Practical Issues in the Management of Polycystic Kidney Disease: Blood Pressure and Water Balance

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Autosomal dominant polycystic kidney disease is the most common hereditary renal disease affecting more than 13 million people worldwide. Renal function deteriorates as the cysts in both kidneys increase in number and size, which eventually results in end-stage kidney failure. Until recently, conservative management for chronic kidney disease such as blood pressure control, low sodium diet, adequate water intake, and weight control were known for the only treatment of polycystic kidney disease. However, the introduction of disease-modifying drug has led to the new paradigm shift in the management of polycystic kidney disease. Tolvaptan, the vasopressin V2 receptor antagonist, has been introduced to the patients with large kidneys since it can inhibit cyclic adenosine monophosphate, attenuates cyst growth, and delays renal failure. This article reviews the two important practical issues in the management of polycystic kidney disease: blood pressure and water balance. Firstly, the article will review the pathogenesis of high blood pressure in polycystic kidney disease and will demonstrate the current up-to-date management plan for blood pressure control. Secondly, this article will explain the mechanism of Tolvaptan on the treatment of polycystic kidney disease and its possible adverse effect on water and sodium balance.

Key Words: Autosomal dominant polycystic kidney disease, Blood pressure, Vasopressin V2 receptor antagonist, Water balance

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease characterized by development of numerous cysts. The kidney function gradually decreases leading to end-stage kidney disease (ESKD) in 50% of patients in their sixth decade¹. It is reported that ADPKD occurs in about 1 in 400 to 1,000 at birth² and estimated that 1 in 10,000 are treated with ADPKD based on the data from the Health Care Big Data Hub in Korea³. ADPKD is caused by mutations in the PKD1 and PKD2 genes. PKD1 and PKD2 account for 85% and 15% of cases, respectively⁴. Mutations in PKD1 have poorer prognosis than that in PKD2⁵.

The general management of ADPKD includes blood pressure control, low sodium diet, adequate water intake, weight control, and cholesterol lowering therapy⁶. Hypertension is one of the earliest renal complications of ADPKD⁷. Intrarenal renin-angiotensin-aldosterone system is known to play the main role in the development and maintenance of hypertension in ADPKD⁸, which result in end-organ damage including left ventricular hypertrophy and progressive renal failure⁹,¹⁰. Therefore, lowering blood pressure was considered important even from the childhood and adoles-
cent at risk\textsuperscript{12}).

Meanwhile, the treatment paradigm for ADPKD has completely changed as Tolvaptan, a vasopressin V2 receptor antagonist, was found to be effective in inhibiting cyst growth and renal function decline\textsuperscript{6,13}). Vasopressin V2 receptor antagonists block the action of vasopressin at the principal cells of the renal collecting and connecting tubules to reduce urine osmolality and increase electrolyte-free water excretion\textsuperscript{14}). Since vasopressin activates cyclic adenosine monophosphate (cAMP) resulting in cell proliferation and cyst development, vasopressin V2 receptor antagonists block the action of cAMP and cyst growth\textsuperscript{15, 16}). Tolvaptan is considered the choice of treatment for rapidly progressive ADPKD with large kidneys\textsuperscript{6}).

This article will review two practical issues in treating ADPKD patients: hypertension and water balance. We will describe the epidemiology and pathogenesis of hypertension in ADPKD as well as current management strategy of hypertension in ADPKD patients. We will demonstrate the main mechanism of Tolvaptan in the treatment of rapidly progressive ADPKD, and the precautions in Tolvaptan treatment regarding water and electrolyte imbalance.

**Epidemiology of hypertension in ADPKD patients**

Hypertension is the most common renal symptom of ADPKD and it has been reported that 80% of patients had hypertension\textsuperscript{17}). The prevalence of hypertension was similar in Korean ADPKD patients. Three hundred and sixty-four patients enrolled in ADPKD sub-cohort of the Korean Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD), a cohort of patients with chronic kidney disease before ESKD, 87.6% of patients had hypertension\textsuperscript{18}). Hwang et al. reported that 85% of patients had hypertension when analyzed the clinical characteristics of 34 Korean ADPKD patients who reached ESKD\textsuperscript{19}).

Children with ADPKD have been reported to show high prevalence of hypertension from an early age. Although the report on the prevalence of hypertension in children differs depending on the number of patients, age, blood pressure measurement method, and definition of hypertension, several studies report that the incidence or prevalence of hypertension in children with ADPKD were between 6% and 35\textsuperscript{20-22}). Masell et al. reported ambulatory blood pressure monitoring data of 292 ADPKD children from 22 European centers with an average age of 11.5 years and eGFR $\geq 45$ ml/min per 1.73 m$^2$ that 35% had hypertension, 52% had no nocturnal dipping, and 18% had isolated nocturnal hypertension\textsuperscript{20}). Children with ADPKD, therefore have a higher prevalence of hypertension and abnormal blood pressure dipping pattern long before the onset of symptoms of ADPKD.

**Pathogenesis of hypertension in ADPKD**

It is hypothesized that since the prevalence of hypertension in ADPKD patients is related to the size of the kidney, the blood vessels in the kidney are stretched and compressed as the cysts growing, resulting in ischemia, activation of renin angiotensin aldosterone system (RAAS), and hypertension\textsuperscript{9}). Although circulating angiotensin is the cause of hypertension in ADPKD is controversial\textsuperscript{24}), there are evidences for local activation of intrarenal RAAS. Administration of ACE inhibitors partially reversed the reduced renal blood flow, increased renal vascular resistance, and increased filtration fraction\textsuperscript{25}). The immunoreactive renin shifts from the juxtaglomerular apparatus to the walls of arterioles and small arteries in ADPKD\textsuperscript{26}). In addition, ectopic renin is produced in the epithelium of dilated cysts and tubules\textsuperscript{27}). ACE-independent angiotensin II production by chymase-like enzyme was reported in human end stage ADPKD kidney tissue\textsuperscript{28}) (Fig. 1).

In addition to kidney tubular epithelial cell, polycystin

![Fig. 1. Mechanisms of Hypertension in ADPKD patients. eNOS: endothelial nitric oxide synthase; NO: nitric oxide; SNS: sympathetic nerve system.](image-url)
1 and polycystin 2 are also expressed in vascular smooth muscle cells and endothelial cells. It can be suggested that polycystin dysfunction enhances vascular smooth muscle cell contraction and impairs endothelial cell-dependent vaso-orelaxation, leading to early development of hypertension \cite{29,30}. Plasma concentrations of Nitric oxide (NO) were reduced and levels of asymmetric dimethylarginine, an inhibitor of NO synthase were increased in patients of ADPKD patients compare with healthy controls \cite{31,32}. Endothelial NO synthase activity and endothelium-dependent relaxation is also decreased in ADPKD patients \cite{33,34}. It is thought that endothelial dysfunction might be an important factor in the pathogenesis of hypertension and other vascular phenotype such as intracranial aneurysm, aortic dissection and hemorrhage in ADPKD patients (Fig. 1).

Activation of sympathetic nerve system has been implicated in another mechanism of hypertension in ADPKD patients. Hypertensive ADPKD patients with normal renal function or those with renal insufficiency had increased muscular sympathetic nerve activity (MSNA) compared with ADPKD controls. MSNA was closely correlated with mean arterial pressure \cite{35} (Fig. 1).

Hypertension as a prognostic factor

Total kidney volume is considered as a strong prognostic and monitoring biomarker \cite{36}, and genetic testing, PKD1 protein truncating mutation (PKD1 PT), is recognized as an important prognostic factor in ADPKD \cite{37}. Hypertension at an early age was also considered as a poor prognostic factor. The predicting renal outcomes in ADPKD (PROPKD) score system, that accurately predicts kidney outcomes, include male, hypertension before 35 years of age, first urologic event before 35 years of age, and PKD1 PT mutation type as poor prognostic factors \cite{38}.

Positive correlations between ambulatory systolic blood pressure and left ventricular mass in young normotensive ADPKD patients had been shown. The nocturnal BP drop was attenuated in these patients \cite{39}. Moreover, biventricular diastolic dysfunction was present in both hypertensive and normotensive ADPKD patients with preserved renal function, suggesting very early cardiac involvement in the course of ADPKD \cite{40}. Cardiac studies in ADPKD adults have reported higher frequency of left ventricular hypertrophy compared with controls. Left ventricular hypertrophy was associated with higher systolic and diastolic blood pressure \cite{41}. These results suggest that hypertension and cardiovascular changes appear early during ADPKD progression and may play an important role as risk factors for cardiovascular events.

Treatment of hypertension

As in the general hypertensive patients, diet and lifestyle changes should be the first line treatment choice in hypertensive ADPKD patients. Moderate sodium restriction, smoking cessation, and regular exercise should be encouraged to all ADPKD patients. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) are recommended as the drugs of choice to treat hypertension in ADPKD patients. β-Blockers and calcium channel blockers should be added for control of hypertension after using ACE inhibitors or ARBs. β-Blockers may be preferred than calcium channel blockers because they have mild RAAS-inhibitory activity. However, there is no clinical study on which class is more effective on prevention of kidney disease progression and cardiovascular events. Diuretics should be administered concurrently with ACE inhibitors or ARBs under careful monitoring of kidney function \cite{42}.

Subgroup analysis of 200 ADPKD patients participated in Modification of Diet in Renal Disease (MDRD) Study demonstrated that glomerular filtration rate (GFR) declined faster with the low blood pressure group compared with the usual treatment group during the first 4 months (4.6 versus 2.8 ml/min per 4 months, respectively) but not after month 4 (5.1 versus 5.4 ml/min per year, respectively) in those with a baseline GFR 25-55 ml/min. In patients with GFR 13-24 ml/min, GFR declined faster with the low blood pressure group than the usual treatment group (4.9 versus 3.9 ml/min per year, respectively). This finding must be interpreted cautiously, because it was a secondary analysis \cite{43}.

The HALT progression of polycystic kidney disease (HALT-PKD) study is the best designed study to analyze the relationship between blood pressure control and kidney disease progression in ADPKD patients. Study A included 558 hypertensive ADPKD patients who were 15 to 49 years old and had an eGFR of > 60 ml/min per 1.73 m². They were
assigned to either the standard blood pressure target (120/70 to 130/80 mmHg) group or the low blood pressure target (95/60 to 110/75 mmHg) group and to either lisinopril plus telmisartan group or lisinopril plus placebo group. In study B, patients between the ages of 18 and 64 with an eGFR of 25 to 60 ml/min per 1.73 m² were enrolled. The patients received lisinopril plus telmisartan or lisinopril plus placebo with the doses adjusted to achieve a blood pressure of 110/70 to 130/80 mmHg. In study A, the annual percentage increase in total kidney volume was significantly lower in the low blood pressure group than in the standard blood pressure group (5.6% vs. 6.6%, P=0.006). These effects were evident in patients with large kidney volume and high eGFR of >80 ml/min per 1.73 m². The effect of rigorous blood pressure control on eGFR was not statistically significant, however, because eGFR was maintained lower in the low blood pressure group for the first 4 months. There was no additional benefit to adding ARB to ACE inhibitor in this study as well. In Study B, blood pressure was well controlled with ACE inhibitor alone, but the addition of an ARB had no additional kidney protective effect in ADPKD patients with CKD stage 3. Based on results of HALT-PKD study, it is recommended that patients aged 18 to 50 years with an eGFR of >60 ml/min per 1.73 m² control their blood pressure to ≤110/75 mmHg and other patients to ≤130/85 mmHg with ACE inhibitors or ARBs.

Although it had not been clearly established whether blood pressure control had a protective effect on kidney function, several studies suggested that blood pressure control might reduce cardiovascular morbidity and mortality in ADPKD patients. Schrier et al. reported that rigorous blood pressure control in ADPKD patients could reduce left ventricular mass without the effect on kidney function. A population-based study using the U.K. General Practice Research Database reported that increased use of antihypertensive drugs over the period from 1991 to 2008 in patients with ADPKD, particularly of agents blocking the RAAS, was accompanied by reduced mortality. The left-ventricular-mass index decreased more in the low-blood-pressure group than in the standard-blood-pressure group and urinary albumin excretion was reduced with the low blood-pressure group while increased with the standard blood-pressure group in HALT-PKD study.

Vasopressin receptor as the target of treatment in polycystic kidney disease

Normally, polycystin 1 and polycystin 2 make a complex on cilium to regulate intracellular calcium level and inhibit cyclic adenosine monophosphate (cAMP). In ADPKD, the functional defects in either polycystin 1 or polycystin 2 result in activation of cAMP and subsequent activation of genes related to cyst proliferation. Vasopressin receptors are G-protein-coupled receptors and consist of three subtypes: V1α, V1β, and V2 receptors. V2 receptors are located at the collecting tubules and vascular endothelium and smooth muscle cell. When vasopressin binds to V2 receptors, aquaporin water channels are inserted into apical membrane, aquaporins are synthesized, and vessels are dilated. In addition, vasopressin acting on V2 receptors activate cAMP and subsequent downstream molecular pathway.

Vasopressin V2 receptor antagonist, Tolvaptan, was initially developed to treat hyponatremia and chronic heart failure. Tolvaptan increases free water excretion through aquaporin channel and lowers urine osmolality. In addition to that, Tolvaptan decreases cAMP level which subsequently reduce fluid secretion, cell proliferation, and cyst growth among the patients with ADPKD. In the recent clinical studies to evaluate the efficacy of Tolvaptan in the patients with ADPKD, Tolvaptan effectively reduced the growth rate of total kidney volume and renal function decline rate.

Aquaretic adverse effects after Tolvaptan treatment

Polyuria and related side effects are the most common reasons for treatment discontinuation with Tolvaptan. Since Tolvaptan increases free water excretion, it can cause hyponatremia without ad libitum water intake according to thirst sense. In addition, the doses of Tolvaptan used to treat ADPKD are higher than those used in congestive heart failure or hyponatremia, which results in massive urination up to 6L per day. In the TEMPO 3:4 and REPRISE clinical trials, there were more frequent adverse events related to free water excretion such as thirst, polyuria, nocturia, pollakiuria, and polydipsia among Tolvaptan group compared to the control group. More patients on Tolvaptan group discontinued clinical trial due to adverse events compared to the control group. Patients that discontinued...
Tolvaptan were younger, have high baseline eGFR, and higher baseline fasting urinary osmolality. Kramer et al. analyzed the major determinants of polyuria in the patients with ADPKD using Tolvaptan. Although a small number of patients were included in the study, they found that 24-hour osmolar excretion was strongly associated with urine volume. The aquaretic effect of Tolvaptan was maintained even in the patients with lower baseline eGFR showing larger fractional free-water clearance, which means higher responses to Tolvaptan per functioning nephron.

Therefore, recent articles suggest using Tolvaptan no matter what the baseline eGFR for rapidly progressive ADPKD.

To improve patient adherence to drug while maintaining the effect of Tolvaptan, the efforts to reduce aquaretic-related symptoms is the must. As Kramer said in his article, osmolar excretion is the major determinant of urine volume. Therefore, we can reduce polyuria by educating the patients to limit osmolar intake during daytime. In addition, the patients can adjust their meal schedule to change the timing of the highest urine output. Recently, metformin and hydrochlorothiazide were evaluated to reduce aquaretic adverse events during Tolvaptan treatment. Both drugs were equally effective in reducing urine output. However, only hydrochlorothiazide reduced the plasma level of copeptin, a biomarker for vasopressin, and improved the quality of life in the patients. Another study by Japanese study group also demonstrated the positive effect of trichlormethiazide in reducing aquaretic side effects.

CONCLUSIONS

Recent introduction of Tolvaptan, the first and the only disease-modifying drug at this moment, changed the treatment paradigm in ADPKD. Both general management and disease-specific treatment are important to delay the progression of ADPKD. Hypertension is one of the earliest renal manifestation of ADPKD. Evaluating 24-hour ambulatory blood pressure may help to detect hypertension in adolescent and to intervene early to maintain adequate blood pressure. ACE inhibitors or ARBs are the choice of the anti-hypertensive agents. It is recommended to control blood pressure below 130/85 mmHg for most of the patients with ADPKD and even lower to ≤110/75 mmHg who are younger than 50 years with normal renal function. Treatment effect of Tolvaptan may maximize when the aquaretic adverse effects are minimized. The increased free water excretion may be minimized when the osmolar intakes are reduced. The use of hydrochlorothiazide may help the patients with ADPKD on Tolvaptan to tolerate the aquaretic adverse events.

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