary condition characterized by the progressive enlargement of innumerable renal cysts that contribute to life-altering morbidity early in the course of the disease. Evidence indicates that the rate of increase in kidney volume can be reliably measured by magnetic resonance or computed tomography imaging, thus providing objective means to judge the effectiveness of therapies that are targeted to the aberrant growth of renal tubules. It is now possible, therefore, to monitor the effectiveness of potential therapies on the signature abnormality in autosomal dominant PKD before irreversible damage has been done by the cysts. Evidence accumulated from human cross-sectional and longitudinal studies and longitudinal studies of PKD models in animals provide strong support for the view that reducing the rate of kidney volume enlargement will ameliorate the late-stage development of renal insufficiency.

Clin J Am Soc Nephrol 1: 148–157, 2006. doi: 10.2215/CJN.00330705

In this review, we propose a new paradigm for the evaluation of progression early in the course of chronic renal diseases that lead to renal insufficiency. In current practice, GFR is considered the gold standard for quantifying the rate of progression in all renal disorders. However, owing to the remarkable degree to which intact nephrons can compensate for the loss of functioning parenchyma, GFR measurements fail to disclose ominous changes in tissue function in the early stages of many diseases. Here, we make a case that sequential measurements of renal volume quantify the rate of disease progression before changes in GFR can be detected in autosomal dominant polycystic kidney disease (ADPKD). We think that this new paradigm for PKD, a chronic progressive disorder, complements a recent recommendation by a distinguished panel of nephrologists that measures should be taken to diagnose acute kidney injury before the rise in serum creatinine heralds severe renal dysfunction (1).

Etiology and Pathogenesis of PKD

PKD1 and *PKD2* are expressed in most organs and tissues of the human body. The proteins that are encoded by *PKD1* and *PKD2*, polycystin1 and polycystin2, seem to function together to regulate the morphologic configuration of epithelial cells (2). The polycystins are expressed in development as early as the blastocyst stage and are expressed in a broad array of terminally differentiated tissues.

The functions of the polycystins have been scrutinized to the greatest extent in epithelial tissues of the kidneys and liver and in vascular smooth muscle. Mutations in either polycystin lead to a clinical phenotype recognized as ADPKD. The hallmarks of this inherited condition are massively enlarged kidneys caused by the sustained expansion of innumerable fluid-filled cysts ranging in equivalent size from a pea to a grapefruit. Cysts derive from microscopic tubule precursors. They are seen with lesser frequency in the liver (approximately 80%), pancreas (approximately 10%), and arachnoid membranes (approximately 8%). Aneurysms occur in approximately 5% of patients with ADPKD and with higher frequency in those with a family history of aneurysm (approximately 20%). In >60% of patients, hypertension develops before the loss of renal function, and the average age of onset, although highly variable, is approximately 30 yr (3–8). Proteinuria, often used as a surrogate marker of disease activity in other kidney disorders, is usually <1 g/d. Proteinuria, observed more frequently in those with large (mean combined renal volume 1190 ml) rather than small (578 ml) renal volumes, is also associated with a greater likelihood of a subsequent loss of renal function (9).

The renal cysts develop in a tiny fraction of the nephrons (estimated to be much less than 1%) (10). In ADPKD, each epithelial cell within a renal tubule harbors a germ-line mutation, yet only a tiny fraction of the tubules develop renal cysts. It is currently held that the cells are protected by the allele inherited from the parent without ADPKD. When this allele is inactivated by a somatic event (mutation or otherwise) within a solitary renal tubule cell, the cell divides repeatedly until a cyst develops, with an aberrant growth program causing endless expansion. The severity of ADPKD is thought to be a direct consequence of the number of times and the frequency with which this cystogenic process occurs within the kidneys over the life of the patient.

Published online ahead of print. Publication date available at www.cjasn.org.

Address correspondence to: Dr. Jared J. Grantham, The Kidney Institute, Mailstop 3018, University of Kansas, Kansas City, Kansas 66103. Phone: 913-588-7605; Fax: 913-588-7606; E-mail: jgrantha@kumc.edu

ISSN: 1555-9041/101-0148

Hyperplasia of renal cyst epithelial cells is unquestioned in this disease; however, the rate of cell proliferation is slow in comparison with transformed and malignant neoplastic cells (11). The hyperplastic cells cause an out-pocketing of the tubule wall, with the formation of a saccular cyst that fills with fluid derived from glomerular filtrate that enters from the afferent tubule segment. Progressive expansion eventually causes most of the emerging cysts to separate from the parent tubule, leaving an isolated sac that fills with fluid by transepithelial secretion. This isolated cyst expands relentlessly as a result of continued proliferation of the mural epithelium together with the transepithelial secretion of NaCl and water into the lumen (12).

The expanding fluid-filled tumor masses elicit secondary and tertiary changes within the renal interstitium evinced by thickening and lamination of the tubule basement membranes, infiltration of macrophages, and neovascularization (13–15). Fibrosis within the interstitium begins early in the course of the disease. Cellular proliferation and fluid secretion may be accelerated by cAMP and growth factors such as EGF (3,12,16,17). In summary, cysts function as autonomous structures and are responsible for progressive kidney enlargement in ADPKD.

Morbidity in ADPKD

Renal Hemorrhage and Hematuria

Polycystic kidneys are unusually susceptible to traumatic injury, with hemorrhage occurring in approximately 60% of individuals (4,5,16–28). Mild trauma can lead to intrarenal hemorrhage or bleeding into the retroperitoneal space accompanied by intense pain that often requires narcotics for relief (29). The cysts are associated with excessive angiogenesis evinced by fragile vessels stretched across their distended walls. When traumatized, these vessels may leak blood into the cyst, causing it to expand rapidly, provoking frightening pain. If bleeding continues, then the cyst may rupture into the collecting system, causing gross hematuria. Alternatively, it may rupture into the subcapsular compartment and eventually dissect through the renal capsule to fill the retroperitoneal space. In massive bleeding, the blood may reach the skin that covers the flank and abdomen, where it is recognized as subcutaneous ecchymoses (Gray-Turner sign).

Evidence from computed tomography scans indicates that intracyst hemorrhage, manifested as "hyperdense" subcapsular cysts, occurs in >90% of those with ADPKD (30). Often, dozens of superficial cysts bear the marks of intracyst bleeding. Direct inspection of the "hyperdense" cysts has revealed them to be filled with cellular debris derived from the breakdown of blood products.

Patients with a history of renal hemorrhage evinced by repeated episodes of gross hematuria have the largest kidneys (Table 1) (4,18) and progress to renal insufficiency faster than those without this history. In a retrospective clinical study, Gabow *et al.* (4,18) found that male athletes who had ADPKD and participated in contact sports had more hematuric episodes and developed renal insufficiency sooner than those who did not participate. In summary, renal hemorrhage caused by cysts occurs at any age and diminishes the quality of life. Hemorrhage is associated with larger kidneys and accelerated loss of renal function.

Pain

Pain with or without hemorrhage is the most frequent symptom (approximately 60%) reported by adult patients with ADPKD (31–42) and frequently begins in individuals with normal renal function (19). Pain (often reported as either diffuse abdominal or bilateral flank pain) is also the most frequent symptom (>35%) reported by children with ADPKD and is associated with increased renal size as determined by ultrasound measurements (43–46). Although pain is commonly re-

Table 1. Relation between kidney volume and variables

Variable	Number Studied	Volume Method	Mean Kidney Volume[a]			Reference
			With variable	Without variable	*P* Value	
Proteinuria	270	US	1190 ± 93	578 ± 32	<0.0001	8
Microalbuminuria	49	US	853 ± 87	535 ± 52	<0.01	8
Hypertension		US				5
males	76		624 ± 47	390 ± 43	<0.0005	
females	89		446 ± 32	338 ± 24	<0.002	
Hypertension	43	CT	976 ± 472	739 ± 311	<0.05	84
	241	MR	628 ± 48	352 ± 33	<0.0001	80
Hypertension children	62	US	2.7 ± 2.3[b]	1.2 ± 2.5[b]	<0.05	85
Hypertension children	70	US	125 ± 7	83 ± 6	<0.0001	42, 43
Gross hematuria	191	US	820 ± 87	588 ± 52	<0.03	3
Progressive loss of renal function	43	CT	895[c]	606[c]		84
	220	US	598 ± 368	366 ± 168	<0.0001	77

[a]Mean kidney volume is combined kidney volume ÷ 2.
[b]Kidney volume corrected for body size.
[c]Derived from combined kidney volume data.

ported in children with ADPKD, it is usually not accompanied by gross hematuria. In older individuals, pain may be clearly associated with renal hemorrhage, the passage of stones (stones are more common in patients with ADPKD [47–52]), infected cysts, and pyelonephritis (52–65). The occurrence of pain, hematuria, and nephrolithiasis has also been found to correlate with the degree of kidney enlargement (6,18,66).

When one or more cysts can be identified as causing the pain, the symptoms can often be abated by open or fiber optic guided surgery to excise the outer walls and drain them (31,32,35,36,38–42,58,67–73). This type of surgery establishes an unmistakable relation between the presence of the cyst and the pain perceived by the patient.

In approximately one half of patients, however, candidate cysts cannot be identified as directly causing the pain. In these cases, indiscriminate excision of dozens of cyst walls that abut the capsule have produced complete symptomatic relief for many months or years (36,40,74). Volumetric reduction of these kidneys usually exceeds 50% but still leaves kidneys larger than normal size. Not every cyst can be removed, and, with time, the residual cysts enlarge and symptoms may reappear.

Approximately one quarter of the patients with the most severe pain do not gain relief from surgery or pharmacologic therapy with narcotics. These individuals usually have inaccessible cysts in the medullary portions of the kidneys. Nephrectomy is used as a last resort to control the pain in these unfortunate patients. In summary, pain that adversely affects the quality of life at any age is caused by renal cysts and is associated with increased renal size.

Cosmetic Deformation of the Abdomen

The kidneys in some patients enlarge to such an extent that belt and dress sizes must be increased substantially. The additional mass within the abdomen affects posture during standing and walking, which contribute to lower back pain that is separate from the renal pain. Although the effect of cosmetic abdominal distortion on lifestyle and quality of life has not been studied formally, nephrologists who treat large numbers of patients with ADPKD report that many of them find the enlarging abdomen highly stressful. Huge kidneys may impair diaphragmatic motion enough to disturb sleep.

Enlarged kidneys as a result of cysts increase the risk that seat belts may cause injury (75). Patients with greatly enlarged polycystic kidneys complain that seat belts increase pain in normal use. In summary, cosmetic deformation of the abdomen at any age is caused by renal cysts and can adversely affect the quality of life.

Hypertension

Hypertension has been associated with renal size in several studies of ADPKD (Table 1) (2–6,28,54,76–85). In children who were aged 3 to 19 and had ADPKD and normal renal function, the number and volume of renal cysts determined with ultrasound were greatest in those with hypertension (Table 1) (43,54,76,79,86–88). In 165 adult patients with ADPKD, renal volumes determined with ultrasound were significantly greater in those with hypertension than in normotensive patients (6). Similarly, in a recent cross-sectional study of 241 patients with ADPKD using magnetic resonance imaging (MRI), mean kidney volume was greater in the hypertensive patients than in the normotensive group (81). Surgical removal of cysts in a large Chinese study of ADPKD patients improved BP control (89,90). In summary, the development of hypertension is associated with the enlargement of ADPKD kidneys secondary to cysts. As explained in these early sections, expanding renal cysts and the vastly enlarged kidneys that they cause provoke serious morbidities that damage the quality of life long before renal function is diminished.

Renal Insufficiency

The development of renal insufficiency is highly variable in ADPKD (5,22–25,27,66,91). Renal failure has been reported in children (92), and, conversely, individuals with the condition may live a normal life expectancy without knowing that they have the disease. An early study estimated that approximately 70% of patients with ADPKD would develop renal insufficiency if they survived to age 65 (93). A 1984 report from Canada found that the probability of being alive and not having renal failure was 77% by age 50, 57% by age 58, and 52% by age 73 (94). Genotyping now has changed the way renal function prognosis is judged. Individuals with mutations in *PKD2* develop renal failure approximately 15 yr later than those with *PKD1* mutations (5,18,66,94–97). However, on clinical inspection, an individual with a *PKD2* mutation does not seem physically different from someone with a *PKD1* mutation.

In studies of large families, no individual who bears a mutated *PKD1* or *PKD2* gene has failed to have renal cysts. Although all patients who inherit *PKD1* or *PKD2* develop renal cysts, not all of them will progress to renal insufficiency that requires dialysis and/or renal transplantation.

In his classic thesis on PKD, Dalgaard (21) presented strong evidence supporting the view that renal cysts caused renal insufficiency. He collected data on 346 individuals in Denmark. Dalgaard recorded the number of patients who developed pain, uremia (determined by measurement of serum creatinine level, symptoms, or death), and palpable kidneys (a surrogate for renal size). In adults, normal kidneys cannot be palpated with certainty. In Dalgaard's study, strict criteria were used to declare the kidneys palpable, and, in many cases, the physical examination was confirmed by intravenous urography or retrograde pyelography. He found that palpable kidneys and pain appeared before the onset of uremia in relatively young individuals, a precedence that was maintained to age 70. Dalgaard concluded that the increase in renal size as a result of the cysts antedated the loss of function.

Many studies, before Dalgaard and after, have found an inverse association between the size of polycystic kidneys and the level of glomerular filtration. Thomsen *et al.* (85) were the first to use radiologic imaging in a cross-sectional study to determine renal volume in patients with ADPKD and normal or abnormal renal function (Table 1). They found a clear association between total renal volume and a decline in creatinine clearance. Franz and Reubi (91) determined GFR and renal plasma flow in individuals relatively late in the course of PKD.

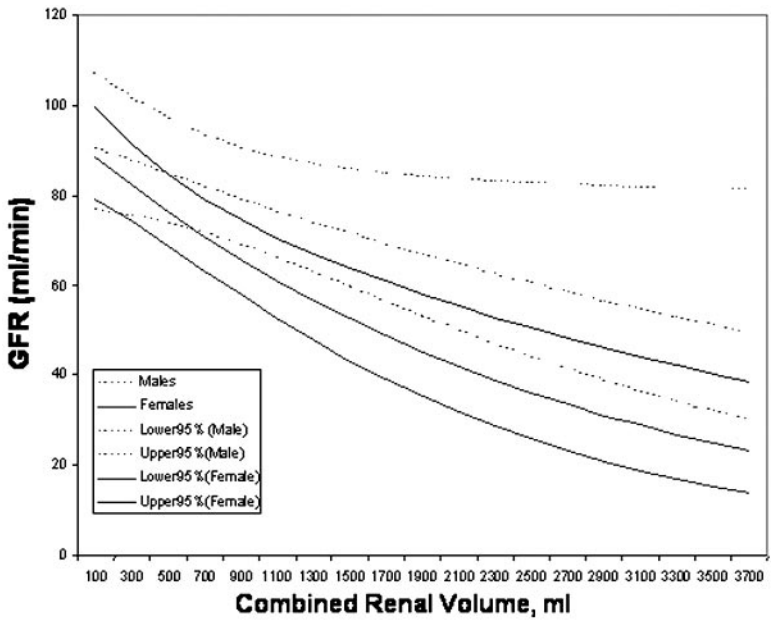

Figure 1. Cross-section magnetic resonance (MR) study relating combined volumes of left and right kidneys and GFR. Mean and 95% confidence limits for males and females shown.

There was a wide variation in the age at which individuals developed the well-known downward fall of GFR that occurred after the kidneys had become markedly enlarged. These researchers also developed a model that, when fit with reasonable estimates of the rate at which renal volume (cysts) expanded in the patients, mimicked the curvilinear relation between GFR and patient age that is typical of the disease as it approaches terminal renal failure.

Fick-Brosnahan *et al.* (80) performed a longitudinal prospective study in 229 adult patients with PKD to determine the relation between kidney volume (determined by ultrasound) and GFR. Ultrasound is relatively inaccurate for determining small changes in kidney volume changes over relatively short intervals of time. In this study, however, measurement intervals averaged 7.8 yr in duration, and the changes in kidney volume were relatively large. Multiple linear regression analysis showed a significant inverse relationship between the rate of renal volume increase and the rate of decline in GFR. There was also a highly significant inverse correlation between absolute kidney volume and GFR. Linear regression analysis also revealed a significant inverse relationship between the rate of renal volume increase and the rate of decline in GFR. This study provided strong support for the view that renal cyst expansion is the forerunner of the decline in GFR observed in patients with ADPKD.

MRI has also been used to determine renal volumes in a cross-sectional study of a relatively large cohort of patients with ADPKD (28). In this study, renal volume was evaluated in relation to the level of renal function (Figure 1). GFR decreased in association with increasing combined renal volumes at a somewhat faster rate in women than in men for reasons that are not clear. A fall in GFR to <80 ml/min per 1.73 m^2, a mean level considered to be the lower limit of "normal" GFR, occurred at approximately 670 ml in women and approximately 1100 ml in men. These findings suggest that early in the course of the disease, structure–function differences are most apparent between women and men, diminishing in older patients.

Computed tomography with contrast enhancement has been used to determine the longitudinal relation between kidney volume and function in a prospective (nine individuals) (98) and a retrospective study (10 individuals) (99) of ADPKD. The data from these studies have been combined and updated to examine the long-term outcomes of the individual patients. Figure 2 shows the relation between kidney volume and age. Two measurements of volume were made (3.3 to 11.9 yr apart). It is plain to see that the renal volumes segregated into two general categories: Those with relatively rapid increases in volume and those in whom renal volume increased more slowly. Serum creatinine levels were determined over an average duration of 17.4 yr (range 13 to 27 yr). Ten patients (Figure 2, open symbols) developed renal insufficiency marked by ESRD ($n = 6$) or a serum creatinine level >1.4 mg/dl ($n = 4$; mean creatinine 3.2 mg/dl). Nine patients (closed symbols) maintained serum creatinine levels within the normal range (mean serum creatinine 1.2 mg/dl; range 1.0 to 1.4 in 2004). The final kidney volume of the azotemic group was 2253 ± 287 (SE) and 1003 ± 148 ml (SE) in the nonazotemic group. The change in kidney volume was 123.2 ± 25.5 (SE) and 29.0 ± 9.6 ml/yr (SE) in the azotemic and nonazotemic groups over periods of 6.3 and 6.9 yr, respectively. It seems apparent from these measurements that the patients who developed azotemia had larger kidneys that expanded at faster rates than those who remained nonazotemic over the period of observation.

Animal models of progressive renal cystic disease emphasize further the importance that cysts play in provoking impairment of renal function. The rates of renal enlargement and renal

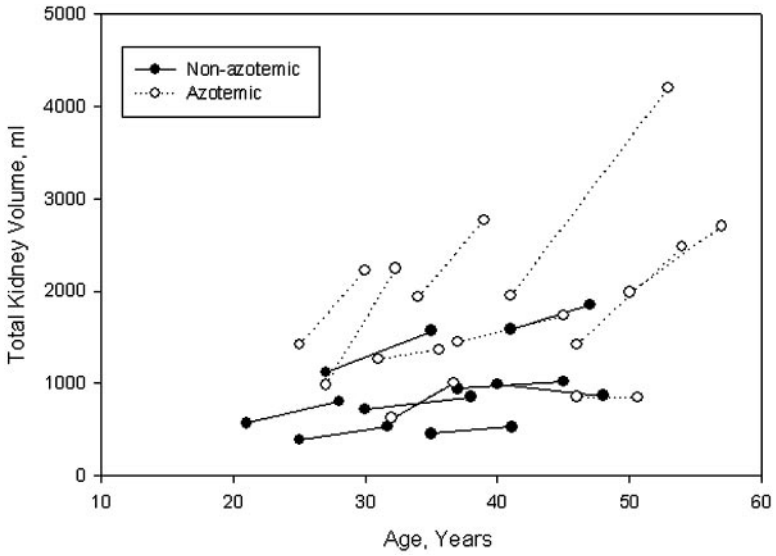

Figure 2. Time-dependent increases in combined left and right kidney volumes determined by computed tomography.

function decline are faster in rodent models of PKD than in humans. As in human ADPKD, kidney enlargement in these animal models consistently precedes the development of renal insufficiency. Table 2 summarizes the results of studies in which measurements of renal volume and function were made in control animals and animals that were treated with several different regimens. Treatments were usually started just after the animals were weaned and maintained for several weeks. Improvements in renal volume and function were evaluated by comparing the kidney weights and functional parameters of treated and untreated cystic animals to wild-type counterparts that served as age and sex-matched controls. Treatments that inhibited renal enlargement consistently reduced the rate of renal function decline (100–111) (Figure 3). The changes in kidney volume caused by the different treatments correlated reasonably well with the changes in renal function, although in

Table 2. Relative beneficial effect of various interventions on kidney volume and function in polycystic kidney disease

	% Improved KW	% Improved BUN	Model	Duration	Reference
Soy versus casein protein	27.4	70[a]	Han:SPRD, M	3 to 10 w	Aukema; *Kidney Int* 59: 52, 2001
Enalapril, 50 mg/L po	22.8	43.9[a]	Han:SPRD, M	3 to 16 w	Keith; *Am J Kidney Dis* 24: 491, 1994
Enalapril, 50 mg/L po	31.0	74.2[a]	Han:SPRD, M	3 to 10 w	Kennefick; *Kidney Int* 56: 2181, 1999
Enalapril, 50 mg/L po	32.7	48.1[b]	Han:SPRD, M	3 to 40 w	Kennefick; *Kidney Int* 56: 2181, 1999
Losartan, 400 mg/L po	12.3	63.4[a]	Han:SPRD, M	3 to 16 w	Keith; *Am J Kidney Dis* 24: 491, 1994
Lovastatin, 4 mg/Kg per day ip	21.7	58.8	Han:SPRD, M	4 to 10 w	Gile; *Am J Kidney Dis* 26: 501, 1995
Methylprednisolone, 1–2 mg/Kg per d po	65.7	74.0	pcy	4 to 18 w	Gattone; *Am J Kidney Dis* 25: 302, 1995
Methylprednisolone, 1–2 mg/Kg per d po	33.1	40.1	Han:SPRD, M	3 to 10 w	Gattone; *Am J Kidney Dis* 25: 302, 1995
WTACE2, 100 mg/kg per d ip	46.7	54.8	bpk	7 to 21 d	Dell; *Kidney Int* 60: 1240, 2001
EKI-785, 90 mg/Kg q3d ip	66.7	100.0	bpk	7 to 24 d	Sweeney; *Kidney Int* 57: 33, 2000
EKI-785, 90 mg/Kg q3d ip	85.5	100.0	bpk	7 to 21 d	Sweeney; *Kidney Int* 64: 1310, 2003
EKI-785, 90 mg/Kg q3d ip	21.2	41.8	Han:SPRD, M	3 to 10 w	Torres; *Kidney Int* 64: 1573, 2003
EKB-569, 90 mg/Kg q3d ip	75.2	94.8	bpk	7 to 21 d	Sweeney; *Kidney Int* 64: 1310, 2003
EKB-569, 30 mg/Kg q3d + WTACE2 100 mg/Kg altd ip	74.3	94.8	bpk	7 to 21 d	Sweeney; *Kidney Int* 64: 1310, 2003
EKB-569, 20 mg/Kg q3d ip	38.1	59.5	Han:SPRD, M	3 to 10 w	Torres; *Kidney Int* 64: 1573, 2003
c-myc antisense oligomer, 30 mcg/d ip	36.7	66.0	cpk	21 d	Ricker; *Kidney Int* 61: S125, 2002
Rapamycin, 0.2 mg/Kg per d ip	64.6	84.6	Han:SPRD, M	3 to 8 w	Tao; *J Am Soc Nephrol* 16: 46, 2005
OPC-31260, 100–200 mcg per d sq	54.4	86.4	cpk	3 to 21 d	Gattone; *Develop Genet* 24: 309, 1999
OPC-31260, 0.1% po	86.2	62.2	pcy	4 to 30 w	Gattone; *Nature Med* 9: 1323, 2003
OPC-31260, 0.1% po	75.0	95.9	PCK	3 to 10 w	Gattone; *Nature Med* 9: 1323, 2003
OPC-31260, 0.05% po	98.4	99.5	Pkd2-/WS25	3 to 16 w	Torres; *Nature Med* 10: 363, 2004

[a]Data are based on serum creatinine values.
[b]Data are based on inulin clearance.

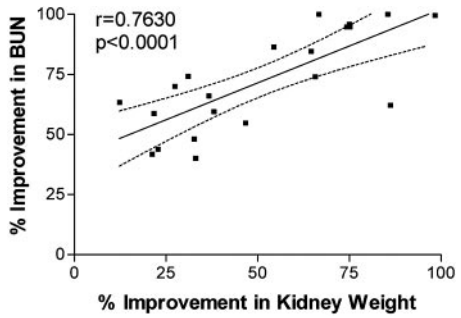

Figure 3. Relation between improvement in kidney size and improvement in renal function in treated animals with polycystic kidney disease.

two studies (not included in Figure 3), a beneficial effect on function was seen occasionally without a corresponding change in kidney volume (112,113). Conversely, in no instance has a beneficial effect on renal volume been observed without a corresponding favorable effect on renal function. All things considered, the animal studies are consistent with the view that cyst development initiates a series of secondary changes that culminates in renal insufficiency. In summary, evidence from cross-sectional and longitudinal studies in human ADPKD and in animal models of PKD strongly implicate enlarging renal cysts and the consequent increase in renal size as a major factor in the development of late-onset renal insufficiency in ADPKD.

Evaluation of Disease Progression in ADPKD

Renal failure is a feared consequence of all progressive renal disorders. Most of the conditions that lead to renal failure, *e.g.*, glomerulonephritis, diabetes, and hypertensive vascular disease, have primary or secondary effects on the glomeruli that generate the glomerular filtrate. Consequently, a high level of emphasis has been placed on the GFR as the prime indicator of disease progression.

The severity of other chronic diseases that do not originate within glomeruli, *e.g.*, ADPKD, tubulointerstitial nephritis, congenital maldevelopment, and hereditary tubulopathies, is also judged by their effect on the GFR. Consequently, the development of treatments for slowly progressive nonglomerular disorders may be compromised if only GFR is used as a primary end point, because no organization would be willing to underwrite the costs of a clinical trial that might last 20 to 40 yr to determine efficacy.

Measurements of GFR can be especially misleading in reporting the progression of ADPKD. The cysts develop at birth and, as noted above, are unquestionably the cause of major morbidities long before renal insufficiency appears. It is widely known that the kidneys have a remarkable capacity to compensate for the loss of glomerular filtration units. This is illustrated daily when donor kidneys are removed from living humans and transplanted into another person. The remaining kidney commences on the day of surgery to compensate for the loss of the partner, and within 30 d, GFR values that are close to the values before nephrectomy are achieved.

In ADPKD, compensation begins with the piecemeal loss of filtering units owing to the local anatomic distortion cause by the expanding cysts. There is associated inflammation, scarring, and apoptosis of normal parenchyma that contributes to the loss of GFR (114). The cysts develop sporadically about the kidneys; thus, there are islands of parenchyma that escape injury for many years. It is in these areas that compensatory adjustments to the loss of glomerular filters takes place. On balance, the GFR is maintained within a range indistinguishable from normal until the fourth or fifth decade of life, a process that is illustrated in the hypothetical case in Figure 4. MRI scans of polycystic kidneys at progressively increased levels of cystic change are shown at the top. The graph illustrates the actual loss of functioning glomeruli (the straight line) and the compensated level of GFR (the curved line). The straight line that relates age to GFR was drawn on the assumption that 36,000 glomeruli were destroyed each year beginning at 10 yr of age. The line above it assumes that each surviving glomerulus increased single-nephron GFR by up to twofold, which is reasonable because after loss of a kidney, the GFR of the remaining organ compensates to within normal.

Eventually, the filtering units that have maintained the normal level of GFR for 40 yr are lost, and it is at this point that the GFR begins to fall precipitously. Physicians generally tell patients with ADPKD at this time that their disease is "progressing more rapidly than before." This is a common misconception that does not acknowledge the strong possibility that the cysts had been forming and expanding and thereby compromising adjacent functioning nephrons at a relatively slow rate all along. This example also serves to illustrate a concern of many clinical scientists in this field that waiting until the serum

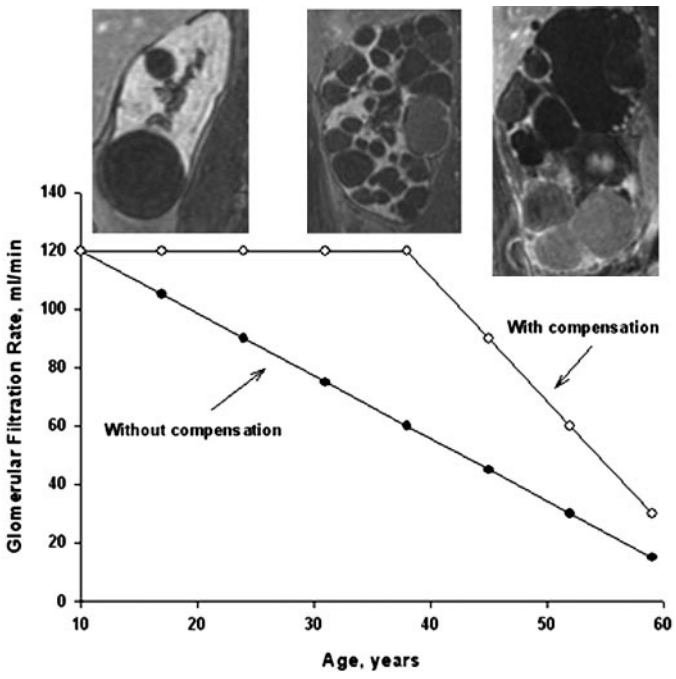

Figure 4. Hypothethical scheme relating GFR and age. Figure insets show MR scans of right kidneys at different ages of disease progression.

creatinine is clearly increased and GFR decreased before beginning to test potential therapeutic agents may doom such trials to failure. As shown in Figure 4, when the GFR has clearly decreased below normal, the MRI images reveal extensive anatomic distortion and parenchymal compression. Drugs that target the formation and growth of cysts would be far less likely to show efficacy than they would had they been given early in the course of the disease, because more than one half of the viable parenchyma would have been destroyed before compensating nephrons started to fail.

Until now, clinical evaluations of potential PKD therapies have monitored preservation of GFR to indicate efficacy. One such end point is the time for the serum creatinine concentration to double. Unfortunately, this end point also ignores that many renal diseases invoke compensatory glomerular hyperfiltration relatively early in the course and thereby maintain overall GFR within a normal range. Consider, for example, two patients who have PKD, are aged 20 and 40, and have serum creatinine levels of 1 mg/dl. Both are destined to double the serum creatinine levels by age 50. For the 20-yr-old patient with PKD, the doubling time would be 30 yr; that of the 40-yr-old patient would be 10 yr. Consequently, it would be impracticable to include relatively young patients with well-preserved renal function in a study lasting <30 yr, forcing studies of shorter duration that would, of necessity, include only those with very advanced disease.

The creatinine-doubling end point forces researchers to select for studies individuals whose GFR have decreased appreciably, *i.e.*, an age- and gender-adjusted serum creatinine level greater than approximately 1.4 and 1.6 mg/ml for women and men, respectively. Consequently, only individuals in whom the functioning renal parenchyma has been reduced to <50% of normal could be enrolled. In patients with PKD, at this juncture, the parenchyma is hideously distorted and fibrotic (Figure 4). It would be extremely difficult for therapies that are targeted to fundamental causative mechanisms to show efficacy. In summary, measures of GFR are too insensitive and require too lengthy a period of follow-up to be used to determine the potential benefits of therapeutic agents that are targeted to the prevention of cyst enlargement.

How Can Progression be Monitored and Quantified in ADPKD?

It stands to reason that the rate of increase in renal volume is a hard measure of the rate of disease progression in ADPKD. Clinicians have known for many years that they should look for a confounding disorder when an patient with ADPKD develops renal insufficiency in the absence of marked renal enlargement. Recently, noninvasive radiologic methods have been developed to monitor the rates of renal cyst and volume enlargement (98,99). Morphometric analysis of sequential computed tomographs were shown to be sufficiently accurate to monitor rates of renal enlargement in ADPKD, and MRI-based methods have been developed (28,81,115).

Patients fall into two general groups of kidney volume increase as shown in Figure 2: (*1*) Those with rapid rates of progression (>5% increase in total kidney volume per year) and (*2*) those with rates of progression <5% per year. The encouraging news is that intervals between measurements as short as 6 mo may be adequate to determine an effect of treatment that reduces the rate of volume progression >50% in those with rapidly progressive disease (116). Newer technology using MRI with gadolinium enhancement avoids ionizing radiation and provides reproducible determinations of cystic volumes (115). Initial preliminary reports from the Consortium for Renal Imaging Studies in Polycystic Kidney Disease indicate that MRI is as least as accurate as computed tomography for determining rates of increase in kidney volume (81).

References

1. American Society of Nephrology: American Society of Nephrology renal research report. *J Am Soc Nephrol* 16: 1886–1903, 2005
2. Ong AC, Harris PC: Molecular pathogenesis of ADPKD: The polycystin complex gets complex. *Kidney Int* 67: 1234–1247, 2005
3. Gabow PA: Autosomal dominant polycystic kidney disease. *N Engl J Med* 329: 332–342, 1993
4. Gabow PA, Duley I, Johnson AM: Clinical profiles of gross hematuria in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 20: 140–143, 1992
5. Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, Duley IT, Jones RH: Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. *Kidney Int* 41: 1311–1319, 1992
6. Gabow PA, Chapman AB, Johnson AM, Tangel DJ, Duley IT, Kaehny WD, Manco-Johnson M, Schrier RW: Renal structure and hypertension in autosomal dominant polycystic kidney disease. *Kidney Int* 38: 1177–1180, 1990
7. Torres VE, Harris PC: Autosomal dominant polycystic kidney disease. *Nefrologia* 23[Suppl 1]: 14–22, 2003
8. Grantham JJ: The etiology, pathogenesis, and treatment of autosomal dominant polycystic kidney disease: Recent advances. *Am J Kidney Dis* 28: 788–803, 1996
9. Chapman AB, Johnson AM, Gabow PA, Schrier RW: Overt proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 5: 1349–1354, 1994
10. Grantham JJ, Geiser JL, Evan AP: Cyst formation and growth in autosomal dominant polycystic kidney disease. *Kidney Int* 31: 1145–1152, 1987
11. Grantham JJ: Polycystic kidney disease: Neoplasia in disguise. *Am J Kidney Dis* 15: 110–116, 1990
12. Grantham J, Cowley BJ, Torres VE: Progression of autosomal dominant polycystic kidney disease (ADPKD) to renal failure. In: *The Kidney: Physiology and Pathophysiology*, Vol. 2, edited by Seldin D, Giebisch G, Philadelphia, Lippincott Williams & Wilkins, 2000, pp 2513–2536
13. Bello-Reuss E, Holubec K, Rajaraman S: Angiogenesis in autosomal-dominant polycystic kidney disease. *Kidney Int* 60: 37–45, 2001
14. Zeier M, Fehrenbach P, Geberth S, Mohring K, Waldherr R, Ritz E: Renal histology in polycystic kidney disease with incipient and advanced renal failure. *Kidney Int* 42: 1259–1265, 1992
15. Zheng D, Wolfe M, Cowley BD Jr, Wallace DP, Yamaguchi T, Grantham JJ: Urinary excretion of monocyte chemoat-

tractant protein-1 in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 14: 2588–2595, 2003
16. Torres VE: Cyclic AMP, at the hub of the cystic cycle. *Kidney Int* 66: 1283–1285, 2004
17. Torres VE: Hypertension, proteinuria, and progression of autosomal dominant polycystic kidney disease: Where do we go from here? *Am J Kidney Dis* 35: 547–550, 2000
18. Johnson AM, Gabow PA: Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. *J Am Soc Nephrol* 8: 1560–1567, 1997
19. Gabow PA, Ikle DW, Holmes JH: Polycystic kidney disease: Prospective analysis of nonazotemic patients and family members. *Ann Intern Med* 101: 238–247, 1984
20. Danovitch GM: Clinical features and pathophysiology of polycystic kidney disease in man. In: *Cystic Diseases of the Kidney*, edited by Gardner KD Jr, New York, John Wiley and Sons, 1976, p 255
21. Dalgaard OZ: Bilateral polycystic disease of the kidneys. *Acta Med Scand* 328: 1–255, 1957
22. Milutinovic J, Fialkow PJ, Agodoa LY, Phillips LA, Rudd TG, Bryant JI: Autosomal dominant polycystic kidney disease: Symptoms and clinical findings. *Q J Med* 53: 511–522, 1984
23. Rall JE, Odel HM: Congenital polycystic disease of the kidney: Review of the literature, and data on 207 cases. *Am J Med Dis* 218: 399–407, 1949
24. Simon HB, Thompson GJ: Congenital renal polycystic disease. *JAMA* 159: 657–662, 1955
25. Higgins CC: Bilateral polycystic kidney disease. *Arch Surg* 65: 318–329, 1952
26. Braasch WF: Clinical data of polycystic kidney. *Surg Gynecol Obstet* 23: 697–702, 1916
27. Braasch WF, Schacht FW: Pathological and clinical data concerning polycystic kidney. *Surg Gynecol Obstet* 57: 467–475, 1933
28. Chapman AB: Cystic disease in women: Clinical characteristics and medical management. *Adv Ren Replace Ther* 10: 24–30, 2003
29. Levine E, Grantham JJ: Perinephric hemorrhage in autosomal dominant polycystic kidney disease: CT and MR findings. *J Comput Assist Tomogr* 11: 108–111, 1987
30. Levine E, Grantham JJ: High-density renal cysts in autosomal dominant polycystic kidney disease demonstrated by CT. *Radiology* 154: 477–482, 1985
31. Bajwa ZH, Gupta S, Warfield CA, Steinman TI: Pain management in polycystic kidney disease. *Kidney Int* 60: 1631–1644, 2001
32. Grantham JJ: Renal pain in polycystic kidney disease: When the hurt won't stop. *J Am Soc Nephrol* 2: 1161–1162, 1992
33. Bajwa ZH, Sial KA, Malik AB, Steinman TI: Pain patterns in patients with polycystic kidney disease. *Kidney Int* 66: 1561–1569, 2004
34. Badani KK, Hemal AK, Menon M: Autosomal dominant polycystic kidney disease and pain—A review of the disease from aetiology, evaluation, past surgical treatment options to current practice. *J Postgrad Med* 50: 222–226, 2004
35. Elzinga LW, Barry JM, Torres VE, Zincke H, Wahner HW, Swan S, Bennett WM: Cyst decompression surgery for autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2: 1219–1226, 1992
36. Elzinga LW, Barry JM, Bennett WM: Surgical management of painful polycystic kidneys. *Am J Kidney Dis* 22: 532–537, 1993
37. Lee YR, Lee KB: Ablation of symptomatic cysts using absolute ethanol in 11 patients with autosomal-dominant polycystic kidney disease. *Korean J Radiol* 4: 239–242, 2003
38. Brown JA, Torres VE, King BF, Segura JW: Laparoscopic marsupialization of symptomatic polycystic kidney disease. *J Urol* 156: 22–27, 1996
39. Fleming TW, Barry JM: Bilateral open transperitoneal cyst reduction surgery for autosomal dominant polycystic kidney disease. *J Urol* 159: 44–47, 1998
40. Bennett WM, Elzinga L, Golper TA, Barry JM: Reduction of cyst volume for symptomatic management of autosomal dominant polycystic kidney disease. *J Urol* 137: 620–622, 1987
41. Lifson BJ, Teichman JM, Hulbert JC: Role and long-term results of laparoscopic decortication in solitary cystic and autosomal dominant polycystic kidney disease. *J Urol* 159: 702–705; discussion 705–706, 1998
42. Segura JW, King BF, Jowsey SG, Martin P, Zinche H: Chronic pain and its medical and surgical management in renal cystic diseases. In: *Polycystic Kidney Disease*, edited by Watson ML, Torres VE, Oxford, Oxford University Press, 1996, p 590
43. Fick GM, Duley IT, Johnson AM, Strain JD, Manco-Johnson ML, Gabow PA: The spectrum of autosomal dominant polycystic kidney disease in children. *J Am Soc Nephrol* 4: 1654–1660, 1994
44. Fick GM, Johnson AM, Strain JD, Kimberling WJ, Kumar S, Manco-Johnson ML, Duley IT, Gabow PA: Characteristics of very early onset autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 3: 1863–1870, 1993
45. Fick-Brosnahan GM, Tran ZV, Johnson AM, Strain JD, Gabow PA: Progression of autosomal-dominant polycystic kidney disease in children. *Kidney Int* 59: 1654–1662, 2001
46. Sharp C, Johnson A, Gabow P: Factors relating to urinary protein excretion in children with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 9: 1908–1914, 1998
47. Torres VE, Wilson DM, Hattery RR, Segura JW: Renal stone disease in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 22: 513–519, 1993
48. Grampsas SA, Chandhoke PS, Fan J, Glass MA, Townsend R, Johnson AM, Gabow P: Anatomic and metabolic risk factors for nephrolithiasis in patients with autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 36: 53–57, 2000
49. Ng CS, Yost A, Streem SB: Nephrolithiasis associated with autosomal dominant polycystic kidney disease: Contemporary urological management. *J Urol* 163: 726–729, 2000
50. Torres VE, Erickson SB, Smith LH, Wilson DM, Hattery RR, Segura JW: The association of nephrolithiasis and autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 11: 318–325, 1988
51. O'Neill M, Breslau NA, Pak CY: Metabolic evaluation of nephrolithiasis in patients with medullary sponge kidney. *JAMA* 245: 1233–1236, 1981
52. Levine E, Grantham JJ: Calcified renal stones and cyst calcifications in autosomal dominant polycystic kidney disease: Clinical and CT study in 84 patients. *AJR Am J Roentgenol* 159: 77–81, 1992

53. Miller-Hjelle MA, Hjelle JT, Jones M, Mayberry WR, Dombrink-Kurtzman MA, Peterson SW, Nowak DM, Darras FS: Polycystic kidney disease: An unrecognized emerging infectious disease? *Emerg Infect Dis* 3: 113–127, 1997
54. Martinez JR, Grantham JJ: Polycystic kidney disease: Etiology, pathogenesis, and treatment. *Dis Mon* 41: 693–765, 1995
55. Chapman AB, Thickman D, Gabow PA: Percutaneous cyst puncture in the treatment of cyst infection in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 16: 252–255, 1990
56. Schwab S, Hinthorn D, Diederich D, Cuppage F, Grantham J: PH-dependent accumulation of clindamycin in a polycystic kidney. *Am J Kidney Dis* 3: 63–66, 1983
57. Elzinga LW, Golper TA, Rashad AL, Carr ME, Bennett WM: Ciprofloxacin activity in cyst fluid from polycystic kidneys. *Antimicrob Agents Chemother* 32: 844–847, 1988
58. Hemal AK, Gupta NP, Rajeev TP, Aron M, Bhowmik D, Jain R: Retroperitoneoscopic management of infected cysts in adult polycystic kidney disease. *Urol Int* 62: 40–43, 1999
59. Gibson P, Watson ML: Cyst infection in polycystic kidney disease: A clinical challenge. *Nephrol Dial Transplant* 13: 2455–2457, 1998
60. Sklar AH, Caruana RJ, Lammers JE, Strauser GD: Renal infections in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 10: 81–88, 1987
61. Schwab SJ, Bander SJ, Klahr S: Renal infection in autosomal dominant polycystic kidney disease. *Am J Med* 82: 714–718, 1987
62. Schwab SJ, Weaver ME: Penetration of trimethoprim and sulfamethoxazole into cysts in a patient with autosomal-dominant polycystic kidney disease. *Am J Kidney Dis* 7: 434–438, 1986
63. Schwab SJ: Efficacy of chloramphenicol in refractory cyst infections in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 5: 258–261, 1985
64. Elzinga LW, Golper TA, Rashad AL, Carr ME, Bennett WM: Trimethoprim-sulfamethoxazole in cyst fluid from autosomal dominant polycystic kidneys. *Kidney Int* 32: 884–888, 1987
65. Muther RS, Bennett WM: Cyst fluid antibiotic concentrations in polycystic kidney disease: Differences between proximal and distal cysts. *Kidney Int* 20: 519–522, 1981
66. Gabow P: Definition and natural history of autosomal dominant polycystic kidney disease. In: *Polycystic Kidney Disease*, edited by Watson ML, Torres VE, Oxford, Oxford University Press, 1996, pp 333–355
67. Lee DI, Andreoni CR, Rehman J, Landman J, Ragab M, Yan Y, Chen C, Shindel A, Middleton W, Shalhav A, McDougall EM, Clayman RV: Laparoscopic cyst decortication in autosomal dominant polycystic kidney disease: Impact on pain, hypertension, and renal function. *J Endourol* 17: 345–354, 2003
68. Dunn MD, Portis AJ, Elbahnasy AM, Shalhav AL, Rothstein M, McDougall EM, Clayman RV: Laparoscopic nephrectomy in patients with end-stage renal disease and autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 35: 720–725, 2000
69. Elashry OM, Nakada SY, Wolf JS Jr, McDougall EM, Clayman RV: Laparoscopy for adult polycystic kidney disease: A promising alternative. *Am J Kidney Dis* 27: 224–233, 1996
70. Seshadri PA, Poulin EC, Pace D, Schlachta CM, Cadeddu MO, Mamazza J: Transperitoneal laparoscopic nephrectomy for giant polycystic kidneys: A case control study. *Urology* 58: 23–27, 2001
71. Dunn MD, Portis AJ, Naughton C, Shalhav A, McDougall EM, Clayman RV: Laparoscopic cyst marsupialization in patients with autosomal dominant polycystic kidney disease. *J Urol* 165: 1888–1892, 2001
72. Uemasu J, Fujiwara M, Munemura C, Tokumoto A, Kawasaki H: Effects of topical instillation of minocycline hydrochloride on cyst size and renal function in polycystic kidney disease. *Clin Nephrol* 39: 140–144, 1993
73. Rehman J, Landman J, Andreoni C, McDougall EM, Clayman RV: Laparoscopic bilateral hand assisted nephrectomy for autosomal dominant polycystic kidney disease: Initial experience. *J Urol* 166: 42–47, 2001
74. Elzinga LW, Barry JM, Bennett WM: Surgery in the management of autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 19: 89–92, 1992
75. Amend WJ: Polycystic kidney disease and seatbelts. *Ann Intern Med* 79: 287, 1973
76. Seeman T, Sikut M, Konrad M, Vondrichova H, Janda J, Scharer K: Blood pressure and renal function in autosomal dominant polycystic kidney disease. *Pediatr Nephrol* 11: 592–596, 1997
77. Grantham JJ: Mechanisms of progression in autosomal dominant polycystic kidney disease. *Kidney Int Suppl* 63: S93–S97, 1997
78. Nicolau C, Torra R, Bianchi L, Vilana R, Gilabert R, Darnell A, Bru C: Abdominal sonographic study of autosomal dominant polycystic kidney disease. *J Clin Ultrasound* 28: 277–282, 2000
79. Seeman T, Dusek J, Vondrichova H, Kyncl M, John U, Misselwitz J, Janda J: Ambulatory blood pressure correlates with renal volume and number of renal cysts in children with autosomal dominant polycystic kidney disease. *Blood Press Monit* 8: 107–110, 2003
80. Fick-Brosnahan GM, Belz MM, McFann KK, Johnson AM, Schrier RW: Relationship between renal volume growth and renal function in autosomal dominant polycystic kidney disease: A longitudinal study. *Am J Kidney Dis* 39: 1127–1134, 2002
81. Chapman AB, Guay-Woodford LM, Grantham JJ, Torres VE, Bae KT, Baumgarten DA, Kenney PJ, King BF Jr, Glockner JF, Wetzel LH, Brummer ME, O'Neill WC, Robbin ML, Bennett WM, Klahr S, Hirschman GH, Kimmel PL, Thompson PA, Miller JP: Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. *Kidney Int* 64: 1035–1045, 2003
82. Kelleher CL, McFann KK, Johnson AM, Schrier RW: Characteristics of hypertension in young adults with autosomal dominant polycystic kidney disease compared with the general US population. *Am J Hypertens* 17: 1029–1034, 2004
83. Schrier RW, McFann KK, Johnson AM: Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease. *Kidney Int* 63: 678–685, 2003
84. Chapman AB, Schrier RW: Pathogenesis of hypertension in autosomal dominant polycystic kidney disease. *Semin Nephrol* 11: 653–660, 1991
85. Thomsen HS, Madsen JK, Thaysen JH, Damgaard-Petersen K: Volume of polycystic kidneys during reduction of renal function. *Urol Radiol* 3: 85–89, 1981
86. Seeman T, Dusek J, Vondrak K, Blahova K, Simkova E, Kreisinger J, Dvorak P, Kyncl M, Hribal Z, Janda J: Renal concentrating capacity is linked to blood pressure in children with autosomal dominant polycystic kidney disease. *Physiol Res* 53: 629–634, 2004

87. Ravine D, Walker RG, Gibson RN, Sheffield LJ, Kincaid-Smith P, Danks DM: Treatable complications in undiagnosed cases of autosomal dominant polycystic kidney disease. *Lancet* 337: 127–129, 1991
88. Zeier M, Geberth S, Schmidt KG, Mandelbaum A, Ritz E: Elevated blood pressure profile and left ventricular mass in children and young adults with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 3: 1451–1457, 1993
89. Ye M: [Etiology and pathogenesis of adult polycystic kidney disease]. *Zhonghua Wai Ke Za Zhi* 22: 44–48, 1984
90. Ye M, An SY, Jiang HM: [Clinical analysis of 141 cases of adult polycystic kidney disease]. *Zhonghua Wai Ke Za Zhi* 24: 73–76, 1986
91. Franz KA, Reubi FC: Rate of functional deterioration in polycystic kidney disease. *Kidney Int* 23: 526–529, 1983
92. Sedman A, Bell P, Manco-Johnson M, Schrier R, Warady BA, Heard EO, Butler-Simon N, Gabow P: Autosomal dominant polycystic kidney disease in childhood: A longitudinal study. *Kidney Int* 31: 1000–1005, 1987
93. Mitcheson H, Williams G, Castro JE: Clinical aspects of polycystic disease of the kidneys. *BMJ* 1: 1196–1199, 1977
94. Churchill DN, Bear JC, Morgan J, Payne RH, McManamon PJ, Gault MH: Prognosis of adult onset polycystic kidney disease re-evaluated. *Kidney Int* 26: 190–193, 1984
95. Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, Torra R, Breuning M, Ravine D: Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. *Lancet* 353: 103–107, 1999
96. Magistroni R, He N, Wang K, Andrew R, Johnson A, Gabow P, Dicks E, Parfrey P, Torra R, San-Millan JL, Coto E, Van Dijk M, Breuning M, Peters D, Bogdanova N, Ligabue G, Albertazzi A, Hateboer N, Demetriou K, Pierides A, Deltas C, St George-Hyslop P, Ravine D, Pei Y: Genotype-renal function correlation in type 2 autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 14: 1164–1174, 2003
97. Torra R, Darnell A, Estivill X, Botey A, Revert L: Interfamilial and intrafamilial variability of clinical expression in ADPKD. *Contrib Nephrol* 115: 97–101, 1995
98. King BF, Reed JE, Bergstralh EJ, Sheedy PF 2nd, Torres VE: Quantification and longitudinal trends of kidney, renal cyst, and renal parenchyma volumes in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 11: 1505–1511, 2000
99. Sise C, Kusaka M, Wetzel LH, Winklhofer F, Cowley BD, Cook LT, Gordon M, Grantham JJ: Volumetric determination of progression in autosomal dominant polycystic kidney disease by computed tomography. *Kidney Int* 58: 2492–2501, 2000
100. Aukema HM, Housini I: Dietary soy protein effects on disease and IGF-I in male and female Han:SPRD-cy rats. *Kidney Int* 59: 52–61, 2001
101. Keith DS, Torres VE, Johnson CM, Holley KE: Effect of sodium chloride, enalapril, and losartan on the development of polycystic kidney disease in Han:SPRD rats. *Am J Kidney Dis* 24: 491–498, 1994
102. Kennefick TM, Al-Nimri MA, Oyama TT, Thompson MM, Kelly FJ, Chapman JG, Anderson S: Hypertension and renal injury in experimental polycystic kidney disease. *Kidney Int* 56: 2181–2190, 1999
103. Gattone VH 2nd, Cowley BD Jr, Barash BD, Nagao S, Takahashi H, Yamaguchi T, Grantham JJ: Methylprednisolone retards the progression of inherited polycystic kidney disease in rodents. *Am J Kidney Dis* 25: 302–313, 1995
104. Dell KM, Nemo R, Sweeney WE Jr, Levin JI, Frost P, Avner ED: A novel inhibitor of tumor necrosis factor-alpha converting enzyme ameliorates polycystic kidney disease. *Kidney Int* 60: 1240–1248, 2001
105. Sweeney WE, Chen Y, Nakanishi K, Frost P, Avner ED: Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor. *Kidney Int* 57: 33–40, 2000
106. Sweeney WE Jr, Hamahira K, Sweeney J, Garcia-Gatrell M, Frost P, Avner ED: Combination treatment of PKD utilizing dual inhibition of EGF-receptor activity and ligand bioavailability. *Kidney Int* 64: 1310–1319, 2003
107. Torres VE, Sweeney WE Jr, Wang X, Qian Q, Harris PC, Frost P, Avner ED: EGF receptor tyrosine kinase inhibition attenuates the development of PKD in Han:SPRD rats. *Kidney Int* 64: 1573–1579, 2003
108. Ricker JL, Mata JE, Iversen PL, Gattone VH: c-myc antisense oligonucleotide treatment ameliorates murine ARPKD. *Kidney Int* 61[Suppl 1]: 125–131, 2002
109. Gattone VH 2nd, Maser RL, Tian C, Rosenberg JM, Branden MG: Developmental expression of urine concentration-associated genes and their altered expression in murine infantile-type polycystic kidney disease. *Dev Genet* 24: 309–318, 1999
110. Gattone VH 2nd, Wang X, Harris PC, Torres VE: Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med* 9: 1323–1326, 2003
111. Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH 2nd: Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. *Nat Med* 10: 363–364, 2004
112. Tanner GA, Tanner JA: Citrate therapy for polycystic kidney disease in rats. *Kidney Int* 58: 1859–1869, 2000
113. Nakanishi K, Sweeney WE Jr, Avner ED, Murcia NS: Expression of the orpk disease gene during kidney development and maturation. *Pediatr Nephrol* 16: 219–226, 2001
114. Woo D: Apoptosis and loss of renal tissue in polycystic kidney diseases. *N Engl J Med* 333: 18–25, 1995
115. Bae KT, Commean PK, Lee J: Volumetric measurement of renal cysts and parenchyma using MRI: Phantoms and patients with polycystic kidney disease. *J Comput Assist Tomogr* 24: 614–619, 2000
116. Ruggenenti P, Remuzzi A, Ondei P, Fasolini G, Antiga L, Ene-Iordache B, Remuzzi G, Epstein FH: Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney Int* 68: 206–216, 2005

This special feature by Grantham, Chapman, and Torres on cyst volume and growth is relevant to the article by Yamaguchi *et al.* in *JASN* (pages 178–187), which relates calcium to cell proliferation in polycystic kidney disease.