

Characteristics of Hypertension in Young Adults With Autosomal Dominant Polycystic Kidney Disease Compared With the General U.S. Population

Catherine L. Kelleher, Kim K. McFann, Ann M. Johnson, and Robert W. Schrier

Background: Patients with autosomal dominant polycystic kidney disease (ADPKD) often develop hypertension before any abnormalities in renal function are detected clinically. Therefore, standard screening (serum creatinine and urinalysis) of young individuals with unexplained hypertension to exclude renal parenchymal disease would rarely detect ADPKD.

Methods: Data from 516 subjects with ADPKD (217 male and 299 female), aged newborn to 55 years with a normal serum creatinine and no proteinuria based on urine dipstick, studied between 1985 and 2000, were compared with data from similar subjects from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) and NHANES IV (1999–2000) data, by gender.

Results: There was a highly significant occurrence of hypertension in young patients with ADPKD when compared to patients aged 20 to 34 years in the U.S. population. The hypertension in patients with ADPKD occurred

in the absence of abnormal renal function or abnormal urinalysis.

Conclusions: These data indicate that renal ultrasound screening of young hypertensive individuals (aged 20 to 34 years) should be considered when searching for causes of secondary hypertension. Identifying affected ADPKD individuals early in their disease will permit aggressive blood pressure treatment and early inhibition of the renin-angiotensin-aldosterone system, which has been shown to reverse left ventricular hypertrophy, an important cardiovascular risk factor. In the present era of renal replacement therapy, cardiovascular complications are the main cause of death in patients with ADPKD. *Am J Hypertens* 2004; 17:1029–1034 © 2004 American Journal of Hypertension, Ltd.

Key Words: Autosomal dominant polycystic kidney disease, hypertension, renin-angiotensin-aldosterone system.

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent life-threatening hereditary disease, occurring in 1 in 400 to 1000 people of European descent.^{1,2} This disease is more frequent than sickle cell anemia, cystic fibrosis, muscular dystrophy, hemophilia, Down's syndrome, and Huntington's disease combined,³ and accounted for 2.3% of end-stage renal disease (ESRD) in the United States between the years 1997 and 2001.⁴ Efforts to slow the progression of this disease and delay the need for renal replacement therapy are being investigated clinically and at the basic science level. From a clinical perspective, it is important to

identify treatable risk factors associated with early progression in the course of the disease. Several factors that predict a more rapid deterioration of renal function include age, male gender, gross hematuria, proteinuria, type 1 gene mutations on chromosome 16 compared with type 2 mutations on chromosome 4, renal cyst volume, hypertension, increased left ventricular mass index (LVMI), and African American ethnicity.^{5–9}

Of these risk factors for renal dysfunction in ADPKD, hypertension is the only treatable condition identified to date. Moreover, hypertension in patients with ADPKD is associated with a high incidence of left ventricular hyper-

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From the Department of Medicine, University of Colorado School of Medicine (CLK, KKM, AMJ, RWS) and the Denver Health Medical Center (CLK), Denver, Colorado.

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Address correspondence and reprint requests to Dr. Robert W. Schrier, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, C283, Denver, CO 80262; e-mail: Robert.Schrier@uchsc.edu

trophy.¹⁰ Left ventricular hypertrophy is a known risk factor for cardiovascular complications, which are now the most common cause of death in patients with ADPKD.¹¹

Studies of hypertension in patients with ADPKD have implicated increased activation of the renin-angiotensin-aldosterone system (RAAS).^{12–14} A prospective randomized study showed angiotensin-converting enzyme inhibitors reversed left ventricular hypertrophy to a greater extent than calcium channel blockers in patients with ADPKD.¹⁵ Moreover, in the same study, aggressive control of blood pressure (BP) (<120/80 mm Hg) in patients with ADPKD was associated with reversal of left ventricular hypertrophy to a greater extent than standard BP control (<135 to 140/85 to 90 mm Hg).¹⁵ The recent improvement in BP control in patients with ADPKD¹⁶ is associated with a later onset of ESRD in both men and women with ADPKD.¹⁷

Therefore, early identification of individuals with ADPKD is imperative to allow aggressive treatment of hypertension. Although family history is helpful in identifying affected individuals, on questioning only 60% of patients with ADPKD reveal a positive family history.¹⁸ In this article, we explore the specific characteristics of hypertension in young patients with ADPKD as compared with hypertension in young individuals in the general U.S. population. With the recent availability of the fourth National Health and Nutrition Examination Survey (NHANES IV), the epidemiology of hypertension in the United States is accessible and current. With the goal of early diagnosis, the purpose of the present study was to analyze the incidence of hypertension in patients with ADPKD versus hypertension in the U.S. population, particularly between the ages of 20 and 34 years.

Methods

Study Population

From June 1985 to December 2000, a total of 828 adults and children with ADPKD without ESRD participated in a longitudinal study at the University of Colorado Health Sciences Center to define the natural history of ADPKD. All protocols were approved by the Colorado Multiple Institutional Review Board, and all subjects provided written informed consent. Of the 828 subjects, 516 met the following inclusion criteria for analysis: 1) one full examination at the University of Colorado General Clinical Research Center (GCRC), 2) a normal serum creatinine concentration (<1.2 mg/dL for women; <1.5 mg/dL for men), 3) a normal dipstick protein (0 or trace; 11 subjects missing dipstick data but with urinary protein excretion <300 mg/24 h were included), 4) age less than 55 years, 5) not of the African American ethnicity, and 6) subjects were not in another hypertension treatment study. Of the 516 ADPKD patients, 123 were the only member in their family in the study and the other 393 patients had an ADPKD relative in the study. The data analyzed were from the subjects' first study visit and reflect care before study participation.

A complete medical history and physical examination were performed at the initial study visit to the GCRC. Blood pressures were measured by trained nurses using a Dinamap apparatus (Critikon Inc., Tampa, FL). In adults, hypertension was defined as mean systolic BP \geq 140 mm Hg or mean diastolic BP >90 mm Hg while sitting or on antihypertensive medication with a previous diagnosis of hypertension. In children (<18 years), hypertension was defined as greater than 50% of measured systolic or diastolic BPs above the 95th percentile for age-, gender-, and height-matched children.¹⁹

Laboratory data obtained at this initial GCRC visit included routine serum chemistries and two 24-h urine collections to measure protein excretion. Urinary protein concentrations were determined by the Coomassie blue dye-binding method. The mean of the two collections was used to assess each individual's level of proteinuria (in milligrams per 24 hours).

Data from patients with ADPKD (ages newborn to 55 years) collected from 1985 to 2000 were compared with NHANES data from two time periods: 1988 to 1994 (NHANES III; 2958 male and 3249 female subjects) and 1999 to 2000 (NHANES IV; 2602 male and 2834 female subjects). The NHANES data were obtained from four sources: 1) a table published by the Centers for Disease Control and Prevention,²⁰ 2) published analysis of NHANES data,²¹ and 3) raw data files from NHANES III and NHANES IV made available to the public.^{22,23} The NHANES III data (1988–1994) were compared with ADPKD data from 1985 through 1994; the years 1985 to 1987 were included in the ADPKD data to have sufficient sample size for comparison. Similarly, the NHANES IV data (1999–2000) were compared with ADPKD data from 1995 through 2000. The presence of hypertension in children (aged newborn to 19 years) could only be compared with the NHANES IV data, as the NHANES III data were incomplete for children. Similarly, NHANES IV data were used for comparisons of BP control and treatment, as these data were not available in NHANES III. The NHANES studies include subjects with secondary hypertension, but presumably 90% to 95% of the subjects have essential hypertension.

Statistical Analyses

The χ^2 test of independence was used to identify gender differences regarding the prevalence and treatment of hypertension among patients with ADPKD. Continuous variables were compared with Student *t* test. Because significant gender differences were identified, all subsequent analyses were performed separately for male and female subjects. The χ^2 tests of independence were performed to compare the ADPKD patients with the general U.S. population (NHANES data) with regard to differences in the percentage with hypertension, the percentage with BP controlled at or below 140/90 mm Hg, and the

Table 1. Characteristics of white men and women with autosomal dominant polycystic kidney disease

	Men	Women	P
n	217	299	
% of patients hypertensive	46%	30%	<.0005
% of hypertensive patients previously diagnosed	68%	79%	NS
% of hypertensive patients on medication	56%	77%	<.005
% of hypertensive patients controlled to 140/90 mm Hg	44%	58%	<.05
Age (y)	24.3 ± 14.2	27.2 ± 14.0	<.05
Serum creatinine (mg/dL)	0.9 ± 0.3	0.8 ± 0.2	<.001
Creatinine clearance (mL/min/1.73 m ²)	107 ± 26	103 ± 26	NS
Urinary protein excretion (mg/24 h)	129 ± 100	135 ± 205	NS

Subjects aged 0 to 55 years, normal serum creatinine and dipstick, studied between 1985 and 2000. Continuous variables are expressed as the mean ± standard deviation.

percentage receiving treatment for hypertension. Results were considered significant at the .05 level.

Results

Comparison of ADPKD Male and Female Patients

Five hundred sixteen subjects with ADPKD were included in the analysis, 217 males and 219 females (Table 1). Only 7% of the subjects were documented to have been screened for ADPKD because of hypertension; the reason for the ADPKD diagnosis was unknown in 28%. Of the 516 subjects in the study, 191 (37%) had a history of hypertension or were hypertensive at the time of the study visit. Of the 516 subjects, 393 had a relative in the study and 123 did not. Inclusion of this information did not alter the conclusions of the study. A significantly higher percentage of ADPKD males than females were hypertensive (Fig. 1), with greater gender differences noted between the ages of 20 and 44 years. Because of these differences, subsequent analyses were separated by gender.

Prevalence of Hypertension in ADPKD Subjects Versus the U.S. Population

The prevalence of hypertension in subjects with ADPKD in our database was compared with the prevalence of

hypertension in the white U.S. population as reported in the NHANES studies for two time periods. The first period is depicted in Fig. 2. Dramatic differences are shown in the prevalence of hypertension in male and female subjects with ADPKD compared with male and female individuals in the general white U.S. population for all age groups. The more recent results are depicted in Fig. 3. Differences are seen in each group under the age of 45 years, but the most dramatic differences are seen in the 20- to 34-year age group.

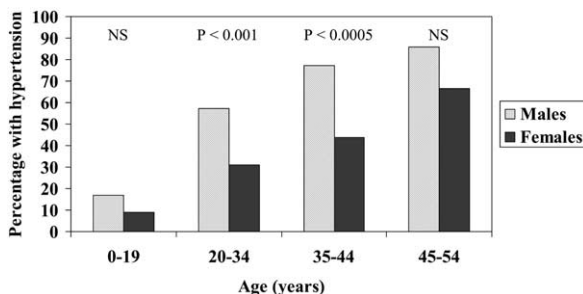
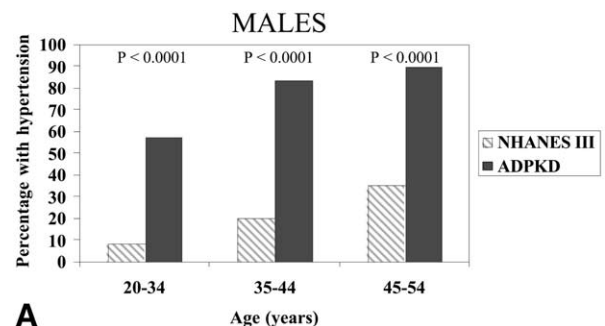
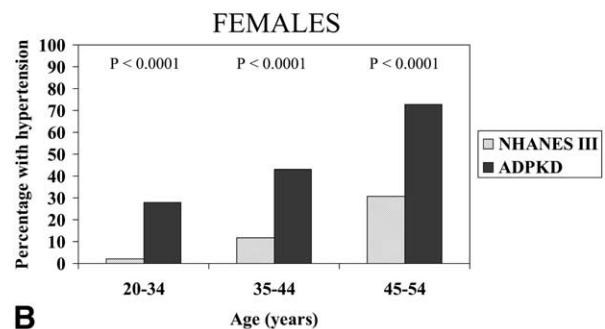


FIG. 1. The prevalence of hypertension in men and women with autosomal dominant polycystic kidney disease by age category, with a normal serum creatinine and negative urine dipstick for protein, studied between 1985 and 2000.



A



B

FIG. 2. **A)** The prevalence of hypertension in men with autosomal dominant polycystic kidney disease (ADPKD) (1985–1994) compared with men in the U.S. population (National Health and Nutrition Examination Survey [NHANES] III, 1988–1994) by age category. **B)** The prevalence of hypertension in women with ADPKD (1985–1994) compared with women in the U.S. population (NHANES III, 1988–1994) by age category.

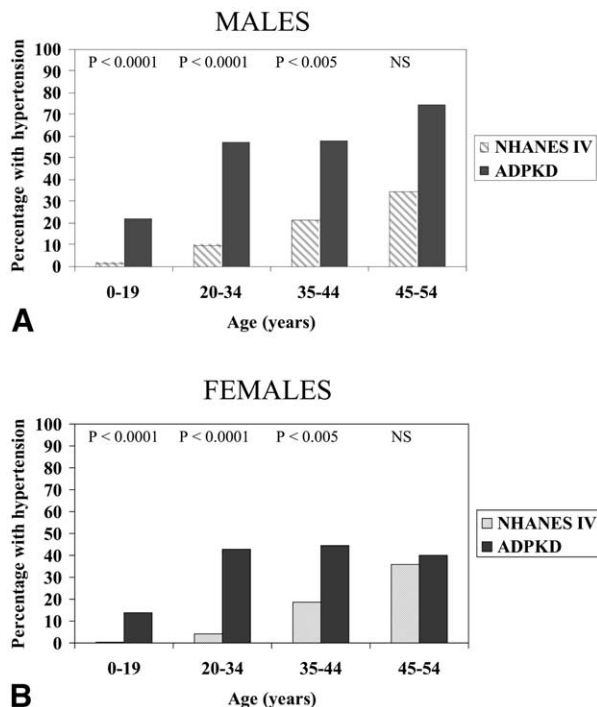


FIG. 3. A) The prevalence of hypertension in men with autosomal dominant polycystic kidney disease (ADPKD) (1995–2000) compared with men in the U.S. population (National Health and Nutrition Examination Survey [NHANES] IV, 1999–2000) by age category. **B)** The prevalence of hypertension in women with ADPKD (1995 to 2000) compared with women in the U.S. population (NHANES IV, 1999–2000) by age category.

Percentage of Hypertensive Patients With BP Controlled at or below 140/90 mm Hg: Percentage Receiving Antihypertensive Therapy

The percentage of male and female hypertensive subjects with BP controlled at or below 140/90 mm Hg in the ADPKD and NHANES IV subjects are shown in Fig. 4A. A significantly greater percentage of ADPKD subjects had their BP controlled (for both genders) as compared with the U.S. white population.

The percentages of both male and female hypertensive subjects receiving antihypertensive therapy in the ADPKD and NHANES IV subjects are shown in Fig. 4B. A greater percentage of both male and female ADPKD patients were receiving antihypertensive treatment; however, this difference was significant only in women.

Discussion

Hypertension is a major cardiovascular risk factor affecting 50 to 60 million U.S. residents.²⁴ Autosomal dominant polycystic kidney disease is associated with hypertension in a large percentage of cases.²⁵ At present, with the availability of renal replacement therapy (dialysis and renal transplantation), the major cause of death in patients with ADPKD is cardiovascular events.¹¹ The observation

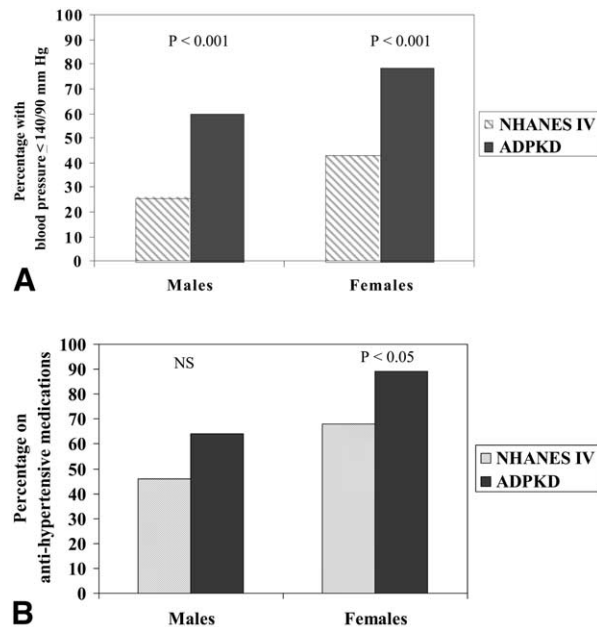


FIG. 4. A) The percentage of hypertensive men and women with blood pressure controlled to $\leq 140/90$ mm Hg, autosomal dominant polycystic kidney disease (ADPKD) (1995–2000) versus National Health and Nutrition Examination Survey (NHANES) IV data (1999–2000). **B)** The percentage of hypertensive men and women receiving antihypertensive therapy, ADPKD (1995–2000) versus NHANES IV data (1999–2000).

that nearly 50% of hypertensive ADPKD subjects (mean age 41 years) exhibit left ventricular hypertrophy¹⁰ suggests that untreated hypertension has been present for a considerable time. This is not unexpected given that hypertension occurs early in ADPKD and precedes any decline in renal function.²⁵ Aggressive BP control ($< 120/80$ mm Hg) in patients with ADPKD more effectively reverses left ventricular hypertrophy than standard BP control.¹⁵ Moreover, improvement in BP control and the use of angiotensin-converting enzyme inhibitors have been associated with later onset of ESRD in both male and female subjects with ADPKD.¹⁷

Unexplained hypertension in young individuals between the ages of 20 to 34 years generally leads to a workup for secondary causes of hypertension, as recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VII.²⁶ A normal serum creatinine, absence of proteinuria by dipstick, and clear urinary sediment are measured to exclude renal parenchymal disease. However, these criteria would miss the diagnosis of ADPKD in young individuals where hypertension occurs before proteinuria or a decrease in renal function.

Because ADPKD has an autosomal dominant pattern of inheritance, one parent usually has the disease. However, on questioning, 40% of ADPKD patients do not have a family history compatible with ADPKD.¹⁸ This may occur because the disease is mild in other affected family members and they did not develop symptoms to prompt a diagnostic evaluation. It may also occur because the pa-

tient has a spontaneous new mutation (de novo mutation) not present in previous generations that may be passed on to the offspring.

The occurrence of ADPKD in the United States is between 1 in 400 to 1000 individuals; thus, as many as 500,000 to 600,000 Americans are affected with ADPKD.¹⁸ It is now clear that sensitive renal ultrasound studies can diagnose ADPKD, even in utero.¹⁸ Nevertheless, such an early diagnostic approach is generally only undertaken in the presence of a family history of ADPKD, an elevated serum creatinine, or an abnormal urinalysis.

Early diagnosis of ADPKD with widespread renal ultrasound screening of all 50 to 60 million hypertensive patients in the United States in the absence of a family history of ADPKD is neither cost effective nor practical. The presence of microalbuminuria, an amount of urinary albumin excretion that is not detected by commercial dipsticks, has been shown to be correlated with a high incidence of left ventricular hypertrophy in patients with ADPKD.⁷ However, detection of microalbuminuria in young hypertensive patients would not be specific for ADPKD. Only renal imaging has been shown to be specific and sensitive for the diagnosis of ADPKD in young individuals.^{27,28} The diagnosis of ADPKD in individuals less than 30 years old is made by either the presence of two cysts (unilateral or bilateral) together with a positive family history for ADPKD or the presence of five cysts bilaterally in the absence of a family history of ADPKD.

In addressing this important issue, the results of the present study were analyzed separately for men and women because of the greater predilection of hypertension in men as compared to premenopausal women. The results in the NHANES IV (1999–2000) data as compared to patients with ADPKD clearly demonstrate that the incidence of hypertension between the ages of 20 and 34 years is 49% in the ADPKD population versus approximately 7% in the general U.S. population. The challenge is to identify ADPKD in young hypertensive individuals without a known family history and during a period when these individuals often have normal renal function and a normal urinalysis.

The present results also show that BP control (<140/90 mm Hg) in patients with ADPKD is improved compared with BP control in the general U.S. hypertensive population. The educational approaches in place for ADPKD patients may account for this difference.¹⁶ The percentage of patients receiving antihypertensive medications was greater in patients with ADPKD than in the NHANES IV subjects (although only significantly different for women). However, treatment patterns probably do not completely explain the difference in control. Because the RAAS is activated in patients with ADPKD more than in patients with essential hypertension,¹³ the recent increased use of inhibitors of the RAAS may contribute to improved BP control in patients with ADPKD.¹⁶

African American subjects were excluded from the present study because too few African American subjects

with ADPKD were enrolled to generate data for a separate comparison with the NHANES data. Autosomal dominant polycystic kidney disease, however, does affect African Americans⁵ and more studies in this population are necessary.

Screening young hypertensive patients for ADPKD (<34 years of age) who have a standard negative workup for other common secondary causes of hypertension, including other renal parenchymal diseases, primary hyperaldosteronism, and renal vascular disease, with a renal ultrasound would add approximately \$300 to the costs. Although ESRD due to ADPKD is estimated to cost \$1.8 billion per year, an analysis of cost savings must await documentation of an effective therapy to decrease or prevent ESRD related to ADPKD. However, some patients want to know whether they have a genetic disease because it makes a difference in their decision making regarding health care and family planning. On the other hand, some individuals may not want to know because of insurance eligibility issues. Given the increased incidence of cerebral aneurysms,²⁹ the diagnosis of ADPKD may also affect the physician's response to neurological complaints. Early diagnosis and aggressive treatment of hypertension offers the potential to prevent development of left ventricular hypertrophy and cardiovascular complications in patients with ADPKD.^{6,10} Although hypertension in patients with ADPKD correlates with increased renal volumes and more rapid progression to ESRD, there is a need for an adequately powered, prospective randomized study to evaluate whether aggressive lowering of BP and blockade of the RAAS will slow the progression of the renal disease. The National Institutes of Health is supporting a 5-year multicenter prospective randomized clinical trial (HALT polycystic kidney disease) that will involve 1250 patients with ADPKD. The hypothesis is that inhibition of the RAAS with a combination of an angiotensin-converting-enzyme inhibitor and an angiotensin receptor blocker will be more effective than angiotensin-converting enzyme inhibitor alone. The Modified Diet in Renal Disease (MDRD) study, which had a 2.2-year average follow-up, included 200 patients with ADPKD but did not randomize the patients in relation to their antihypertensive medications.³⁰ No improvement in renal function was observed with more aggressive BP control but the study may have been underpowered.

In summary, the results of the present study indicate that when the diagnostic workup for a secondary cause of hypertension in patients between the ages of 20 and 34 years is negative, even in the presence of a normal serum creatinine and urinalysis and a negative family history, the physician still should consider the possibility of ADPKD. This diagnosis can be confirmed in nearly 100% of patients with ADPKD by age 30 years with a renal ultrasound. The potential prevention of cardiovascular complications by early intervention with blockade of the RAAS and a lower BP goal of 125/75 mm Hg may decrease morbidity and mortality. Although uncontrolled

hypertension may accelerate progression of most renal diseases, the role of aggressive BP control and blockade of the RAAS in the renal progression of ADPKD must await the HALT PKD results.

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