Glomerular Hyperfiltration and Renal Progression in Children with Autosomal Dominant Polycystic Kidney Disease

Imed Helal, Berenice Reed, Kim McFann, Xiang-Dong Yan, Godela M. Fick-Brosnahan, Melissa Cadnapaphornchai, and Robert W. Schrier

Summary
Background and objectives The purpose of this study was to determine whether glomerular hyperfiltration (GH) occurring early in autosomal dominant polycystic kidney disease (ADPKD) is indicative of more rapid disease progression in children.

Design, setting, participants, & measurements One hundred eighty children with ADPKD (ages 4 to 18 years) with normal renal function were examined by renal ultrasound. Renal volume was calculated using a standard formula for a modified ellipsoid. Creatinine clearance was calculated from serum creatinine and 24-hour urine creatinine. GH was defined as creatinine clearance $= 140$ ml/min per 1.73 m$^2$.

Results Thirty-two children had GH (mean age 11.4 ± 3.6 years) and 148 had normal renal function (mean age 10.8 ± 3.9 years). Patients with GH at baseline demonstrated an increased rate of total renal volume growth ($\beta$ rate of change $= +19.3 \pm 10.8$ cm$^3$/year) over 5 years compared with those without GH at baseline ($\beta = -4.3 \pm 7.7$ cm$^3$/year), $P = 0.008$. Those with GH at baseline experienced a faster decline in creatinine clearance in subsequent years ($\beta = -5.0 \pm 0.8$ ml/min per 1.73 m$^2$ per year) compared with those without GH at baseline ($\beta = +1.0 \pm 0.4$ ml/min per 1.73 m$^2$ per year), $P < 0.0001$.

Conclusions This study revealed that occurrence of GH in ADPKD children is associated with a significantly faster decline in renal function and higher rate of kidney enlargement over time. GH combined with the increased renal volume may therefore be used as an early marker for a more severe progression of ADPKD in children.

Introduction
Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary disorder, affecting 1 in 400 to 1 in 1000 people, and is the most common single cause of ESRD after diabetes and hypertension (1,2). Although previously considered to be an adult disease, it has become clear that symptoms may manifest early in childhood, and a diagnosis is even possible in utero (3,4).

ADPKD is characterized by progressive growth of renal cysts, resulting in renal enlargement and, eventually, renal failure. However, the GFR may remain stable into the fifth decade or longer because of compensatory mechanisms (5). By the time renal function starts to decline, the kidneys are usually substantially enlarged, with significant reduction in the normal renal parenchyma. Thus, early intervention in ADPKD promises more therapeutic benefit than late treatment, since the cysts have not yet replaced the bulk of intact renal parenchyma and renal function is still maintained (5–7). After a long phase of arterial hypertension, there appears a rather abrupt and relentless fall of kidney function, leading to ESRD in >50% of patients (5). Whereas monitoring of ADPKD progression by measuring or estimating the decline in GFR is well established, few studies have dealt with the clinical significance of glomerular hyperfiltration (GH) in early phases of the disease.

The purpose of this study was to examine whether GH occurring early in ADPKD is related to renal size and rate of disease progression in affected children.

Materials and Methods
Patient Selection
One hundred eighty children with ADPKD (age 4 to 18 years) with normal renal function were examined by renal ultrasound between 1985 and 2002. The diagnosis of ADPKD was confirmed by ultrasound using Ravine diagnostic criteria (8). Children were evaluated by a 2-day inpatient visit at the pediatric Clinical Research Center at the Children’s Hospital Aurora, Colorado. At each study visit, subjects had blood drawn to determine routine serum chemistry.
values. Serum and urine creatinine measurements were performed using the Jaffe reaction and a Beckman 2 autoanalyzer. Urine creatinine was calculated based on the mean of two 24-hour urine collections. Renal function was estimated using creatinine clearance (CrCl) (9), which has recently been shown to be more accurate in children with GH than eGFR calculated by the Schwartz formula eGFR (10,11). GH was defined as CrCl ≥140 ml/min per 1.73 m², which is the GH criteria used in diabetic children (12).

### Volumetric Analysis

Sequential renal ultrasound examinations were performed in each study subject. All were performed in the radiology department at the Children’s Hospital using the same standards to measure renal volume. Renal volume was defined as the total volume of both kidneys and was calculated as described previously (13). Renal volume growth rate was defined as the increase in renal volume per yr and was corrected for body surface area (BSA) in all analyses.

### Statistical Analyses

Data are expressed as mean ± SD for normally distributed data, median and interquartile ranges for skewed data, or as rate of change (β) ± SE. To compare baseline characteristics of those with GH versus those without GH, the Wilcoxon rank sum test was used for continuous variables and the chi-squared test of independence or Fisher exact test was used for categorical variables. Longitudinal data were collected and analyzed using mixed models to estimate the slopes of those with GH versus those without GH. An exponential power error structure was used because patients were measured at unequal time intervals.

### Results

#### Baseline Analysis

A total of 180 ADPKD children with available data on CrCl and total renal volume were studied. The median period between two evaluations was 1.1 (0.9–2.9) years and the median number of evaluations in each patient was 2.5 (2–5).

Thirty-two children had GH and 148 had normal renal function. The demographic and clinical data of all patients are summarized in Table 1. There were no significant differences between those with GH and those without GH in any baseline characteristics except for serum creatinine (0.6 [0.4 to 0.7] versus 0.7 [0.6 to 0.8] mg/dl, P = 0.005) and CrCl (153.9 [145.1 to 168.6] versus 111.7 [93.2 to 124.5] ml/min per 1.73 m², P < 0.0001). Those with GH also had significantly larger BSA adjusted renal volumes (399.3 [292.5 to 501.6] versus 325.1 [264.7 to 405.0] cm³, P = 0.04) despite no age difference between groups.

There was no significant relationship between baseline GH and total kidney volume (TKV) after further adjusting for age and gender (least squares mean ± SEM: GH, 420 ± 52 cm³ versus No GH, 404 ± 24 cm³, P = 0.77). Similarly using log10 transformed values, there was no relationship between baseline GH and total renal volume (GH, 2.59 ± 0.03 versus no GH, 2.55 ± 0.01, P = 0.25).

#### Longitudinal Analysis

A total of 140 patients had longitudinal data based on two or more study visits. Median (interquartile range) follow-up for these 140 patients was 5.8 (3.9 to 8.0) years.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GH</th>
<th>Without GH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.4 ± 3.6</td>
<td>10.8 ± 3.9</td>
<td>0.27</td>
</tr>
<tr>
<td>Male/Female</td>
<td>19/13</td>
<td>63/85</td>
<td>0.08</td>
</tr>
<tr>
<td>Median follow-up (years)</td>
<td>4.6 (2.6 to 7.1)</td>
<td>5.7 (1.3 to 7.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.4 ± 5.2</td>
<td>20.0 ± 5.9</td>
<td>0.40</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 18</td>
<td>114 ± 14</td>
<td>0.09</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72 ± 12</td>
<td>71 ± 11</td>
<td>0.70</td>
</tr>
<tr>
<td>Symptoms and complications of ADPKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (53.13%)</td>
<td>51 (34.6%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Recurrent flank pain</td>
<td>4 (12.5%)</td>
<td>24 (16.4%)</td>
<td>0.08</td>
</tr>
<tr>
<td>History of macrohematuria</td>
<td>8 (25.0%)</td>
<td>18 (12.16%)</td>
<td>0.15</td>
</tr>
<tr>
<td>History of cyst infection</td>
<td>5 (15.63%)</td>
<td>38 (25.85%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Median serum creatinine (mg/dl)</td>
<td>0.6 (0.4 to 0.7)</td>
<td>0.7 (0.6 to 0.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Median CrCl (ml/min per 1.73 m²)</td>
<td>153.9 (145.1 to 168.6)</td>
<td>111.7 (93.2 to 124.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total kidney volume (cm³)</td>
<td>431.9 ± 196.0</td>
<td>400.1 ± 317.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIU</td>
<td>0 (0%)</td>
<td>1 (0.68%)</td>
<td>0.82</td>
</tr>
<tr>
<td>ACEI</td>
<td>3 (9.38%)</td>
<td>13 (8.9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>ARB</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>1 (3.23%)</td>
<td>10 (6.94%)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

ADPKD, autosomal dominant polycystic kidney disease; GH, glomerular hyperfiltration; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; CrCl, creatinine clearance; DIU, diuretic; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drugs. Values are numbers of patients (%), mean ± SD, or median (interquartile range).
Patients with GH at baseline demonstrated an increased rate of BSA-corrected total renal volume growth ($\beta$; rate of change $= +19.3 \pm 10.8 \text{ cm}^3/\text{years}$) over 5 years compared with those without GH at baseline ($\beta = -4.3 \pm 7.7 \text{ cm}^3/\text{year}$), $P = 0.008$ (Table 2), after adjustment for age, gender, and baseline BSA-corrected renal volume.

After also adjusting for angiotensin-converting enzyme inhibitor (ACEI) and or angiotensin receptor blocker (ARB) use, hypertension, and baseline renal volume, patients with GH at baseline demonstrated an increased rate of total renal volume increase ($\beta = +37.2 \pm 7.8 \text{ cm}^3/\text{year}$) compared with those without GH at baseline ($\beta = +15.3 \pm 4.1 \text{ cm}^3/\text{year}$), $P = 0.005$. The percent increase in renal volume was comparable between those with GH (mean $\pm$ SD: $9.2 \pm 9.1\%$/year) compared with those without GH at baseline, ($8.8 \pm 10.4\%$/year), $P = 0.45$. Since the children with GH had larger kidneys at baseline, the same percentage of growth resulted in much larger absolute TKVs.

After adjusting for gender and age, those with GH at baseline experienced a faster decline in CrCl in subsequent years ($\beta = -5.0 \pm 0.8 \text{ ml/min per 1.73 m}^2$/year) compared with those without GH at baseline ($\beta = +1.0 \pm 0.4 \text{ ml/min per 1.73 m}^2$/year), $P < 0.0001$ (Figure 1). After also adjusting for ACEI or ARB use and hypertension, patients with GH at baseline experienced a faster decline in renal function in subsequent years ($\beta = -5 \pm 0.8 \text{ ml/} \text{min per 1.73 m}^2$/year) compared with those without GH at baseline ($\beta = +0.9 \pm 0.4 \text{ ml/} \text{min per 1.73 m}^2$/year), $P < 0.0001$.

After adjusting for gender and age, those with GH at baseline experienced a faster increase in serum creatinine ($\beta = +0.01 \pm 0.005 \text{ mg/dl per year}$) compared with those without GH at baseline ($\beta = -0.007 \pm 0.002 \text{ mg/dl per year}$), $P = 0.0003$.

To further investigate GH, we applied a more stringent definition of GH of ever having CrCl $\geq 150 \text{ ml/min per 1.73 m}^2$, and the results were quite similar. With this definition, 38 of 140 patients with longitudinal data met the criteria of GH. Using all data points after the first incident of GH, and adjusting for age, gender, ACEI or ARB use, and presence of hypertension, those with GH had a more rapid decline of renal function, as measured by CrCl, compared with those who never had GH ($\beta = -3.8 \pm 0.6 \text{ ml/min per 1.73 m}^2$/year versus $\beta = -0.06 \pm 0.4 \text{ ml/min per 1.73 m}^2$/year, $P < 0.0001$). Similarly, those with GH had a faster increase in serum creatinine compared with those who never had GH ($\beta = +0.02 \pm 0.003 \text{ ml/min per 1.73 m}^2$/year versus $\beta = +0.008 \pm 0.003 \text{ ml/min per 1.73 m}^2$/year, $P = 0.009$). Percent increase in renal volume was comparable between GH ($9.2 \pm 8.9\%$/year) and no-GH groups ($8.8 \pm 10.6\%$/year), $P = 0.42$.

Table 2. Annual total kidney volume in autosomal dominant polycystic kidney disease patients without and with GH in relation to time

<table>
<thead>
<tr>
<th>Incremental Rate of TKV / BSA Growth Per Year</th>
<th>GH</th>
<th>Without GH</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age, gender</td>
<td>+19.3 $\pm$ 10.8 cm$^3$</td>
<td>$-4.3 \pm 7.7 \text{ cm}^3$</td>
<td>0.008</td>
</tr>
<tr>
<td>Adjusted for age, gender, ACEI/ARB use, hypertension</td>
<td>+37.2 $\pm$ 7.8 cm$^3$</td>
<td>$+15.3 \pm 4.1 \text{ cm}^3$</td>
<td>0.005</td>
</tr>
<tr>
<td>% increase in TKV (year)</td>
<td>9.2 $\pm$ 9.1%</td>
<td>8.8 $\pm$ 10.4%</td>
<td>0.45</td>
</tr>
</tbody>
</table>

GH, glomerular hyperfiltration; TKV/BSA, total kidney volume/body surface area; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Figure 1. Creatinine clearance (ml/min per 1.73 m$^2$) in autosomal dominant polycystic kidney disease patients with (A) and without (B) glomerular hyperfiltration in relation to time.

Discussion

Children with ADPKD are usually asymptomatic. Nonetheless, it is estimated that as many as 1% to 2% of patients may present with early-onset disease, defined as symptoms occurring before 15 years (14,15). In fact, in the most severe cases, ADPKD may present with significant neonatal and perinatal morbidity and mortality (16). More commonly, symptoms of disease begin between the ages of 30 to 50 years, and include acute abdominal or flank pain and gross or microscopic hematuria (18). However, in ADPKD children, longitudinal magnetic resonance imaging (MRI) studies have shown progressive increase in renal size, which is more pronounced in those children with overt hypertension or borderline hypertension (13).

The rate of progression of ADPKD to ESRD is highly variable, with age at onset of ESRD ranging from childhood to old age (18). In adults, several risk factors for faster progression have been identified, including the PKD-1 gene mutation; male gender; a young age at diagnosis; presence of hypertension, hematuria, and proteinuria; young age at onset of hypertension and hematuria; and larger kidneys (18–21). The disease course and risk factors for progression have not been well described in a large
series of children. Because the disease starts in childhood and progresses to ESRD over decades, identifying risk factors early in children might provide the greatest potential for effective early intervention in high-risk ADPKD patients.

Despite the slow and steady cystic growth in ADPKD patients, renal function within the normal range is maintained for years, and even decades, typically remaining relatively stable until a critical kidney size is reached, after which the decline in renal function is more rapid (22).

Much of the data on the natural history of ADPKD comes from longitudinal studies (23–28), which show that renal function and rate of decline in renal function in patients with ADPKD correlate with renal volume and the rate of increase in renal volume. Moreover, the Consortium of Radiologic Imaging Study of PKD (CRISP) cohort (23) confirmed the notion that cystic growth and renal enlargement is significant before impairment of renal function. The CRISP cohort (24) also revealed that normotensive patients have smaller cyst and renal volumes compared with hypertensive counterparts.

There are very few studies that have examined GH in patients with ADPKD. Dimitrakov et al. (29) proposed that GH and increased serum beta 2 microglobulin levels are early markers in the diagnosis of ADPKD. In another study (30), GFR was measured by technetium 99m diethylenetriamine pentaacetic acid in 18 children with ADPKD and 41 control patients. Mean GFR was 142 ± 33.2 ml/min per 1.73 m² in the ADPKD group, which was significantly greater than that in controls (110 ± 12 ml/min per 1.73 m²; P < 0.0001). A further study demonstrated that young adults with ADPKD have a decreased effective renal plasma flow and increased filtration fraction (31). To our knowledge, there has not been a longitudinal study examining the effect of GH on the rate of decline in renal function in ADPKD children.

In the current study in ADPKD children, the presence of GH was associated with a decline in renal function and increased rate of kidney enlargement over time. This finding is similar in diabetic patients with GH who are at increased risk of progression to diabetic nephropathy (32,33). Thus, early intervention in ADPKD in children with GH may be optimal to slow progression of the disease. Recent prospective randomized studies in adult patients with ADPKD to examine intervention to slow deterioration in renal function and renal kidney growth have been somewhat disappointing (34,35). This may indicate that intervention may be more effective when initiated in children with ADPKD.

The increase in GH in ADPKD children perhaps could be attenuated by blocking the vasoconstrictive effect of angiotensin II on the glomerular efferent arteriole. This could decrease any deleterious effect of the increased glomerular hydrostatic pressure associated with GH. In this regard, there has been a 5-year prospective randomized study in ADPKD children designed to block the renin-angiotensin-aldosterone system (RAAS) with an angiotensin converting enzyme inhibitor (ACEI). ADPKD children with borderline hypertension (75th – 95th percentile BP for their age) were shown to have a stable creatinine clearance when they received an ACEI, while the untreated children had a significant decline in creatinine clearance at the 5-year follow-up (13).

There is a potential mechanism for the relationship in the present study between GH and the increase in TKV. The renal RAAS is known to be stimulated in ADPKD, and angiotensin II (ANG II) may increase renal cyst volume by enhanced proliferation, inflammation, oxidant injury, and fibrosis (36). Furthermore, ANGII may contribute to GH in ADPKD children by increasing glomerular efferent arteriolar resistance.

There are limitations in our study. We measured renal function by CrCl; however, due to tubular secretion of creatinine, clearance of inulin or an accepted isotopic measure of glomerular function would be preferred. In addition, a larger number of ADPKD children followed prospectively for a longer period of time will be necessary to support the current findings. There were insufficient results to examine urinary proteinuria or microalbuminuria, but this measurement should be included in future studies. Also, measurement of renal volume by MRI is more accurate than ultrasound, as used in the current study.

In conclusion, the present study has potential implications for the design of future clinical trials in ADPKD. Several potential therapeutic agents target the mechanism responsible for the early growth and expansion of cysts (37). It may be futile to administer such agents late in the course of ADPKD when a host of different processes combine to produce renal dysfunction. Since renal enlargement due to cysts is the underlying disease process, it would seem most prudent to find an agent with efficacy early in the course of the disease. The present study demonstrated that GH in ADPKD children is associated with a significantly faster decline in renal function and higher rate of kidney enlargement over time. GH and increased renal volumes therefore may be early markers for a more severe form of ADPKD in children.

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Disclosures
None.

References
3. Pretorius DH, Lee ME, Manco-Johnson ML, Weingast GR, Sedman AB, Gabow PA: Diagnosis of autosomal dominant

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