Overt Proteinuria and Microalbuminuria in Autosomal Dominant Polycystic Kidney Disease[1, 2]

Arlene B. Chapman,[3] Ann M. Johnson, Patricia A. Gabow, and Robert W. Schrier

A.B. Chapman, A.M. Johnson, P.A. Gabow, R.W. Schrier, University of Colorado Health Sciences Center, Denver, CO

P.A. Gabow, Denver Health and Hospitals, Denver, CO

(J. Am. Soc. Nephrol. 1994; 5:1349–1354)

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.

[1] Received May 31, 1994. Accepted August 1, 1994.

[2] This material was presented in part at the Fifth International Workshop on Polycystic Kidney Disease in Kansas City, MO, June 19–20, 1992, and at the 26th American Society of Nephrology meeting in Boston, MA, November 14–17, 1993.

[3] Correspondence to Dr. A.B. Chapman, Box C283, University of Colorado Health Sciences Center, 4200 East Ninth Ave., Denver, CO 80262.

1046-6673/0506-01349$03.00/0
Journal of the American Society of Nephrology

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-

sure, 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/m^2 in men and 110 g/m^2 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 + ([systolic − diastolic blood pressure]/3). 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 Jaffé 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, presence of hypertension, standing mean arterial pressure, class of antihypertensive agent, creatinine clearance, renal volume, age, smoking habits, weight, body surface area, hematuria, 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, standing 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 was 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

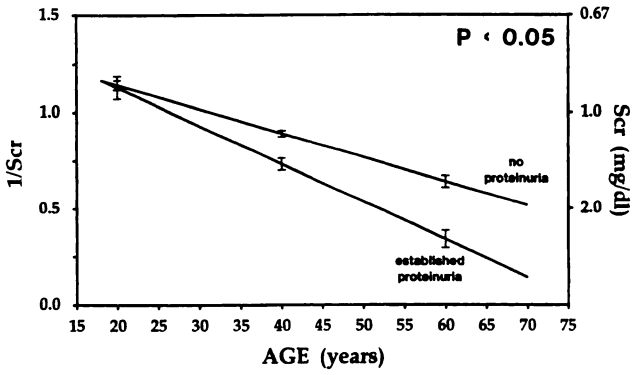

Figure 1. Estimate of slope of reciprocal of serum creatinine (1/Scr) in ADPKD patients with ($N = 48$) and without ($N = 222$) established proteinuria.

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

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

[a] Ccr, creatinine clearance; NS, not significant; BSA, body surface area.

TABLE 2. Hypertensive ADPKD patients with left ventricular hypertrophy with and without MA[a]

Characteristic	<30 μg/min (N =29)	30 to 208 μg/min (N = 20)	P Value
Albuminuria (μg/min)	21 ± 2	120 ± 17	<0.0001
Age (yr)	42 ± 2	40 ± 2	NS
Male:Female	10:19	13:7	<0.05
% Men	34	65	
Weight (kg)	75.9 ± 3.0	82.3 ± 2.7	NS
BSA (m^2)	1.88 ± 0.04	1.98 ± 0.04	NS
LVM (g/m^2)	146 ± 4	146 ± 5	NS
Cholesterol (mg/dL)	201 ± 7	203 ± 10	NS
Triglycerides (mg/dL)	119 ± 16	162 ± 22	NS
% Smoker	17	25	NS
Pack Years	7.9 ± 3.1	7.2 ± 2.5	NS

[a] 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[a]

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

[a] HBP, high blood pressure; MAP, mean arterial pressure; Cin, inulin clearance; CPAH, *para*-aminohippurate clearance; FF, filtration fraction; RVR, renal vascular resistance; NS, not significant.

were compared, standing mean arterial pressure (113 ± 2 versus 107 ± 2 mm Hg; $P < 0.05$), renal volume (853 ± 87 versus 535 ± 52 cm^3; $P < 0.01$), 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, inulin 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. Sitting 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-

ume), 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 250 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 (9,39).

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

1. **Jarett RJ, Viberti GB, Argyropoulus A, Hill RD, Mahmud U, Murrels TJ:** Microalbuminuria predicts mortality in non insulin-dependent diabetes. Diabetes Med 1984;1: 17–19.
2. **Mogensen CE:** Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984;310:356–360.
3. **Neelakantappa K, Gallo GR, Baldwin DS:** Proteinuria in IgA nephropathy. Kidney Int 1988;33:716–721.
4. **Cattran DC, Delmore T, Roscoe J, *et al.*:** A randomized

controlled trial of cyclophosphamide in patients with idiopathic membranous nephropathy. N Engl J Med 1989;320:210–215.
5. **Dalgaard OZ:** Bilateral polycystic disease of the kidneys: A follow-up of two hundred and eighty-four patients and their families. Acta Med Scand (Suppl) 1957;328:1–255.
6. **Delaney VB, Adler S, Bruns FJ, Licinia M, Segel DP, Fraley DS:** Autosomal dominant polycystic kidney disease: Presentation, complications, and prognosis. Am J Kidney Dis 1985;5:104–111.
7. **Oppenheimer GD:** Polycystic disease of the kidney. Ann Surg 1934;100:1136–1158.
8. **Preuss H, Geoly K, Johnson M, Chester A, Kliger A, Schreiner G:** Tubular function in adult polycystic kidney disease. Nephron 1979;24:198–204.
9. **Iglesias CG, Torres VE, Offord KP, Holley KE, Beard CM, Kurland LT:** Epidemiology of adult polycystic kidney disease, Olmstead County, Minnesota: 1935–1980. Am J Kidney Dis 1983;2:630–639.
10. **Levey AS, Beck GJ, Laggiula AW, Hensicker L, Kusik JW, Stricker G:** The effects if dietary protein restriction and blood pressure control in the progression of chronic renal disease. N Engl J Med 1994;330:877–884.
11. **Parving HH, Jensen HAE, Mogensen CE, Evrin PE:** Increased urinary albumin excretion rate in benign essential hypertension. Lancet 1974;1:1190–1192.
12. **Ljungman S:** Microalbuminuria in essential hypertension. Am J Hypertens 1990;3:956–960.
13. **Gabow PA, Chapman AB, Johnson AM, *et al.*:** Renal structure and hypertension in autosomal dominant polycystic kidney disease. Kidney Int 1990;38:1177–1180.
14. **Gabow PA, Johnson AM, Kaehny WD, *et al.*:** Factors affecting the progression of renal disease in autosomal dominant polycystic kidney disease. Kidney Int 1992;41:1311–1319.
15. **Yeh J:** Albuminuria and cardiovascular disease risk factors in American Indians. Circulation 1990;82:620–630.
16. **Yudkin JS, Forrest RD, Jackson CA:** Microalbuminuria as a predictor of vascular disease in non-diabetic subjects: Islington diabetes survey. Lancet 1988;2:530–533.
17. **Kannel WB, Stampfer MJ, Castelli WP, Verter J:** The prognostic significance of proteinuria: The Framingham Study. Am Heart J 1984;108:1347–1352.
18. **Gabow PA, Iklé DW, Holmes JH:** Polycystic kidney disease: Prospective analysis of nonazotemic patients and family members. Ann Intern Med 1984;101:238–247.
19. **Sahn DJ, DeMaria A, Kissio J, Weyman A:** Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978;58:1072–1083.
20. **Devereux RB, Alonso DR, Lutas EM, *et al.*:** Echocardiographic assessment of left ventricular hypertrophy: Comparison of necropsy findings. Am J Cardiol 1986;57:450–458.
21. **Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H:** Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1:1430–1432.
22. **Howey JEA, Browning MCK, Fraser CG:** Biologic variation of urinary albumin: Consequences for analysis specimen collection, interpretation of results, and screening programs. Am J Kidney Dis 1989;13:35–37.
23. **Lott JA, Stephan VA, Prichard KA:** Evaluation of the Coomassie brilliant blue G-250 method for urinary protein. Clin Chem 1983;29:1946–1950.
24. **Walser M, Davidson DG, Orloff J:** The renal clearance of alkali-stable inulin. J Clin Invest 1955;34:1520–1530.
25. **Elving LD, Bakkeren JA, Jansen MJ, de Kat Angelino CM, de Nobel E, van Munster PJ:** Screening of microalbuminuria in patients with diabetes mellitus: Frozen storage of urine samples decreases their albumin content. Clin Chem 1989;35:308–310.
26. **Murphy G, Tzamaloukas AH, Listrom MB, Gibel LJ, Smith SM, Gardner KD Jr:** Nephrotic syndrome and rapid renal failure in autosomal dominant polycystic kidney disease. Am J Nephrol 1990;10:69–72.
27. **Panisello JM, Martinez-Vea A, Garcia C, Carrera M, Oliver JA, Richart C:** IgA nephropathy and polycystic kidney disease. Am J Nephrol 1988;8:477–478.
28. **Shikata K, Makino H, Ota ZA:** A membranous nephropathy associated with adult polycystic kidney disease. Clin Nephrol 1991;36:223–227.
29. **Villar MTA, Bass P, Dewhurst G, Theaker JM, Dathan JRE:** Autosomal dominant polycystic kidney disease complicated by glomerulonephritis. Nephron 1992;62:226–228.
30. **Braasch WF, Schacht FW:** Pathological and clinical data concerning polycystic kidney. Surg Gynecol Obstet 1933;57:467–475.
31. **Rall JE, Odel HM:** Congenital polycystic disease of the kidney: Review of the literature, and data on 207 cases. Am J Med Sci 1949;218:399–407.
32. **Sedman A, Bell P, Manco-Johnson M, *et al.*:** Autosomal dominant polycystic kidney disease in childhood: A longitudinal study. Kidney Int 1987;31:1000–1005.
33. **Cerasola A, Cottone S, D'Ignoto G:** Microalbuminuria as a predictor of cardiovascular damage in essential hypertension. J Hypertens 1989;7:S332–333.
34. **Bigassi R, Bianchi S, Campese VM, Baldari G:** Prevalence of microalbuminuria in a large population of patients with mild to moderate essential hypertension. Hypertension 1992;61:94–97.
35. **Giaconi S, Levanti C, Fommei E, *et al.*:** Microalbuminuria and casual and ambulatory blood pressure monitoring in normotensives and in patients with borderline and mild essential hypertension. Am J Hypertens 1989;2:259–261.
36. **Bechgaard P:** Arterial hypertension: A follow-up study of 100 hypertonics. Acta Med Scand (Suppl) 1946;172:3–358.
37. **Bianchi S, Bigazzi R, Baldari G:** Evidence of different daily urinary albumin excretion in patients with mild to moderate essential hypertension. J Nephrol 1989;2:13A.
38. **Berrut G, Chameau AM, Bouhanick B, *et al.*:** Microalbuminurie et hypertrophie ventriculaire gauche au cours de l'hypertension arterielle essentielle: Etude chez des sujets non diabetiques. Presse Med 1992;21:1275–1278.
39. **Fick GM, Johnson AM, Gabow PA:** Causes of death in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 1993;4:262.
40. **Fick GM, Duley IT, Johnson AM, Strain JD, Manco-Johnson ML, Gabow PA:** The spectrum of autosomal dominant polycystic kidney disease in children. J Am Soc Nephrol 1994;4:1654–1660.
41. **Reaven GM, Hoffman BB:** Hypertension as a disease of carbohydrate and lipoprotein metabolism. Am J Med 1989;87:6A25–6A65.
42. **Shamiss A, Carroll J, Rosenthal T:** Insulin resistance in secondary hypertension. Am J Hypertens 1992;5:26–28.
43. **Chapman AB, Johnson A, Gabow PA, Schrier RW:** The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. N Engl J Med 1990;323:1091–1096.
44. **Williams JD, Coles GA:** Proteinuria—a direct cause of renal morbidity? Kidney Int 1994;45:443–450.