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Hypertension in Autosomal-Dominant Polycystic Kidney Disease: Early Occurrence and Unique Aspects

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Autosomal-dominant polycystic kidney disease (ADPKD) is a systemic hereditary disorder characterized by renal and extrarenal involvement with cystic and noncystic manifestations (1). Hypertension is an early and frequent finding of ADPKD, occurring in approximately 60% of the patients before the renal function has become impaired (2,3). Hypertension has an important impact on the morbidity and mortality of these patients. ADPKD patients with hypertension have a more rapid loss of renal function (4). Moreover, hypertension is an important risk factor for cardiovascular death, the most frequent cause of mortality in ADPKD patients (5).

Prevalence of Hypertension in ADPKD

The recognition of the frequent occurrence of hypertension in ADPKD began in the early 20th century. In 1916, Braasch (6) reported that 72% of patients with ADPKD had hypertension. In 1931, in a retrospective postmortem study of 74 cases of PKD, Schacht (7) reported a 75% incidence in systolic BP greater than or equal to 145 mmHg, whereas age- and gender-matched patients with chronic pyelonephritis had only a 26% incidence of hypertension. In a report on 207 cases of PKD in 1949, Rall and Odel (8) found a 73% incidence of hypertension, which was defined as BP greater than 140/90 mmHg. Dalgaard (9), who followed 284 ADPKD patients, found 41% incidence of hypertension. Although this rate was lower than the previous studies, hypertension was defined as BP greater than or equal to 160/100 mmHg or systolic BP greater than or equal to 180 mmHg in this study.

Hansson *et al.* (10) studied the incidence of hypertension among 59 hospitalized patients with ADPKD. Hypertension, defined as a resting recumbent BP of greater than or equal to 160/100 mmHg, was found in 82% of the patients. In this study, the incidence of hypertension was 75% among patients with normal serum creatinine concentrations, indicating that an increased BP commonly precedes impairment of renal function. Similarly, in a study of 94 ADPKD patients, Calabrese *et al.* (11) found that patients who had ADPKD and normal renal function were more frequently hypertensive than were patients who had other renal diseases. In this study, 61.5% of the ADPKD patients who had a normal serum creatinine concentration had a diastolic BP above 95 mmHg, whereas this rate was 33% in those who had tubulointerstitial nephropathies and 30% in those who had chronic glomerulonephritis. Milutinovic *et al.* (12) reported a 33% incidence of hypertension ($\geq$150/90 mmHg) in 65 ADPKD patients who had creatinine clearances greater than or equal to 90 ml/min. In this study, hypertension was found in 29% of ADPKD patients who were younger than 30 yr. In a prospective analysis of 164 nonazotemic ADPKD patients and 250 family members without the disease, Gabow *et al.* (13) found that the prevalence of hypertension was 62% in ADPKD patients. Conversely, this rate was 21% in normal family members. In another prospective study of 147 ADPKD patients with creatinine clearances greater than 75 ml/min per 1.73 m^2, Gabow *et al.* (3) demonstrated that 52% of the participants had BP greater than 150/90 mmHg. In this study, the mean age of initial diagnosis of hypertension was 29 yr, an age much younger than the onset of essential hypertension in the general population.

Hypertension in ADPKD is not limited to adult patients with ADPKD. In a study of 154 children from 83 families with ADPKD, Sedman *et al.* (14) reported that 22% of children with ADPKD had hypertension at the time of diagnosis, compared with 5% in children without the disease. Similarly, Fick *et al.* (15) found that children with ADPKD had an 18% incidence of hypertension.

Pathogenesis of Hypertension in ADPKD

In 1929, Ritter and Baehr (16) proposed a relationship between vascular structural abnormalities and hypertension in ADPKD. Nephrectomy specimens from ADPKD patients and control subjects were injected with an opaque mixture of barium sulfate and gelatin and x-rays were then taken. Normal kidneys showed a great number of arterioles with good definition of the finer vessels, especially in the cortex. However, in the polycystic kidneys, a marked attenuation of the renal vascular tree and stretching of the interlobar and interlobular arterioles were observed. Microscopic analyses of these specimens showed tubular atrophy between cysts and completely

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hyalinized glomeruli, suggesting that renal vascular ischemia as well as local tubular compression play an important role in renal failure in PKD. The observation of cysts compressing renal arterioles in this postmortem study was later confirmed in the renal angiographic examinations of patients with PKD (17).

To investigate both the early and the late histologic changes in polycystic kidneys, Zeier *et al.* (18) studied the renal specimens of 12 patients who had ADPKD without advanced renal failure (kidneys removed for several reasons, including stones, infection, and bleeding) and 50 specimens of ADPKD patients with end-stage renal disease (ESRD). Advanced sclerosis of preglomerular vessels, interstitial fibrosis, and tubular atrophy were observed even in patients with normal renal function or early renal failure. More severe vascular and interstitial lesions were detected in specimens from patients with more advanced disease. Another interesting finding in this study was that the major pathology in the glomeruli was global sclerosis, which is a putative histologic marker of glomerular ischemia (19), whereas segmental glomerular sclerosis, which is more typical of hyperperfusion injury (20), was absent. This global sclerosis may be explained by the areas of local ischemia as a result of cystic compression.

In a study of 71 normotensive and 76 hypertensive ADPKD patients with creatinine clearances greater than 75 ml/min per 1.73 m^2, Gabow *et al.* (3) found that hypertensive patients had significantly greater renal volume compared with normotensive counterparts. A similar relationship between hypertension and cystic involvement was also found in children with ADPKD (15). These studies support the proposal for renal structural involvement as a factor in the prevalence of hypertension in ADPKD. Improvement in BP in response to percutaneous cyst aspiration as a result of refractory pain also supports the role of cystic compression in the development of hypertension in ADPKD (21).

The above-mentioned studies showing the relationship between renal structural abnormalities and hypertension in ADPKD led investigators to test the hypothesis that activation of the renin-angiotensin-aldosterone system (RAAS) as a result of cyst expansion and local renal ischemia play an important role in the development of hypertension in this disease.

To study the anatomy and distribution of renin-secreting cells in ADPKD, Graham and Lindop (22) performed immunohistochemical staining for renin on kidney tissues of nephrectomy and autopsy cases of ADPKD patients. They showed an increased number of renin granules in juxtaglomerular apparatuses, suggesting chronic stimulation of the RAAS. Moreover, there was an abnormal distribution of renin-containing cells located along the arterioles and within cyst walls. Torres *et al.* (23) also found increased amounts of tubular immunoreactive renin in kidney specimens of ADPKD patients. In addition, they showed that the renin concentration was increased in ADPKD cyst fluid compared with the concentration in fluid from simple renal cysts, and renin messenger RNA was expressed in the tubulocystic epithelium of patients with ADPKD.

The clinical studies searching the role of the RAAS in the pathogenesis of hypertension in ADPKD started in the late 1970s. Nash (24) reported that plasma volumes were elevated and plasma renin activities varied from normal to inappropriately elevated levels for measured plasma volumes in hypertensive ADPKD patients. Anderson *et al.* (25) examined the BP response to angiotensin II antagonism with saralasin in hypertensive ADPKD patients and concluded that the RAAS did not play a role in the pathogenesis of hypertension in ADPKD. In this study, they compared hypertensive patients with ADPKD and patients with unilateral renal artery stenosis with similar mean arterial pressures (MAP), age, and renal function. The patients with unilateral renal artery stenosis demonstrated higher plasma renin activities and aldosterone concentrations than the ADPKD patients. A significant decrease in MAP during saralasin infusion occurred only in the patients with unilateral renal artery stenosis. However, because ADPKD is a bilateral renal disease, the comparison with bilateral rather than a unilateral renal artery stenosis is most appropriate. In the two-kidney one-clip model of unilateral renal artery stenosis hypertension, BP decreases during angiotensin II inhibition (26). However, as shown by Gavras *et al.* (27), in the one-kidney one-clip hypertension model that is akin to bilateral renal artery stenosis, no change is expected in MAP after angiotensin II inhibition in the sodium-replete state. However, a profound fall in BP was seen when the angiotensin II inhibitor was given after sodium depletion. Taken together, therefore, the bilateral renal involvement in ADPKD is most compatible with a role of both the RAAS and sodium retention in the pathogenesis of the hypertension, as occurs with bilateral renal artery stenosis.

Valvo *et al.* (28) studied 12 normotensive and 20 hypertensive patients with PKD. No differences in plasma renin activity were found between the normotensive and hypertensive groups, whereas plasma volumes were found to be significantly greater in the hypertensive group. Although the authors concluded that plasma volume expansion rather than the RAAS system was important to the development of hypertension in ADPKD, the plasma renin levels should not have been normal but rather suppressed secondary to the higher blood volumes.

Bell *et al.* (29) studied nine hypertensive and seven normotensive ADPKD patients with normal renal function. The hemodynamic response to the angiotensin converting enzyme (ACE) inhibitor captopril was investigated during low (20 mEq/d) and high (300 mEq/d) sodium intakes. The hypertensive group demonstrated more of an increase in plasma renin activity with captopril than did the normotensive group during both low- and high-sodium diets. In this study, hypertensive ADPKD patients with normal renal function also showed a greater increase in supine atrial natriuretic peptide (ANP) concentration when going from a low- to a high-sodium diet as compared with normotensive ADPKD patients. On the high-sodium diet, a greater increase in cardiac output in the ADPKD patients also occurred. The finding of a greater increase in cardiac output and plasma ANP levels, despite similar plasma volumes, during high-sodium diet in hypertensive ADPKD patients suggested greater venoconstriction by angiotensin II. In support of this possibility, significantly decreased forearm venous volumes, reflecting increased venous tone, were shown

in hypertensive ADPKD patients as compared with normotensive counterparts (30).

To confirm the pathogenetic role of the RAAS in the development of hypertension in ADPKD, Chapman *et al.* (31) compared essential hypertensive and hypertensive ADPKD patients who were similar in age, gender, body surface area, sodium excretion, renal function, and MAP. Hypertensive ADPKD patients demonstrated significantly greater plasma renin activities in the supine and upright positions, as well as 1 h after captopril ingestion when compared with essential hypertensive patients. In addition, after 6 wk of ACE inhibition with enalapril, renal plasma flow increased significantly and both renal vascular resistance and filtration fraction decreased significantly in the hypertensive ADPKD patients but not in the essential hypertensive patients. This study showed that the RAAS is stimulated significantly more in hypertensive patients with ADPKD than in comparable patients with essential hypertension. Chapman *et al.* (32) also reported eight episodes of acute renal failure in five patients with ADPKD with severe renal involvement during therapy with ACE inhibitors or when becoming sodium depleted during ACE inhibitor therapy. The acute deterioration was reversed in all patients after the withdrawal of the ACE inhibitor, supporting the similarity of ADPKD to bilateral renal artery stenosis, in which reversible acute renal failure has been described with ACE inhibition (33).

Another study showing the role of the RAAS in ADPKD was performed by Torres *et al.* (34), who found that ACE inhibition with enalapril resulted in significant increases in the renal plasma flow and significant reductions in MAP, renal vascular resistance, and filtration fraction in hypertensive patients with ADPKD. Similarly, Watson *et al.* (35) found greater decreases with ACE inhibition (10 mg of lisinopril) in renal vascular resistance, filtration fraction, and BP in hypertensive ADPKD patients than they did in unaffected family members.

To investigate the early hemodynamic abnormalities, Harrap *et al.* (36) studied young normotensive ADPKD patients (mean age, 24 yr) with good renal function and minimal renal impairment and compared them with unaffected matched family members. The total exchangeable sodium, plasma renin activity, and plasma aldosterone levels were significantly higher in these ADPKD patients when compared with unaffected relatives. This study showed that the stimulation of the RAAS started at an early stage and preceded hypertension and the major clinical manifestations of ADPKD. Similarly, Barrett *et al.* (37) studied 21 normotensive ADPKD patients with creatinine clearances greater than 70 ml/min per 1.73 m^2 and 12 unaffected controls from the same families. They showed that during a chronically high sodium intake, the plasma renin activity in ADPKD patients tended to be higher than in the control group.

Several studies have investigated the tubular handling of sodium in patients with ADPKD. Similar to bilateral renal artery stenosis, sodium excretion would not be expected to increase appropriately in response to plasma volume expansion in ADPKD patients, because of bilateral renal involvement. Moreover, the increased activity of angiotensin II and aldosterone would stimulate proximal and distal tubular sodium reabsorption, respectively. Conversely, tubular cell dysfunction as a result of cystic involvement may diminish tubular sodium handling, confounding the interpretation of sodium excretion in ADPKD patients. In this regard, decreased, normal, and increased natriuresis after acute volume expansion has been found in ADPKD patients (38–40). D'Angelo *et al.* (38) reported an inadequate natriuresis after extracellular volume expansion. Danielsen *et al.* (39), however, reported increased baseline urinary sodium excretion in ADPKD patients compared with healthy controls and an exaggerated natriuresis in response to volume expansion in hypertensive and normotensive ADPKD patients. However, the increased baseline sodium excretion in this study suggests increased sodium intake, a known determinant of increased natriuresis with volume expansion. In a study by Sorensen *et al.* (40), plasma ANP concentrations were found to be increased in ADPKD patients with reduced renal function, and this was interpreted as a compensatory change secondary to a decreased renal capacity to eliminate sodium with declining GFR and extracellular fluid volume expansion.

Most important, a disturbed relationship between the BP and the urinary excretion of sodium has been found in patients with ADPKD (41,42). In a study investigating the natriuretic response to volume expansion, the pressure–natriuresis relationship was significantly shifted to the right in hypertensive patients with ADPKD, suggesting that sodium balance was maintained at the cost of a higher BP (41). In this study, plasma renin activity was not suppressed in response to volume expansion, showing the relative stimulation of the RAAS.

There are differing results about the role of the sympathetic nervous system in the pathogenesis of hypertension in ADPKD (29,43,44). Bell *et al.* (29) reported that plasma noradrenaline levels were not significantly different between hypertensive and normotensive ADPKD patients. Conversely, Iversen *et al.* (43) found that muscle sympathetic nervous activity was higher in hypertensive ADPKD patients than in normal controls. This increased sympathetic activity could be secondary to RAAS stimulation induced by renal cyst expansion (45). In this regard, it is well established that the RAAS is a potent stimulator of the sympathetic nervous system (46). In a more recent study, Cerasola *et al.* (44) investigated the sympathetic activity in 30 hypertensive ADPKD patients and 50 patients with essential hypertension who were matched for gender, body mass index, duration of hypertension, and BP. Plasma catecholamine levels were higher in hypertensive ADPKD patients without renal failure than in essential hypertensive patients, suggesting that an increased activity of the sympathetic nervous system may play a role in the pathogenesis of hypertension in these patients.

The cystic epithelium of kidney specimens from patients with ADPKD demonstrates increased expression of endothelin-1 (ET-1) (47). Giusti *et al.* (48) studied the plasma levels of ET-1 in 10 normotensive and 11 hypertensive ADPKD patients, 11 patients with essential hypertension, and 12 healthy control subjects. Plasma concentrations of ET-1 were found to be increased in ADPKD patients compared with the healthy subjects and essential hypertensive patients. They hypothe-

sized that ET-1 secreted by tubular cell proliferation may contribute to the development of the hypertension in ADPKD patients, a provocative hypothesis that needs further study.

Role of Hypertension in Renal and Patient Outcome in ADPKD

Gabow *et al.* (3) reported that 197 hypertensive ADPKD patients had worse renal disease progression than 84 normotensive subjects. They observed that mean serum creatinine exceeded 1.5 mg/dl at 47 yr of age in hypertensive ADPKD subjects, whereas in normotensive ADPKD patients, this mean serum creatinine value was projected only to be exceeded at age 66.

In a retrospective study of 30 patients with ADPKD, Gonzalo *et al.* (49) reported the potential effect of hypertension on early renal function deterioration. During 7 yr of follow-up, hypertensive ADPKD patients with normal renal function lost renal function at a faster rate than did similar normotensive patients.

The increased activity of the RAAS observed in patients with ADPKD may not only cause or aggravate hypertension but also contribute to accelerated cyst growth. Angiotensin II has been shown to be a growth factor for proximal tubular epithelial cells (50). Angiotensin II also stimulates the release of transforming growth factor-β and the accumulation of extracellular matrix, thus potentially contributing to renal fibrosis (51). Moreover, increased structural severity of the renal disease promotes increased severity of hypertension and creates a vicious cycle of cyst growth, increased activity of angiotensin II, and further cyst growth (Figure 1).

The most common cause of death in patients with ADPKD is cardiovascular diseases (5). Hypertension is known to be an important risk factor for cardiovascular causes of mortality. There is a significant correlation between hypertension and left ventricular mass index (LVMI) both in children and in adults with ADPKD (52,53). Ivy *et al.* (52) found a relationship between systolic BP and LVMI in children with ADPKD, a finding that was not observed in unaffected siblings. Using cardiac echocardiographic examination of 116 consecutive hypertensive ADPKD patients, Chapman *et al.* (53) reported a 48% prevalence of left ventricular hypertrophy (LVH), with 46% in men and 37% in women. In this study, LVH was detected even in 23% of normotensive ADPKD patients. A recent study (54) also showed that young normotensive ADPKD patients had higher LVMI that was closely related to the ambulatory systolic BP, and the normal nocturnal fall in BP was attenuated in these ADPKD patients.

Treatment of Hypertension in ADPKD

Despite the importance of hypertension in renal structural progression and functional deterioration in ADPKD, there have been few intervention studies to examine the role of antihypertensive therapy in preventing or slowing the progression of renal and cardiovascular complications. In the Modification of Diet in Renal Disease (MDRD) study, which included 200 ADPKD patients, aggressive *versus* standard BP control was

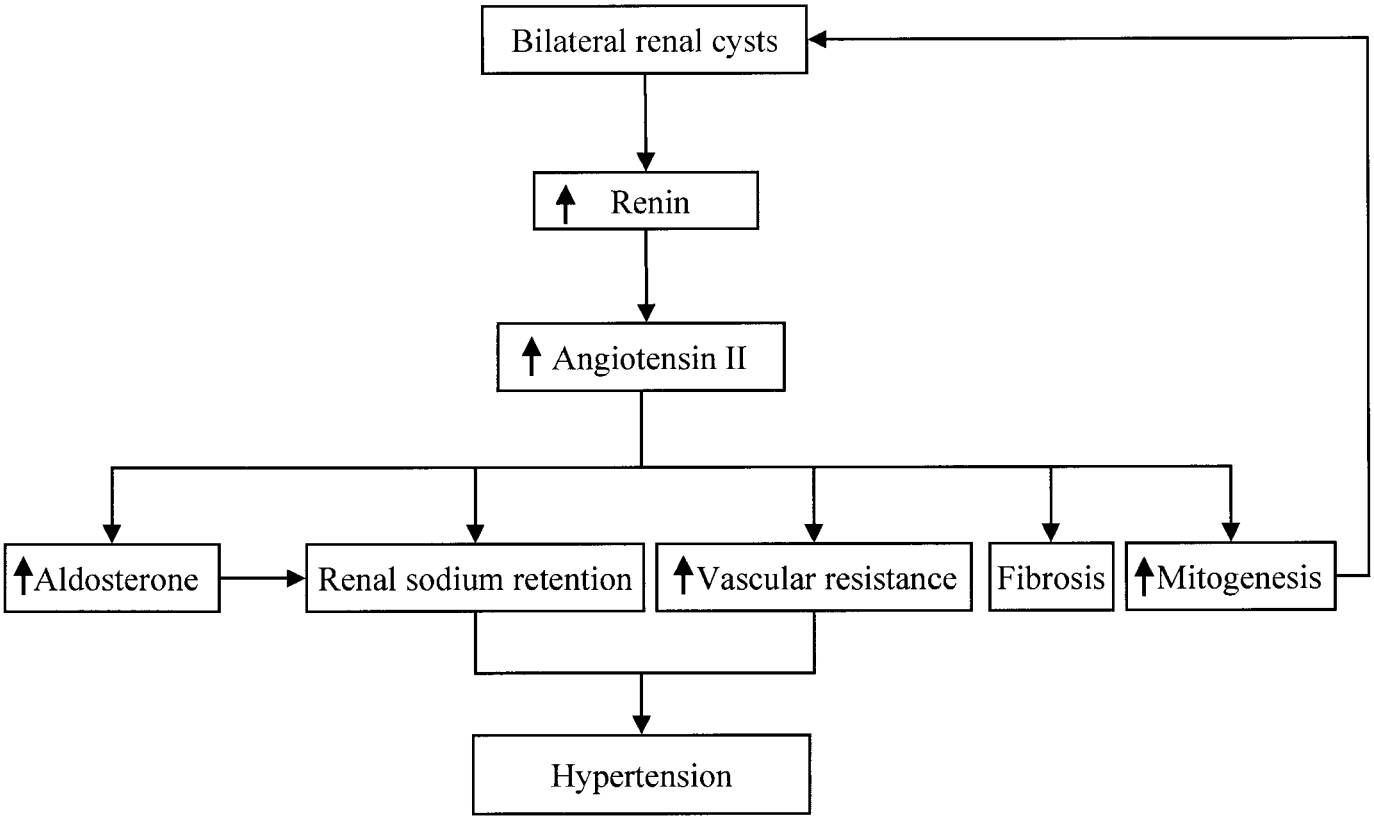

Figure 1. The effect of the RAAS in the development of hypertension and progression of ADPKD.

not associated with a slowing of loss of GFR in ADPKD (55). However, rather than the goal of a 15-mmHg difference in MAP (92 *versus* 107 mmHg), there was an average of only 4.7 mmHg MAP difference between the aggressive and standard BP treatment groups. Moreover, the study was performed in ADPKD patients with advanced renal disease (GFR <55 ml/min per 1.73 m^2), the average follow-up was only 2.2 yr, the type of antihypertensive therapy used was not controlled, and the structural progression and cardiovascular events were not assessed.

In the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study by Maschio *et al.* (56), 64 patients with ADPKD were included. While the patients with glomerular diseases and diabetes mellitus benefited the most from treatment with benazepril, those with ADPKD benefited the least. However, similar to the MDRD trial, the patients already had substantial renal failure with a mean baseline creatinine clearance of only 43 ml/min and the duration of the study was 3 yr.

There is also no consensus about the type of antihypertensive therapy that is most appropriate for hypertensive patients with ADPKD. Although experimental and clinical data suggest that ACE inhibitors should be the primary agent in the treatment of hypertension in patients with ADPKD, there is no randomized prospective study showing that ACE inhibitors are superior in these patients. Kanno *et al.* (57) compared the effects of calcium channel blockers and ACE inhibitors in 26 ADPKD patients with hypertension. After 2 yr of follow-up, patients who were receiving calcium channel blockers had a smaller annual decrease in creatinine clearance (1.5 ± 0.4 *versus* 2.7 ± 0.3 ml/min per year; $P < 0.05$) than those in the ACE group. Although the baseline creatinine clearances in this study were comparable to the patients in the MDRD study, *i.e.*, a creatinine clearance of 44.2 ml/min in the calcium channel blocker group and 51.9 ml/min in the ACE group, the rate of renal function loss was much lower than in the MDRD study.

Early intervention strategies should be considered in ADPKD patients because a more rapid deterioration of renal function has been reported in later stages of the disease (58). In a randomized, prospective 5-yr study of 24 patients with well-preserved renal function, we found that BP control less than 140/90 mmHg with a long-acting calcium channel blocker, amlodipine, or an ACE inhibitor, enalapril, was associated with a mean annual loss of renal function of 3.4 ml/min per 1.73m^2 (59). In this study, ACE inhibition but not treatment with calcium channel blockers showed a sustained antialbuminuric effect. Although urinary protein excretion has been shown to correlate with increased rate of progression of ADPKD (60), additional studies are needed to confirm whether this antialbuminuric effect of ACE inhibitors has any benefit in the long-term prognosis of ADPKD. In another randomized, prospective study on patients with normal renal function, Watson *et al.* (61) compared the effects of the ACE inhibitor enalapril and the β-blocker atenolol in 54 hypertensive patients with ADPKD. After a follow-up of 3 yr with good BP control with these agents, both of which inhibit the RAAS, renal function decreased 19.3 ml/min per 1.73 m^2 in the atenolol group and 14.3 ml/min per 1.73 m^2 in the enalapril group. The difference between the rates of decline, however, was not significant.

Because the RAAS plays an important role in the development of hypertension in ADPKD, a randomized, prospective study comparing the effects of an ACE inhibitor and a diuretic would be very important in these patients. Thus, controlling BP either with an ACE inhibitor that inhibits the RAAS or with a diuretic that stimulates the RAAS system could detect a role of the RAAS apart from its effect on BP. In this regard, in a historical prospective study, we compared the effects of diuretics *versus* ACE inhibitors in our hypertensive patients with ADPKD (62). During a mean follow-up of 5 yr, patients who were receiving diuretics without any ACE inhibitors had a faster loss of renal function compared with patients who were taking ACE inhibitors without any diuretics (annual increase in serum creatinine concentration, 0.25 *versus* 0.04 mg/dl; $P < 0.05$), despite similar BP control. Prospective, randomized studies are needed to confirm these preliminary findings.

The early and effective treatment of hypertension is also important for the prevention of cardiovascular complications. In this regard, treatment of hypertension with an ACE inhibitor has been shown to reverse LVH dramatically over a 7-yr follow-up period, thus decreasing an important risk factor for cardiovascular death in patients with ADPKD (63).

Although the control of BP in ADPKD patients is critical in decreasing ESRD and cardiovascular complications, only 30% of ADPKD patients who entered our ADPKD Center with well-preserved renal function had BP below 150/90 mmHg (3). This percentage is comparable to the 27% of patients with essential hypertension who were found in the National Health and Nutrition Examination Surveys (NHANES) (phase 2) to have their BP controlled below 140/90 mmHg in the United States (64). However, with an extensive education program for both ADPKD patients and their primary care physicians, the rate of BP control increased significantly to 64% (65).

Conclusions

Hypertension occurs in approximately 60% of the patients with ADPKD before renal function has become impaired. Hypertension is associated with a faster progression to ESRD and is the most important potentially treatable variable in ADPKD. Hypertension also plays an important role in cardiovascular disease, which is the most frequent cause of death in ADPKD patients. Experimental and clinical studies show that the RAAS is an important factor in the development and maintenance of hypertension in ADPKD. Early and effective treatment of hypertension is very important to decrease the morbidity and mortality of ADPKD patients. Prospective randomized studies are needed to determine the most appropriate agents for the treatment of hypertension in these patients.

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