

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

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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.

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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.

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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 col-

lecting 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

^aMean kidney volume is combined kidney volume ÷ 2.

^bKidney volume corrected for body size.

^cDerived 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.

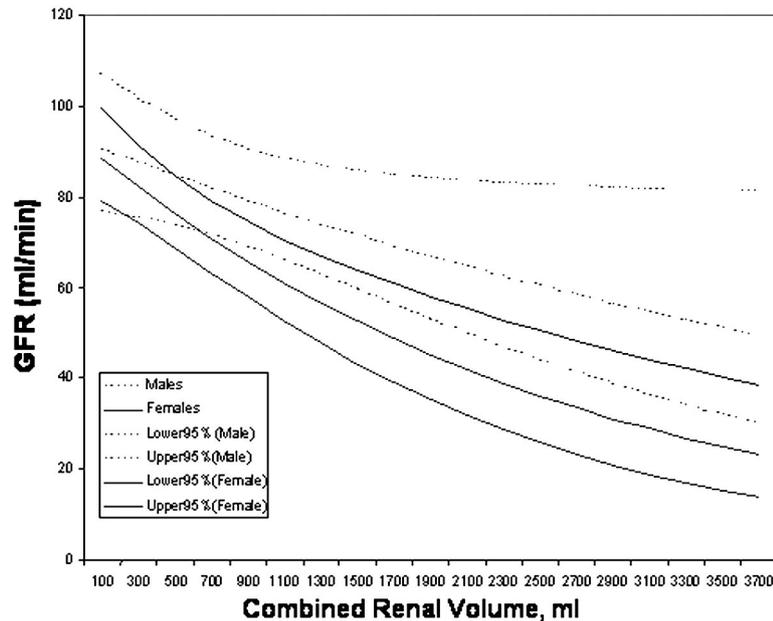


Figure 1. Cross-section magnetic resonance (MR) study relating combined volumes of left and right kidneys and GFR. Mean and 95% confidence limits for males and females shown.

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 m², 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

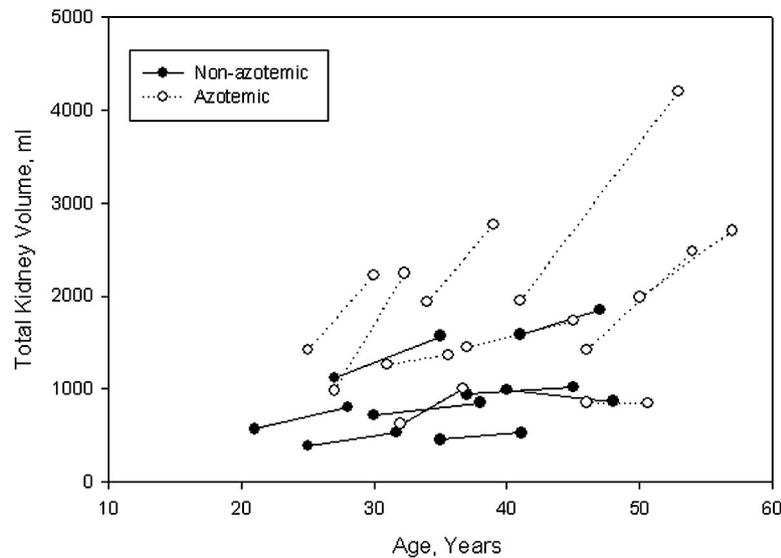


Figure 2. Time-dependent increases in combined left and right kidney volumes determined by computed tomography.

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

^aData are based on serum creatinine values.

^bData are based on inulin clearance.

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).

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