Factors Influencing Progression of Renal Failure in Autosomal Dominant Polycystic Kidney Disease

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) frequently leads to end-stage renal failure (ESRF) in the sixth decade of life, but considerable heterogeneity exists in the rate of progression of renal failure. The respective contribution of genetic factors and of potentially amendable factors, such as blood pressure control or protein intake limitation, on the rate of progression in ADPKD patients is still debated. To evaluate the role of factors influencing the rate of progression of renal failure in ADPKD, we retrospectively analyzed the annual rate of decline of creatinine clearance (Ccr) in 109 ADPKD patients followed from the time a Ccr value of 30 to 50 mL per min/1.73 m² was measured until ESRD and need for hemodialysis (Study A), and in 48 undialyzed ADPKD patients followed for at least 4 yr from the time a Ccr value of 50 to 60 mL per min/1.73 m² was measured (Study B). In Study A, the decline in Ccr (ΔCcr) (mean ± SE) was 5.8 ± 0.2 mL per min/1.73 m² per year in the whole series, and was lower in females than in males (5.0 ± 0.2 versus 6.4 ± 0.2, P < 0.001). Accordingly, ESRF was reached at a later age in female patients (55.1 ± 1.2 versus 50.6 ± 1.2 yr, P < 0.01). The age at ESRF in male patients was lower when the disease was transmitted by mother than by father (46.3 ± 1.9 versus 54.1 ± 1.8 yr, P < 0.01), whereas no significant effect of the gender of the affected parent was apparent in female patients. By regression analysis, there was a positive but weak relationship between ΔCcr and mean arterial pressure (average value during follow-up, 107 ± 1 mm Hg, r = 0.224, P < 0.05) but not with dietary protein intake (mean value in follow-up, 0.87 ± 0.03 g/kg per day, r = 0.10, P = 0.33) nor with proteinuria at baseline, which was lower than 0.3 g/day in 104 cases (r = 0.10, P = 0.28). There was a negative relationship between age at ESRF and ΔCcr (r = 0.245, P < 0.05), with a later and slower progression in older subjects. In Study B, the mean decline in renal function during follow-up was 5.3 ± 0.4 mL/min/1.73 m² per year, a value close to that observed in Study A. By multiple regression analysis of the overall population (studies A and B combined), only MAP, age and gender were independent predictive factors of ΔCcr but all studied parameters taken together accounted for at best 20% of ΔCcr variation. We conclude that the rate of progression of renal failure in ADPKD patients is mainly determined by gene expression, with female gender and older age associated with a slower progression, whereas blood pressure control, but not protein intake, exerts a limited beneficial influence on the rate of progression in patients with advanced polycystic kidney disease who already have significant renal insufficiency.

Key Words: Polycystic kidney disease, chronic renal failure, blood pressure, dietary protein intake, gender

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disorder, responsible for 8 to 10 percent of cases of end-stage renal failure (ESRF) in western countries. The disease is genetically heterogeneous, as there is information to suggest three ADPKD genes, the most established being PKD1 located on the short arm of chromosome 16 (1,2) responsible for the disease in 86% of families, and PKD2 located on chromosome 4 (3). Patients with ADPKD generally maintain normal renal function for a prolonged time, usually up to the fifth decade of life (4–6), but once renal failure starts, the progression to ESRF generally takes less than 10 years (7) and approximately 60% of affected individuals develop ESRF by the sixth decade (4–6,8,9). However, the age at onset of renal dysfunction varies widely. Some patients with ADPKD still exhibit normal renal function after 65 years of age while others, sometimes in the same family, reach ESRF before 40 years of age (6,9,10). Such heterogeneity in the development of renal failure and in its rate of progression to ESRF suggests that factors other than the gene defect may contribute to the progression of renal disease. Accordingly, progression probably depends on the interplay between genetic and non genetic factors.

The role of genetic factors has been well underlined (6,11,12). These authors showed that in non-PKD1 disease, renal cysts develop later and more slowly,
and renal failure progresses less rapidly than in PKD1 families. The variable expression of the gene defect may also explain the wide variations in renal function involvement between affected patients. Recently, almost complete de novo deletions of the PKD1 gene have been shown to be associated with early and severe renal cystic disease in patients with tuberous sclerosis (TSC2) (13).

Among the non genetic factors that may influence renal progression, many studies suggest that elevated blood pressure, or a family history of primary hypertension are determinants of the renal prognosis in ADPKD (14,15). Hypertension in ADPKD is associated with a more pronounced stimulation of the renin-angiotensin-aldosterone system than in essential hypertension (16-18), probably due to cyst enlargement causing renal ischemia and renin release (19). Some preliminary results suggest that ACE inhibitors should therefore be of particular benefit in these patients (20,21).

In an attempt to identify factors that may affect the progression of renal failure in ADPKD, we analyzed retrospectively in a large cohort of patients followed in our institution over the past 10 years, the correlation between the rate of decline of renal function and factors likely to influence the progression to ESRF. Multivariate analysis helped to identify factors having an independent influence on the rate of decline in renal function.

PATIENTS AND METHODS

Patients

The study population consisted of 157 adult caucasian patients with ADPKD, who followed in our department. Of these 157, 109 reached ESRF and were placed on maintenance dialysis (Study A), whereas 48 established chronic renal failure (CRF) of different degrees but are still undiagnosed and on conservative treatment.

ADPKD was defined by the presence of at least five renal cysts distributed between both kidneys. In patients over 60 yr of age, in the absence of associated hepatic cysts or a positive family history, presence of at least four cysts in each kidney was required for participation in the study. This definition is in agreement with the data of Gabow et al. and of Ravine et al. (22,23). In any case, all patients had bilateral renal enlargement and innumerable cysts responsible for progressive renal failure and are therefore likely to be ADPKD1. However, DNA linkage analysis was performed in only a limited number of the patients' families.

In Study A, we reviewed the charts of all 130 adult ADPKD patients who reached ESRF and had to start hemodialysis in our department between January 1984 and December 1993. Of these 130 patients, 21 had been referred at a very advanced stage of renal failure without previous follow-up and were excluded from the study. The other 109 had been followed in our institution from the time a creatinine clearance (Ccr) value of 30 to 50 mL per min/1.73 m² was measured up to the time of ESRF, and were eligible for the study.

In Study B, all nondialysis patients with ADPKD and moderate renal failure (defined by a Ccr value of 50 to 70 mL per min/1.73 m²), who had been followed for at least 4 yr by December 1993 and who had been seen at least once a year, were included in the study. Among 94 ADPKD patients with moderate renal failure referred to us during the past decade, 48 fulfilled these criteria and were eligible for the study.

For every patient, we recorded the gender and the age of the affected parent at ESRF to determine the influence of gender transmission on the progression of the disease and to compare the age of studied subjects at ESRF to that of the affected carrier parent.

All patients were advised to reduce protein intake to 1 g/kg body weight per day at onset of renal failure, and to 0.7 to 0.8 g/kg body weight per day at the later stages of renal failure, and to limit sodium intake to approximately 120 mmol per day. Resting supine systolic (SBP) and diastolic blood pressure (DBP), body weight, and plasma creatinine (Pcr) levels were measured at least two to three times each year: 24-h urinary protein and urea excretion values were determined at least once each year. The median number of study visits was 14 (range, 7 to 30) in Study A and 9 (range, 5 to 15) in Study B. Hypertension was defined by one of the following: current antihypertensive drug therapy, SBP over 160 mm Hg, or DBP greater than 95 mm Hg at the visit. Attempts were made to maintain an SBP <150 mm Hg and a DBP <90 mm Hg by using antihypertensive drugs when needed. Drugs were used in various combinations and included furosemide, β-adrenergic blocking agents, calcium-channel blockers, and/or angiotensin-converting enzyme inhibitors (ACEI).

Methods

Progression of renal failure was evaluated in each patient by the rate of decline of estimated Ccr (ΔCcr) from the start of follow up (T₀) until either ESRF (TₚESRF) or the final value recorded at last outpatient clinic examination (T₀), expressed in mL per min/1.73 m² per year. Ccr was estimated according to the Cockcroft and Gault formula (24), which has been shown to closely parallel the true glomerular filtration rate (GFR) as determined by inulin clearance or isotopic methods in patients with impaired renal function, whether diabetic or not, if the cohort is large and the observation period is more than 4 yr (25,26). Age and weight were updated for the calculation of all Ccr values. Plasma creatinine (Pcr) levels were determined by the Jaffé kinetic method, adapted to an automatic multianalyzer Hitachi 717 (Hitachi Ltd., Tokyo Japan). Urinary protein excretion values were determined by colorimetric method with a pyrogallol red-molybdate complex. The proteinuria taken into account in the analysis was the 24-h protein excretion value at baseline, in order to assess its predictive value on the subsequent rate of progression. For blood pressure, urinary urea excretion values, and hemoglobin levels, we used the average of all values recorded throughout follow-up: blood pressure at baseline was also analyzed to assess its predictive value on renal progression. Blood pressure was expressed as mean arterial pressure (MAP = DBP + 1/3 (SBP−DBP)). Dietary protein intake (DPI) was estimated from urea excretion values measured in 24-h urine collection, according to Maroni et al. (27).

All results are expressed as mean ± SE unless otherwise stated. Data were analyzed using the Statistica software package (Statsoft, Tulsa, OK). The t test was used to compare means of groups of independent variables. Analysis of variance (ANOVA) was used to assess the relative contribution of nominal variables (gender of patient and affected parent), as well as covariates including age, proteinuria, blood pressure.
dietary protein intake, hemoglobin level and calcemia, to the rate of progression of chronic renal failure (ΔCcr). Forward stepwise-multiple regression was used to assess the effects of predictive variables (age, gender, proteinuria, MAP, dietary protein intake) on ΔCcr. Statistical significance was set at a P value of less than 0.05.

RESULTS

Study A

General characteristics of the ADPKD patients. At the start of study (T0), the mean age of the 109 dialysis patients (57 males, 52 females) was 46.1 ± 0.9 yr. Their mean Ccr was 42.1 ± 1.1 mL per min/1.73 m². The mean follow-up duration until ESRF was 6.7 ± 0.3 yr and the Ccr value at start of hemodialysis was 7.2 ± 0.1 mL per min/1.73 m² (Table 1). The overall slope of ΔCcr was 5.76 ± 0.24 mL per min/1.73 m² per year.

At baseline, 98 patients (90%) were hypertensive and six others developed permanent hypertension during follow-up. ACEI were part of antihypertensive therapy in 25 of the 104 patients treated for hypertension.

Influence of gender on progression to ESRF. Male patients were younger than females at T0, but renal function was not significantly different (Table 2). The age distribution at ESRF is shown on Figure 1. The mean age at ESRF was higher in females than in males (55.1 ± 1.2 versus 50.6 ± 1.2 yr, P < 0.01). This difference is primarily because of the subgroup of patients who reached ESRF at 45 yr of age or less, among whom men outnumbered women (21 versus 4), whereas the opposite sex ratio was found in the 66 to 70 yr age group.

The mean decline in Ccr was 6.4 ± 0.2 mL per min/1.73 m² per year in males and 5.0 ± 0.2 mL per min/1.73 m² per year in females (P < 0.001). The time elapsed from T0 until ESRF was therefore longer in females than in males (7.3 ± 0.4 versus 6.2 ± 0.3 years; P < 0.05) despite a slightly lower Ccr at T0 in females patients. The time elapsing from a GFR adjusted on a common value of 50 mL/min/1.73 m² until time to ESRF was less than 8 yr in men and more than 10 yr in women. Estimated DPI and MAP did not differ during the study period in both sexes, but as expected (28), more women than men had hepatic cysts (87% versus 87%, P < 0.05).

### TABLE 1. Characteristics of dialysis patients

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Body weight (kg)</th>
<th>Pcr (μmol/l)</th>
<th>Ccr (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>TESRF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.1 ± 0.9 (23-65)</td>
<td>52.7 ± 0.9 (31-70)</td>
<td>176 ± 5 (135-260)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>67.4 ± 1.1 (46-99)</td>
<td>66.4 ± 1.1 (48-98)</td>
<td>907 ± 13 (635-1178)</td>
</tr>
</tbody>
</table>

**NOTE:** These ranges are given in brackets.

### TABLE 2. Influence of gender on progression to end-stage renal failure

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 Age (yr)</td>
<td>44.4 ± 1.3</td>
<td>48.0 ± 1.2*</td>
</tr>
<tr>
<td>Ccr (ml/min/1.73 m²)</td>
<td>44.0 ± 1.4</td>
<td>40.0 ± 1.7</td>
</tr>
<tr>
<td>Pcr (μmol/l)</td>
<td>184 ± 6</td>
<td>167 ± 8</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>0.05 ± 0.01</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>TESRF Age (yr)</td>
<td>50.6 ± 1.2</td>
<td>55.1 ± 1.2**</td>
</tr>
<tr>
<td>Ccr (ml/min/1.73 m²)</td>
<td>957 ± 16</td>
<td>852 ± 18</td>
</tr>
<tr>
<td>ΔCcr (ml/min/1.73 m² per year)</td>
<td>7.6 ± 0.1</td>
<td>6.7 ± 0.1***</td>
</tr>
</tbody>
</table>

* Abbreviations: Pcr, plasma creatinine; Ccr, creatinine clearance; ΔCcr, rate of decline of Ccr during follow-up; MAP, mean arterial pressure (at start of study and during the follow-up); T0-TEESR, follow-up period from the start of the study to the initiation of dialysis; DPI, dietary protein intake. * P < 0.05; ** P < 0.01; *** P < 0.001, males versus females.

![Figure 1. Distribution of patients according to age at end-stage renal failure (ESRF) and gender (Males, N = 57; Females, N = 52).](image-url)
TABLE 3. Influence of gender of affected parent

<table>
<thead>
<tr>
<th>Transmission of the disease by</th>
<th>Father</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>Age at T₀ (yr)</td>
<td>46.5 ± 1.4</td>
<td>45.3 ± 1.5</td>
</tr>
<tr>
<td>Age at T_ESRF (yr)</td>
<td>53.4 ± 1.4</td>
<td>51.8 ± 1.5</td>
</tr>
<tr>
<td>ΔCcr (mL per min/1.73 m² per yr)</td>
<td>5.3 ± 0.2</td>
<td>6.0 ± 0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>Males</th>
<th>Females</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at T_ESRF (yr)</td>
<td>54.1 ± 1.8</td>
<td>52.6 ± 2.3</td>
<td>46.3 ± 1.9*</td>
<td>55.8 ± 1.7</td>
</tr>
<tr>
<td>ΔCcr (mL per min/1.73 m² per yr)</td>
<td>5.6 ± 0.4</td>
<td>4.8 ± 0.5</td>
<td>6.6 ± 0.5</td>
<td>5.5 ± 0.4</td>
</tr>
</tbody>
</table>

* P < 0.01, for males with disease inherited from mother versus father.

Patients according to the rate of progression (slow, ΔCcr < 3.6 mL per min/1.73 m² per year; moderate, ΔCcr 3.6 to 7.2 mL per min/1.73 m² per year; rapid, ΔCcr > 7.2 mL per min/1.73 m² per year). More females were found among the "slow" progressors (18 versus 7 males) and more males among the "rapid" progressors (13 versus 2 females). Mean blood pressure was higher in the latter than in the former (110 ± 2 versus 105 ± 2 mm Hg, P < 0.05).

TABLE 4. Influence of age at start of the study (T₀) on the rate of progression to ESRF (T_ESRF)²

<table>
<thead>
<tr>
<th>Age at T₀ (yr)</th>
<th>A: 21 to 40</th>
<th>B: 41 to 50</th>
<th>C: 51 to 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>23/9</td>
<td>17/22</td>
<td>17/21</td>
</tr>
<tr>
<td>T₀ Age (yr)</td>
<td>34.7 ± 0.8</td>
<td>45.9 ± 0.4</td>
<td>56.0 ± 0.6</td>
</tr>
<tr>
<td>Ccr (mL per min/1.73 m²)</td>
<td>47.8 ± 1.8</td>
<td>44.5 ± 1.9</td>
<td>34.9 ± 1.5**</td>
</tr>
<tr>
<td>T_ESRF Age (yr)</td>
<td>41.7 ± 0.9</td>
<td>52.4 ± 0.6</td>
<td>62.3 ± 0.7</td>
</tr>
<tr>
<td>Ccr (mL per min/1.73 m²)</td>
<td>7.9 ± 0.2</td>
<td>7.1 ± 0.2*</td>
<td>6.7 ± 0.2***</td>
</tr>
<tr>
<td>ΔCcr (mL per min/1.73 m² per year)</td>
<td>6.4 ± 0.4</td>
<td>6.1 ± 0.2</td>
<td>4.8 ± 0.2**</td>
</tr>
<tr>
<td>MAP in follow-up (mm Hg)</td>
<td>106 ± 1</td>
<td>107 ± 1</td>
<td>108 ± 1</td>
</tr>
<tr>
<td>DPI (g/kg per day)</td>
<td>0.86 ± 0.03</td>
<td>0.88 ± 0.04</td>
<td>0.83 ± 0.02</td>
</tr>
</tbody>
</table>

² Abbreviations: Pcr, plasma creatinine; Ccr, creatinine clearance; ΔCcr, rate of decline of Ccr during follow-up; MAP, mean arterial pressure; DPI, dietary protein intake. * P < 0.01, B versus A; ** P < 0.001, C versus B and A; *** P < 0.001, C versus A.
with hepatic cysts than in 26 patients without (5.5 ± 0.2 versus 6.5 ± 0.4 mL per min/1.73 m² per year, \( P < 0.01 \)) (Table 5). This is probably because of the preponderance of females in the group with liver cysts.

**Influence of dietary protein intake.** The mean value of estimated DPI was 0.87 ± 0.03 g/kg per day during follow-up, without significant difference between males and females (Table 2). Regression analysis did not disclose any significant relationship between DPI and ΔCcr (\( r = 0.109, P = 0.33 \)) (Figure 3).

**Influence of urinary protein excretion.** At T₀, 104 (95%) of the ADPKD patients had an urinary protein excretion of 0.3 g/day or less and five patients had a proteinuria value between 0.3 to 5 g/day. No correlation was found between urinary protein excretion amounts and ΔCcr in the 104 patients with low proteinuria values (\( r = 0.10, P = 0.28 \)). The mean ΔCcr value in the five patients with proteinuria values of >0.3 g/day was 7.5 ± 1, versus 5.6 ± 0.2 mL per min/1.73 m² per year in those with proteinuria values of <0.3 g/day (NS, Mann-Whitney U test).

**Influence of other parameters.** The mean blood hemoglobin level during the follow-up was 11.2 ± 0.2 and 10.2 ± 0.2 g/mL, respectively, in males and females. No correlation was found between the severity of anemia and ΔCcr (\( r = 0.16, P = 0.097 \)). In addition, serum calcium, phosphate and uric acid concentrations were not correlated with the rate of progression estimated by ΔCcr.

**TABLE 5. Hepatic cysts**

<table>
<thead>
<tr>
<th>Present (83)</th>
<th>Absent (26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at T₀E (yr)</td>
<td>53.2 ± 1.0</td>
</tr>
<tr>
<td>ΔCcr (mL per min/1.73 m² per year)</td>
<td>5.5 ± 0.2</td>
</tr>
<tr>
<td>Age at T₀E (yr)</td>
<td>50.3 ± 1.3**</td>
</tr>
<tr>
<td>ΔCcr (mL per min/1.73 m² per year)</td>
<td>6.1 ± 0.2</td>
</tr>
<tr>
<td>males (38)</td>
<td>females (45)</td>
</tr>
<tr>
<td>males (19)</td>
<td>females (7)</td>
</tr>
</tbody>
</table>

\( ^* P < 0.05, \text{ present versus absent; } ^{**} P < 0.01, \text{ males versus females.} \)

**Study B**

Characteristics of nondialysis patients are summarized in Table 6. Their mean Ccr value at baseline was 55.5 ± 2.1 mL per min/1.73 m². In this group, no difference in ΔCcr was apparent between males and females (5.3 ± 0.5 versus 5.2 ± 0.5 mL per min/1.73 m² per year). Of note, the mean value of ΔCcr did not significantly differ between Study A and Study B patients (5.8 ± 0.2 and 5.3 ± 0.4 mL per min/1.73 m² per year, respectively) (Figure 4).

All 48 patients in this group were hypertensive. MAP at baseline was 113 ± 1 mm Hg and the average MAP in follow-up was 104 ± 1 mm Hg, a slightly lower level than in Study A. The rate of decline in renal function was significantly but weakly correlated with MAP recorded during follow-up (\( r = 0.286, P < 0.05 \)) (Figure 5), but not with MAP at baseline. Twenty-five patients were treated by ACEI; their MAP values were similar to those of patients who did not receive such drugs and ΔCcr did not differ whether ACEI were part of antihypertensive therapy or not (5.3 ± 0.6 versus 5.2 ± 0.4 mL per min/1.73 m² per year).

**Multifactorial Analysis**

Multifactorial analysis indicated that the only factors independently affecting progression of renal function in ADPKD were the gender of affected patient, age at incipient renal failure, and blood pressure level.
TABLE 6. Characteristics of nondialysis patients

<table>
<thead>
<tr>
<th>N</th>
<th>(M/F)</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>27/21</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>49.3 ± 1.5 (24–66)</td>
<td></td>
</tr>
<tr>
<td>Ccr (mL per min/1.73 m²)</td>
<td>54.5 ± 1.5 (29–72)</td>
<td></td>
</tr>
<tr>
<td>ΔCcr (mL per min/1.73 m² per year)</td>
<td>55.5 ± 2.1 (36.8–71.8)</td>
<td></td>
</tr>
<tr>
<td>Follow-up T₀–Tₚ (yr)</td>
<td>29.3 ± 1.8 (8.7–56.5)</td>
<td></td>
</tr>
</tbody>
</table>

![Graph](https://via.placeholder.com/150)

Figure 4. Comparison of the rate of decline in estimated Ccr in dialysis (Study A) and nondialysis (Study B) male and female patients. The mean follow-up was 80.4 ± 3.6 and 64.8 ± 3.6 months in Study A and in Study B, respectively, and the mean value of ΔCcr did not differ between the groups (5.8 ± 0.2 versus 5.3 ± 0.4 mL per min/1.73 m² per year).

![Graph](https://via.placeholder.com/150)

Figure 5. Influence of average mean arterial pressure (MAP) recorded during follow-up on progression rate of renal failure in nondialysis patients (regression analysis). r = 0.286, P < 0.05.

However, when taken together, these factors accounted for only 18% of the variation in ΔCcr.

**DISCUSSION**

Progressive renal failure is the most common complication of ADPKD. However, not all ADPKD patients progress to ESRF, and in patients who develop renal failure, the age at onset of renal dysfunction and the rate of decline in renal function exhibits wide interindividual variation. In our study, the age at the start of hemodialysis in 109 patients was close to 53 yr, similar to the age reported in recent studies (6,9). Interestingly, the age at ESRD presently observed does not differ from that observed in the 1970s (29,30) and even from data reported by Dalgaard et al. in 1957, before the availability of supportive dialysis (8). In Germany, Geberth et al. also reported the same finding; that the comparison of age at death of ADPKD patients in the 1950s and age at renal death in the 1980s was similar (58 and 59 years respectively) (31). This suggests that improvement in therapeutics, especially in antihypertensive therapy, was not accompanied by a dramatic reduction in the rate of renal-failure progression in ADPKD (32). The data obtained in this report’s Study A show that approximately 15% of ADPKD patients progressed to ESRF before 40 yr of age, and 10% later than 65 yr (Figure 1). In Study B, 23% (11 of 48) of undialyzed ADPKD patients with moderate chronic renal failure are age 65 yr or over.

Genetic factors are known to influence the rate of progression to ESRF in ADPKD. This has been well demonstrated by comparing PKD1 versus non-PKD1 families (6,10,11,33). This genetic effect, however, does not account for the heterogeneity within a given family. Bear et al. reported that in PKD1 families, age at onset of ESRF was earlier when the disease was inherited from mothers than from fathers (50.5 versus 64.8 yr) but they did not analyze their data according
to the sex of the patients (34). We are able to confirm this unfavorable maternal effect (ESRF reached approximately 8 yr earlier when the mother was the carrier) only in male patients, whereas this effect was not found in female patients in our study. However, our study population is small; a study using a larger number of female patients could possibly modify this finding.

Gretz et al. first pointed out the gender difference in ADPKD progression, with ESRF occurring later in female than in male patients (35). This observation was subsequently confirmed in several large series (33,36,37). Our study indicates that the progression of renal failure is more rapid in ADPKD males, by about 1.5 mL per min per year as a mean, and that renal function impairment manifests earlier in males than in females. This sexual heterogeneity is not fully understood. Sex hormones are possibly involved in this phenomenon, because renal diseases with prepubertal progression to ESRF do not show such a gender influence (35).

Gabow et al. suggested that females with hepatic cysts have more severe renal disease that those without this localization (33). In our study, we observed the opposite: the rate of progression of renal failure was slower in patients with hepatic cysts, possibly because of the preponderance of females in this group with their essentially slower progression. There is a need for other studies to determine if such, or other, extrarenal manifestations of the disease are associated with a different severity in progression toward renal failure in ADPKD.

Regarding the mean rate of decline in GFR in ADPKD patients, our retrospective data are in accordance with those recently reported in the Modification of Diet in Renal Disease trial (38). In this prospective study, 141 ADPKD patients with moderate renal failure were included, with a male to female ratio of 79:62. The mean GFR loss (measured by repeated iothalamate clearances) was 5.9 mL/min per year, which is very similar to our findings (5.8 mL per min/year on the basis of the decline in estimated Ccr). At variance with findings in a murine model of polycystic kidney disease (39), both the MDRD trial, the study presented here, and other previous studies as well (29) indicate that dietary protein intake in the range of 0.7 to 1.2 g/kg of body weight per day has no significant effect on progression in ADPKD patients. However, in the above-mentioned animal model, dietary intervention occurred early in the course of the disease, contrary to the MDRD trial and the study presented here.

A crucial issue is whether blood-pressure control may slow the rate of progression of renal failure in ADPKD patients. In our patients, most of whom had an average MAP value of 100 to 120 mm Hg during follow-up, the beneficial effect of BP control on the rate of progression was much more modest than that reported by Gabow et al. (33). However, other groups have reported a similarly poor effect of blood pressure control on progression in ADPKD patients. Abdelhamane et al. did not find any relationship between the rate of progression and blood pressure level in 32 hypertensive ADPKD patients (37). In the MDRD study, there was no demonstrable relation between MAP level and the rate of decline in GFR (40); in addition, a subgroup of patients submitted to a more stringent blood-pressure control with an average MAP close to 95 mm Hg did not experience a further beneficial effect, but instead experienced a deleterious effect. Such a "U-type" relationship between MAP and progression has also been reported by Gonzalo et al., who observed a faster progression rate in patients with MAP lower than 100 or higher than 115 mm Hg (41). Such findings contrast with the beneficial effect of blood-pressure control on progression reported in other nondiabetic renal diseases, and especially the beneficial effects of stringent blood-pressure control in patients with proteinuria values of more than 1 g/day at baseline and (electively) in those with proteinuria values in excess of 3 g/day (40). Of note, proteinuria at the early stage of renal failure in our patients was very low (below 0.3 g/day in 95% of cases).

Another debated point is whether or not ACEI are of particular benefit in slowing progression of renal failure in ADPKD patients, as has been reported in a recent prospective study, in terms of blood-pressure control (20,21) and in terms of decline in GFR in nondiabetic renal diseases (42). In our retrospective study, no benefit of ACEI over other antihypertensive treatment was apparent, and a similar finding was reported in the MDRD study. However, in both studies, ACEI were not prescribed from the incipient stage of renal failure, and in our patients they were primarily prescribed to those with the most severe hypertension. Thus, specific prospective studies are warranted to evaluate whether ACEI given from the very incipient stage of renal failure should exert a better renoprotective effect than other antihypertensive treatment in ADPKD patients. The obvious need of blood-pressure control for preventing cardiovascular complications is beyond the scope of our discussion.

The absent, or very low, protein excretion in ADPKD patients at the early stage of renal failure is a salient finding in our study, as is the lack of significant relationship between proteinuria values at baseline and the subsequent rate of decline in Ccr. This contrasts with findings in other nondiabetic renal diseases, especially glomerular diseases, in which a strong correlation between proteinuria values and decline in GFR has been observed by a number of authors (43,44) and by our group in a recent study (45). A low urinary protein excretion value in ADPKD patients has also been reported by Zeier et al. (46) and more recently by Chapman et al. (47). The latter authors observed a protein excretion value of lower than 300 mg/day in all of 222 ADPKD patients with preserved or moderately altered renal function, whereas the average protein excretion value was be-
The fact that proteinuria values are markedly lower at values were lower than 0.3 g/day in all but a few cases at the incipient stage, and between 0.5 and 2 g/day at the advanced stage of renal failure (data not shown). The fact that proteinuria values are markedly lower at the early stage of renal failure in ADPKD than in most glomerular diseases at a comparable degree of GFR reduction suggests that the mechanism involved in progression in ADPKD patients does not rely on the development of lesions of focal glomerular sclerosis as a result of glomerular hypertension and/or hypotrophy, which usually correlate with proteinuria and progression (at least in murine models) (48). As a matter of fact, pathologic examination of polycystic kidneys removed in patients with ESRF, as reported by Zeier et al., disclosed a very low percentage of glomeruli with focal glomerular hyalinosis and sclerosis, but predominant vascular and tubulointerstitial lesions (46). We made a similar observation with histological examinations of polycystic kidneys removed in 19 of our patients (data not shown). These considerations may be of clinical concern, because they provide evidence that genetic factors, i.e., the phenotypic expression of the gene governing the development (and the rate of progression) of cysts and the consequent destruction of renal parenchyma, are the most important factor of progression toward ESRF in ADPKD patients, as already proposed by Frantz and Reubi (7). This explains why blood-pressure control or limitation in protein intake has a limited effect on progression in this disease, at least in patients with established renal failure.

In conclusion, the rate of progression of renal failure in ADPKD patients appears to be influenced chiefly by genetic factors, with wide interindividual variations in the phenotypic expression of the gene disorder. In contrast, potentially alterable factors such as blood-pressure control appear to exert only a limited beneficial effect, at least in the range of values achieved in our patients, whereas dietary protein intake in the range of 0.7 to 1.2 g/kg per day had no demonstrable effect on progression rate in patients with advanced polycystic kidney disease and already significantly impaired renal function. Such results clearly point out the need for therapeutic approaches aimed at slowing or halting the development in number and size of renal cysts.

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REFERENCES

Progression of Polycystic Kidney Disease


