Overt Proteinuria and Microalbuminuria in Autosomal Dominant Polycystic Kidney Disease

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ABSTRACT
The amount of proteinuria is a prognostic indicator in a variety of glomerular disorders. To examine the importance of urinary protein excretion in autosomal dominant polycystic kidney disease, this study determined the clinical characteristics of autosomal dominant polycystic kidney disease patients with established proteinuria and the frequency of microalbuminuria in hypertensive autosomal dominant polycystic kidney disease patients without proteinuria. In 270 autosomal dominant polycystic kidney disease patients, mean 24-h urinary protein excretion was 259 ± 22 mg/day. Forty-eight of 270 autosomal dominant polycystic kidney disease patients had overt proteinuria (>300 mg/day). The patients with established proteinuria had higher mean arterial pressures, larger renal volumes, and lower creatinine clearances than did their nonproteinuric counterparts (all P < 0.0001), a greater pack year smoking history (P < 0.05), and the projection of a more aggressive course of renal disease (P < 0.05). All autosomal dominant polycystic kidney disease patients with established proteinuria were hypertensive, as compared with 67% without established proteinuria (P < 0.001). Forty-nine patients with hypertension and left ventricular hypertrophy without established proteinuria were examined for microalbuminuria; 41% demonstrated microalbuminuria. Those with microalbuminuria had higher mean arterial pressure, larger renal volumes and increased filtration fraction. Therefore, established proteinuria and microalbuminuria in autosomal dominant polycystic kidney disease patients are associated with increased mean arterial pressure and more severe renal cystic involvement.

Key Words: Proteinuria, microalbuminuria, hypertension, renal volume, creatinine clearance

Although established proteinuria in patients with glomerular disease characterizes a group of patients who have a worse renal prognosis (1-4), this relationship has not been well established in patients with tubulointerstitial disease. Autosomal dominant polycystic kidney disease (ADPKD) is the most common tubulointerstitial renal disease, and therefore, defining the significance of proteinuria in this disorder could have clinical importance. Although proteinuria has been reported to occur commonly in ADPKD (5-7), few studies have quantified protein excretion (8) or have characterized the implications of its presence in the disease (9). Recently, however, in a preliminary report, a negative effect of proteinuria on renal outcome in ADPKD patients has been suggested (10). In addition, a relationship between proteinuria and essential hypertension exists, identifying those who have had prolonged, poorly controlled blood pressure and renal insufficiency (11,12). Given that ADPKD patients are affected with hypertension early in the course of their disease (13) and that the most significant variable to affect renal outcome besides gene type is the level of blood pressure control (14), the presence of proteinuria in ADPKD patients may define a group with more severe hypertension.

Microalbuminuria (MA), a sensitive measure of urinary albumin excretion, has been useful in identifying type 1 insulin-dependent diabetics who are at risk for developing diabetic nephropathy and is a risk factor for cardiovascular mortality in essential hypertensive patients, particularly those who are older, obese, and male (15-17). The cause of MA in essential hypertension is unclear; however, it is associated with hypertensive end-organ damage, including left ventricular hypertrophy and retinopathy due to prolonged, poorly controlled hypertension (15). Similarly, MA may more readily identify those ADPKD patients who have more serious hypertensive disease.

This study was therefore undertaken to evaluate the occurrence of established proteinuria in 270 ADPKD patients and to determine if the presence of hypertension, level of renal function, renal structural involvement, body surface area, gender, smoking habits, and medication use were different in those patients with fixed proteinuria. The urinary albumin excretion rate was also measured in a subset of hypertensive ADPKD patients with left ventricular hypertrophy, a group that is more likely to progress to end-stage renal failure (14). Those ADPKD patients with and without MA were compared with regard to level of blood pres-
ure, renal function, renal structural involvement, and left ventricular mass.

METHODS

Correlates With Established Proteinuria in the General ADPKD Population

ADPKD patients were seen at the University of Colorado Health Sciences Center (UCHSC) on the General Clinical Research Center (GCRC) between 1985 and 1993. After signing informed written consent, patients underwent a formalized history and physical examination. One pack year is 365 packs of cigarettes smoked, regardless of time frame. Hypertension was defined as a blood pressure of greater than 140/90 mm Hg in the sitting position or a history of hypertension and taking antihypertensive medication. Abdominal ultrasonography was performed for the determination of renal volume as described elsewhere (13). Patients diagnosed with ADPKD were required to have more than five renal cysts bilaterally (18). Patients collected urine for two consecutive 24-h periods for the determination of creatinine and protein excretion rates. Those 24-h urine collections where creatinine excretions differed by more than 300 mg/day and had a coefficient of variation greater than 15% were excluded from the analysis. A blood sample was obtained for serum creatinine concentration determination. A first morning voided urine specimen was also obtained for standard urinalysis. Patients were considered to have hematuria or leukocyturia if there were more than five cells per high-power field. Patients were considered to have established proteinuria if levels were higher than 300 mg/day and nephrotic-range proteinuria if levels were higher than 3.0 g/day.

Correlates With Microalbuminuria in Hypertensive ADPKD Patients From the Original Study Population

A subset of 54 hypertensive ADPKD patients with left ventricular hypertrophy were also studied on the GCRC at the UCHSC between February 1992 and October 1993. Screening echocardiograms were performed before study to determine left ventricular mass. Two-dimensional M-mode echocardiography was performed by use of the established American Society of Echocardiography recommendations for measurement (19). Left ventricular mass was determined on the basis of the Penn convention (20), and left ventricular hypertrophy was defined as a left ventricular mass greater than 125 g/m² in men and 110 g/m² in women. Abdominal ultrasonography was performed to determine renal volume in patients who had not had a determination within the previous year.

After qualifying and signing informed written consent, patients taking antihypertensive medications discontinued those medications for a minimum of 2 wk. Patients were then admitted to the GCRC for 4 days. Patients were placed on a standard dietary intake of 150 mEq of sodium, 80 mEq of potassium, and 1 g/kg of protein per day. Blood was drawn on the first hospital day for the measurement of hematocrit, creatinine, cholesterol, and triglyceride concentrations. Every study day, three blood pressures were taken 5 min apart in the supine, sitting, and standing positions. Blood pressures were measured in the dominant arm oscillometrically with the Dinemap (Critikon, Tampa, FL). Mean arterial pressure was calculated according to the following formula: diastolic blood pressure + (1/3[systolic – diastolic blood pressure]). Blood pressures are reported as the mean of the four study days.

Inulin and para-aminohippurate clearances were performed on the morning of the third day after an overnight fast with the exception of water intake. Hydration was maintained throughout the clearance study by oral water intake. One hour after the initial bolus and the infusion of inulin and para-aminohippurate, three 30-min urine collections were obtained. Blood samples were obtained at the midpoint of each urine collection period for the determination of serum inulin and para-aminohippurate concentrations. On the morning of the fourth hospital day, after an overnight fast, urine was collected over 8 h to determine the urinary albumin excretion rate. MA was defined as a urinary excretion greater than 30 µg/min (45 mg/day) but less than 208 µg/min (300 mg/day) (21,22).

Cholesterol and triglyceride concentrations and hematocrits were determined by standard laboratory techniques. Serum and urinary creatinine concentrations were determined by the modified Jaffe picrate reaction with a Gilford Stasar 4 System 2035 (Ciba-Corning, Oberlin, OH). Urinary protein concentrations were determined by use of the Coomassie blue dye-binding method (23). Inulin and para-aminohippurate concentrations were determined by standard colorimetric techniques (24). Urinary albumin concentrations were determined by radioimmunoassay (25), which has a detection limit of <0.3 mg/L and a coefficient of variation of <2.7%.

Analyses of variance and covariance were performed simultaneously to determine the effects of gender, age, smoking habits, weight, body surface area, and leukocyturia on 24-h urinary protein excretion. Analyses of variance and covariance were also used to determine the effects of gender, duration of high blood pressure, mean arterial pressure (mean of 4 days), inulin and para-aminohippurate clearance, filtration fraction, renal vascular resistance, renal volume, smoking habits, age, weight, body surface area, left ventricular mass, cholesterol, and triglyceride level on urinary albumin excretion rates. Step-down selection was used. Each of these variables was also examined separately by standard analyses.

The method of Jones and Boadi-Boatang (14) was used to determine if urinary protein excretion had an effect on the reciprocal of serum creatinine. Serum creatinine values obtained before or during the study visit were used. Sixty-six percent of the subjects had multiple serum creatinine measurements. The reciprocal of serum creatinine versus age was modeled as a straight line, and urinary protein excretion was included as a continuous variable. The resultant model is displayed for the mean urinary protein excretion of subjects with >300 mg/day versus subjects with less than 300 mg/day. Statistical significance is defined as a P value less than 0.05, with significant P values provided in the text. All values are reported as the mean ± SE.

RESULTS

Correlates With Established Proteinuria in the General ADPKD Population

Three-hundred four ADPKD patients were eligible for study. Thirty-two patients had variable creatinine excretions and were excluded from further analysis. Twenty-four-hour urinary protein excretion rates
were greater than 3 g in two patients. Because previously reported ADPKD patients with nephrotic-range proteinuria who underwent biopsy had a second renal disease (26–29), these patients were also excluded from further analysis. This left 270 patients (94 men and 176 women) available for study. The mean 24-h urinary protein excretion rate was 259 ± 22 mg/day, ranging from 7 to 2.049 mg/day. Eighty-two percent had less than 300 mg/day of proteinuria (Table 1). Men had higher levels of proteinuria than did women (346 ± 47 versus 212 ± 23 mg/day; P < 0.05). Importantly, all normotensive patients with normal renal function excreted less than 300 mg of urinary protein a day. Several of the variables examined for their relationship to urinary protein excretion were significantly different between subjects with and without established proteinuria (Table 1).

Thirty-seven percent of the patients were from known ADPKD1 families, 58% did not have linkage status determined, and 5% (13 patients) were from a single ADPKD2 family. There was no difference in the frequency of established proteinuria between the ADPKD2 patients (15%) and the other patients (18%; P = not significant).

Analyses of variance and covariance demonstrated in decreasing order of importance that creatinine clearance (P < 0.0001, inverse relationship), mean arterial pressure (P < 0.0001), renal volume corrected for body surface area (P < 0.01), the presence of hematuria (P < 0.01), age (P < 0.05, inverse relationship), and smoking history (P < 0.05) were significantly related to the level of proteinuria. When ADPKD patients older than 70 yr of age were excluded, age did not have a significant relationship to proteinuria. Those patients with established proteinuria had a higher mean serum creatinine concentration at any given age as compared with those without proteinuria (P < 0.05; Figure 1). By the use of longitudinal data analysis, patients with established proteinuria reached a serum creatinine concentration of 1.5 mg/dL at 44 yr of age as compared with 58 yr in the nonproteinuric group.

**Correlates With MA in Hypertensive ADPKD Patients**

Fifty-nine hypertensive ADPKD patients with left ventricular hypertrophy had urinary albumin excretion rates determined. The characteristics of the subjects are shown in Table 2. Of the 41% of patients (20 of 49) with MA, men were more frequently affected than women (57 versus 27%; P < 0.05). Only one patient was from a known ADPKD2 family; he did not have MA. When ADPKD patients with and without MA

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**TABLE 1. Characteristics of ADPKD patients with and without established proteinuria (urinary protein excretion >300 mg/day)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0 to 300 mg/day</th>
<th>&gt;300 mg/day</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>222</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (mg/day)</td>
<td>121 ± 4</td>
<td>894 ± 74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male:Female</td>
<td>69:153</td>
<td>25:23</td>
<td></td>
</tr>
<tr>
<td>% Men</td>
<td>31</td>
<td>52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>% Hypertensive</td>
<td>67</td>
<td>100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standing Mean Arterial Pressure (mm Hg)</td>
<td>106 ± 1</td>
<td>115 ± 2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ccr (ml/min per 1.73 m²)</td>
<td>82 ± 2</td>
<td>37 ± 4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal Volume (cm³)</td>
<td>578 ± 32</td>
<td>1,190 ± 93</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39 ± 1</td>
<td>48 ± 2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Smoker</td>
<td>28</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Pack Years</td>
<td>9.1 ± 1.1</td>
<td>16.7 ± 3.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 1</td>
<td>81 ± 2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.82 ± 0.01</td>
<td>1.94 ± 0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Hematuria</td>
<td>3</td>
<td>17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% Leukocyturia</td>
<td>17</td>
<td>27</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Ccr, creatinine clearance; NS, not significant; BSA, body surface area.

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**Figure 1. Estimate of slope of reciprocal of serum creatinine (1/Scr) in ADPKD patients with (N = 48) and without (N = 222) established proteinuria.**
were compared, standing mean arterial pressure (113 ± 2 versus 107 ± 2 mm Hg; P < 0.05), renal volume (853 ± 87 versus 535 ± 52 cm³; P < 0.01), and filtration fraction (0.24 ± 0.01 versus 0.21 ± 0.004; P < 0.05) were greater in the group with MA (Table 3). Analyses of variance and covariance determined that renal vascular resistance (P < 0.01), mean arterial blood pressure (P < 0.05), and mean renal volume corrected for body surface area (P < 0.05) were significantly related to urinary albumin excretion, whereas gender, duration of hypertension, insulin and para-aminohippurate clearances, filtration fraction, smoking habits, age, weight, body surface area, left ventricular mass, cholesterol, and triglyceride levels were not.

**DISCUSSION**

By the use of a reliable method for determining urinary protein excretion, the majority (82%) of ADPKD patients do not have established or fixed proteinuria (>300 mg/day). Forty-eight (18%) of 270 ADPKD patients, however, were found to have established proteinuria. Although a minority of ADPKD patients have established proteinuria, its presence identified a more severely affected patient group that is significantly older, with lower creatinine clearances, nearly twofold greater renal volumes, and an increased incidence of hematuria. Hypertension was present in 100% of those with established proteinuria as compared with 67% of patients without proteinuria. Siting mean arterial pressures were also significantly greater in those with established proteinuria. Thus, these screening results indicate a very strong correlation between proteinuria, hypertension, and renal dysfunction. Of the previously mentioned variables, blood pressure level was one of the most important in determining urinary protein excretion. Iglesias et al. noted that ADPKD patients who had proteinuria at the time of diagnosis appeared to have a worse renal outcome, and recent data from the Modification in Dietary Protein in Renal Disease study indicate that increased baseline levels of proteinuria impart a poorer renal outcome in all patients, including ADPKD patients specifically (9, 10). Although male gender, increased body weight, and pack year smoking history were characteristic of those ADPKD patients with detectable proteinuria, only smoking history was a significant independent variable in determining the level of proteinuria. Although patients with proteinuria were older than patients without, after adjusting for other factors including several that are related to age (particularly creatinine clearance and renal vol-

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**TABLE 2. Hypertensive ADPKD patients with left ventricular hypertrophy with and without MA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;30 µg/min (N = 29)</th>
<th>30 to 208 µg/min (N = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuminuria (µg/min)</td>
<td>21 ± 2</td>
<td>120 ± 17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42 ± 2</td>
<td>40 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Male:Female</td>
<td>10:19</td>
<td>13.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% Men</td>
<td>34</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.9 ± 3.0</td>
<td>82.3 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.86 ± 0.04</td>
<td>1.98 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>LVM (g/m²)</td>
<td>146 ± 4</td>
<td>146 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>201 ± 7</td>
<td>203 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>119 ± 16</td>
<td>162 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>% Smoker</td>
<td>17</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Pack Years</td>
<td>7.9 ± 3.1</td>
<td>7.2 ± 2.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

*BSA, body surface area; LVM, left ventricular mass; NS, not significant.*

**TABLE 3. Systemic and renal hemodynamics of hypertensive ADPKD patients with left ventricular hypertrophy with and without MA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;30 µg/min (N = 29)</th>
<th>30 to 208 µg/min (N = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of HBP (yr)</td>
<td>4.9 ± 0.7</td>
<td>6.6 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>107 ± 2</td>
<td>113 ± 2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CÌn (mL/min per 1.73 m²)</td>
<td>76 ± 4</td>
<td>72 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>CPAH (mL/min per 1.73 m²)</td>
<td>369 ± 20</td>
<td>315 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>Renal Volume (cm³)</td>
<td>535 ± 52</td>
<td>853 ± 87</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FF</td>
<td>0.21 ± 0.004</td>
<td>0.24 ± 0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RVR (dyn/s·cm⁻⁵)</td>
<td>14,684 ± 1,034</td>
<td>20,746 ± 3,397</td>
<td>NS</td>
</tr>
</tbody>
</table>

*HBP, high blood pressure; MAP, mean arterial pressure; CÌn, inulin clearance; CPAH, para-aminohippurate clearance; FF, filtration fraction; RVR, renal vascular resistance; NS, not significant.*
volume), we found a significant (P < 0.05) inverse relationship between age and urinary protein excretion. This study population excludes ESRD patients; therefore, the more elderly patient has a milder form of disease. When we exclude the geriatric patients over 70 yr of age (N = 5), no relationship between age and proteinuria was found. Therefore, the inverse relationship with age may represent a study population bias from a less severe disease in the elderly.

The 18% incidence of established proteinuria found in this study of ADPKD patients is less than that reported in other studies (6,7,30,31). The frequency of detectable proteinuria when qualitatively assessed has been reported to range from 14% in ADPKD children (32) to 34% of nonazotemic adult ADPKD patients (18) to approximately 70 to 80% of ADPKD adults with advanced disease (6,7,30,31). The patient populations in the older studies were likely to have more severe disease because they were not identified in a screening protocol, as were many patients in our study population. Quantitative data available in four ADPKD patients (8) demonstrated that all had more than 25% mg of urinary protein excretion per day and all had impaired renal function. Established proteinuria therefore appears to occur late in the course of ADPKD because patients have markedly diminished creatinine clearances and extremely large renal volumes. Importantly, normotensive patients with normal renal function in this study did not demonstrate established proteinuria.

Although serum creatinine has limitations in assessing the progression of renal disease, the difference in the rates of the progression of renal disease in proteinuric and nonproteinuric ADPKD patients in this study was not small. Those with proteinuria reached a serum creatinine concentration of 1.5 mg/dL by 44 yr of age as compared with nonproteinuric patients, who attained this level at age 58 yr. Of all other factors that related to a worse renal outcome in ADPKD patients, only gene type and the presence of hypertension demonstrated a stronger relationship (14).

Proteinuria is more common in ADPKD patients as compared with essential hypertensive patients, in whom a 4 to 7% incidence rate is usually found (33). However, the frequency of MA, a precursor to established proteinuria, appears to be similar. Forty-one percent of hypertensive ADPKD patients with left ventricular hypertrophy demonstrated MA, consistent with the frequency found in essential hypertensive patients with or without left ventricular hypertrophy (30 to 45%) (33–38). As in the essential hypertensive population with MA, ADPKD patients with MA may be at increased risk for cardiovascular morbidity and mortality—the most common cause of death in ADPKD patients (39). The hypertensive ADPKD patients with MA had greater mean arterial pressures, renal volumes, and filtration fractions as compared with those without MA. Importantly, effective RPF, GFR, and left ventricular mass were similar between the two groups of patients. The lack of these latter differences between groups may simply reflect a population of subjects that are at a relatively early stage in the course of their disease. The already apparent difference in renal volume is consistent with the observation that structural abnormalities precede functional changes in ADPKD by many years (19,40).

Other investigators have found a relationship between obesity and triglyceride and cholesterol levels in essential hypertensive patients with MA (41). A link between these parameters and MA in this study population was also investigated; however, no relationships between body weight, body surface area, and cholesterol or triglyceride level and MA were found. Similarly, no relationships between body surface area, triglyceride and cholesterol levels, and albuminuria have been found in other secondary forms of hypertension (42).

In summary, proteinuria occurs in a minority of ADPKD patients and its presence identifies a subset of patients with more severe renal involvement both structurally and functionally. Importantly, proteinuria most strongly correlated with the severity of the hypertensive state. Approximately 40% of hypertensive ADPKD patients with left ventricular hypertrophy but without established proteinuria exhibit MA. MA also correlated with blood pressure level and renal volume, an index of cystic involvement. Given that hypertension in ADPKD is mediated by the activation of the renin-angiotensin-aldosterone axis (43), angiotensin-converting enzyme inhibition therapy may provide benefits in reducing the rate of progression of renal disease and reducing the level of proteinuria independent of the level of systemic blood pressure. If the reabsorption of urinary protein itself contributes to tubular interstitial disease (44), then the reduction of proteinuria may provide renal protection. Long-term studies are necessary to examine whether antihypertensive therapy with angiotensin-converting enzyme inhibition or other agents in hypertensive ADPKD patients reduces proteinuria and slows the progression of renal disease.

ACKNOWLEDGMENTS

This research was supported by Grant 5 P01 DK34039, Human Polycystic Kidney Disease (PKD), awarded by the Department of Health and Human Services, Public Health Service, NIDDK and the Clinical Research Center, Grant MORR-00051 from the General Clinical Research Centers Research Program of the Division of Research Resources, NIH; and Grant 90-S-0010, Pfizer Inc.

REFERENCES