KI REPORTS
KIReports.org
CLINICAL RESEARCH

Open-Label, Randomized, Controlled, Crossover Trial on the Effect of Dapagliflozin in Patients With ADPKD Receiving Tolvaptan

Kiyotaka Uchiyama[1,2], Daisuke Kamano[2], Tomoki Nagasaka[3], Eriko Yoshida Hama[3], Ryoichi Shirai[2], Rena Sumura[2], Ei Kusahana[3], Akane Yanai[4], Takashin Nakayama[3], Takahide Kimura[5], Rina Takahashi[3], Takahiro Kasai[5], Takaya Tajima[3], Koji Hosoya[6], Tatsuhiko Azegami[3], Shintaro Yamaguchi[3], Jun Yoshino[7], Jun Ito[1], Matsuhiko Hayashi[8], Takeshi Kanda[7], Yoshitaka Ishibashi[2], Naoki Washida[1], Hiroshi Itoh[3] and Kaori Hayashi[3]

[1]Department of Nephrology, International University of Health and Welfare Narita Hospital, Chiba, Japan; [2]Department of Nephrology, Japanese Red Cross Medical Center, Tokyo, Japan; [3]Division of Endocrinology, Metabolism and Nephrology Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan; [4]Department of Nephrology, Tokyo Shinagawa Hospital, Tokyo, Japan; [5]Department of Nephrology, International University of Health and Welfare Atami Hospital, Shizuoka, Japan; [6]Department of Nephrology, International University of Health and Welfare Hospital, Tochigi, Japan; [7]Division of Nephrology, Shimane University Hospital, Shimane, Japan; and [8]Department of Nephrology, Kawakita General Hospital, Tokyo, Japan

Introduction: Although dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, delays the progression of chronic kidney disease (CKD), its effect on patients with autosomal dominant polycystic kidney disease (ADPKD) has not been established. We conducted an open-label, randomized controlled crossover trial to evaluate the additive effects of dapagliflozin in patients with ADPKD receiving tolvaptan.

Methods: A total of 27 patients were randomly counterbalanced to receive dapagliflozin 10 mg or usual care without dapagliflozin for 6 months. The primary endpoint was the slope of the estimated glomerular filtration rate (eGFR) determined by linear regression from 1 to 6 months, and the secondary endpoints included changes in total kidney volume (TKV). eGFR was calculated based on creatinine levels ($eGFR_{cr}$), cystatin C levels ($eGFR_{cys}$), and the mean of $eGFR_{cr}$ and $eGFR_{cys}$ ($eGFR_{cr\text{-}cys}$).

Results: There were significant attenuations in the $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ slopes during the dapagliflozin trial compared with the one without dapagliflozin (2.57 ± 7.88 vs. -5.65 ± 9.57 ml/min per 1.73 m^2 per year, $P = 0.002$; 3.91 ± 11.40 vs. -8.43 ± 13.44 ml/min per 1.73 m^2 per year, $P = 0.003$, respectively). Meanwhile, the $eGFR_{cr}$ slope was potentially moderate during the trial with dapagliflozin (1.03 ± 10.78 vs. -3.66 ± 8.88 ml/min per 1.73 m^2 per year, $P = 0.06$). The 6-month change in TKV was significantly attenuated during the trial with dapagliflozin compared with the one without dapagliflozin ($-0.44 \pm 4.91\%$ vs. $5.04 \pm 8.09\%$, $P = 0.01$).

Conclusion: In patients with ADPKD treated with tolvaptan, dapagliflozin may have an additive effect in slowing ADPKD progression.

Kidney Int Rep (2025) **10,** 1063–1075; https://doi.org/10.1016/j.ekir.2025.01.023
KEYWORDS: autosomal dominant polycystic kidney disease; dapagliflozin; estimated glomerular filtration rate; sodium–glucose cotransporter 2 inhibitor; tolvaptan; total kidney volume

ADPKD, a common genetic kidney disorder, often leads to kidney failure.[1] The vasopressin V2 receptor antagonist, tolvaptan, has been found to delay the increase in TKV and decline the kidney function compared with placebo in patients with ADPKD via a randomized controlled trial (RCT), and tolvaptan is the only contemporary, widely used, and effective specific treatment for patients with ADPKD.[2,3] Tolvaptan became available for patients with progressive ADPKD who have a TKV $>$ 750 ml and an annual TKV growth $>$ 5% in Japan in 2014.

Correspondence: Kiyotaka Uchiyama, Department of Nephrology International University of Health and Welfare Narita Hospital Narita, 852 Hatakeda, Narita, Chiba, Japan. E-mail: kiyo.0817.piyo@gmail.com

Received 13 September 2024; revised 12 January 2025; accepted 13 January 2025; published online 18 January 2025

Recently, the SGLT2 inhibitors dapagliflozin and empagliflozin have been shown to improve composite outcomes that include kidney disease progression (a sustained reduction in the eGFR of ≥ 40%–50% from baseline) and kidney failure with or without kidney replacement therapy, and have also shown reduction in the annual change in eGFR compared with placebo in nondiabetic patients with CKD and in diabetic patients in large-scale RCTs.[4,5] However, patients with ADPKD were excluded from both trials; thus, the impact of SGLT2 inhibitors on these patients is yet to be determined. Although SGLT2 inhibitors may inhibit ADPKD progression and other etiologies of CKD, SGLT2 inhibitors increase plasma levels of vasopressin or its surrogate marker, copeptin, a key molecule that promotes disease progression in patients with ADPKD.[6] From this perspective, these elevations would not be an issue as far as tolvaptan antagonizes the vasopressin V2 receptor. Conversely, another report suggested that in patients with ADPKD receiving tolvaptan treatment, the copeptin level was directly proportional to the treatment effect, as measured by the TKV growth rate and eGFR.[7]

Designing a trial on SGLT2 inhibitors alone is ethically undesirable because of the high risk of exacerbating ADPKD. Tolvaptan is the only established effective treatment option for ADPKD. Thus, we could not prioritize any drug, including SGLT2 inhibitors over tolvaptan for patients with ADPKD. Consequently, an open-label, randomized, controlled crossover trial of patients with ADPKD who received tolvaptan was designed to validate the additive effect of dapagliflozin, the first SGLT2 inhibitor to be covered by insurance for patients with CKD in Japan, on kidney function decline. The additive effects of dapagliflozin on TKV growth, plasma vasopressin levels, and other anthropometric and serum parameters, which are considered secondary outcomes, were evaluated.

METHODS

Study Population

Outpatients with ADPKD at the nephrology departments of the Japanese Red Cross Medical Center, Keio University Hospital, International University of Health and Welfare Narita Hospital, International University of Health and Welfare Hospital, and International University of Health and Welfare Atami Hospital were included in this RCT from December 2021 to March 2024. The criteria for trial eligibility included stable patients aged > 20 years diagnosed with ADPKD based on the Japan-specific diagnostic criteria proposed by the Ministry of Health, Labour and Welfare (https://jsn.or.jp/academicinfo/report/evidence_PKD_guideline2020.pdf) and receiving high-dose tolvaptan (> 60 mg/d) for > 3 months, with an eGFR > 25 ml/min per 1.73 m^2.[4] The participants met the following criteria on the use of tolvaptan: a TKV > 750 ml and an annual TKV growth > 5%. We excluded patients with diabetes and those with contraindications to SGLT2 inhibitor use (such as hypersensitivity, severe ketosis, or severe infections). Patients already taking dapagliflozin or other SGLT2 inhibitors were also excluded.

Study Design and Randomization

The study protocol was reviewed and approved by the Ethics Committee of Keio University Hospital (approval number: 20211065) and the protocol adhered to the principles of the Declaration of Helsinki. This study was registered in a public trial registry (UMIN-CTR number: UMIN000046275; 6/12/2021). All study participants provided written informed consent.

Although several large clinical trials have reported the relative safety of dapagliflozin in patients with diabetes and CKD, its safety in patients with ADPKD has not yet been confirmed. Therefore, an open-label study was preferred because it would allow physicians to use SGLT2 inhibitors cautiously, monitor adverse events, determine their causality, and promptly address adverse events if they occur. In addition, the study initially included only a small number of participants. To decrease the calculated sample size, a crossover study rather than a parallel study was performed. Furthermore, the follow-up period was kept short, to minimize potential harm to the participants.

At baseline, data including age; sex; family history of ADPKD; presence or absence of hypertension; use of renin-angiotensin aldosterone system inhibitors; ADPKD complications such as hypertension, liver cysts, brain aneurysm, and valvular disease; dose of tolvaptan (mg); and duration of tolvaptan administration (years) were obtained from medical records. Patients' height (cm) and weight (kg) were measured, and the body mass index (kg/m^2) was calculated. Office blood pressure (BP) was assessed in the sitting position using an automated BP device. After baseline assessment, a neutral person randomly assigned patients to the 2 groups using minimization with the MinimPy (an open-source minimization program in Python programming language), as previously described.[8]

The participants received dapagliflozin 10 mg or the usual treatment without dapagliflozin for 6 months in a counterbalanced fashion (the same patients received both treatments in random order) as per the open-label crossover design (Figure 1). The dapagliflozin dose was maintained and adherence to dapagliflozin was assessed by checking the empty dapagliflozin blister pack at

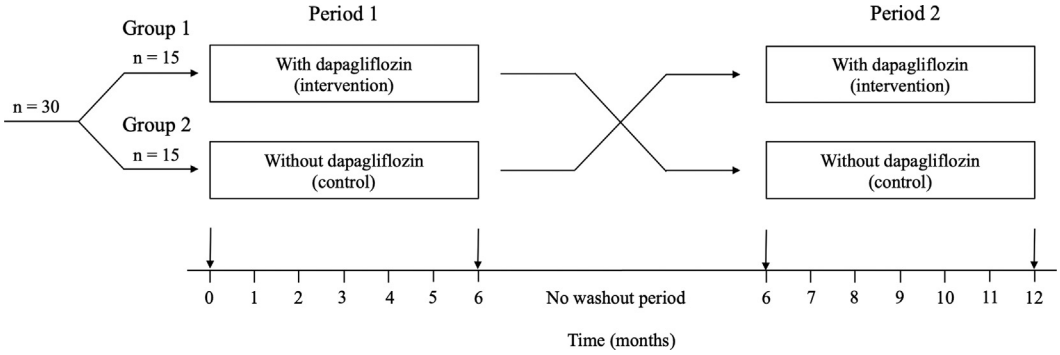

Figure 1. Crossover flow chart of the trial process.

each outpatient visit. An intertrial washout period was not set. Patients visited the hospital every 1 to 2 months, including the first visit (0-month), the 1-month, and the 6-month final visit for each 6-month-long trial (treatment without [DAPA− trial] or with [DAPA+ trial] dapagliflozin). The anthropometric profiles and blood test results were recorded at each visit. In addition, the participants were instructed to collect their 24-hour urine samples and underwent abdominal computed tomography or magnetic resonance imaging for TKV evaluation at 0 and 6 months of each trial (i.e., 0, 6, and 12 months of the entire trial period). Each patient consistently underwent either a computed tomography scan or magnetic resonance imaging for each of their measurements because the difference in the imaging techniques (computed tomography scan vs. magnetic resonance imaging) can introduce errors in TKV measurement. The tolvaptan dose was maintained by the treating nephrologists throughout the study period because it may have affected ADPKD progression. However, unlike for dapagliflozin, adherence to tolvaptan was not monitored. Prescriptions for other medications (including antihypertensive drugs) could be adjusted by the treating nephrologists.

Outcome Measures

The primary study endpoint was the rate of kidney function decline, which was assessed based on the rate of change in eGFR as calculated using a linear regression model. Given the initial decrease in eGFR observed with dapagliflozin administration and the absence of a washout period, the eGFR slope was calculated using eGFR values from 1 to 6 months in each trial rather than from baseline. eGFR was calculated in 3 ways using the 3-variable Japanese equations: $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr\text{-}cys}$, of which $eGFR_{cr\text{-}cys}$ was the most accurate estimate of kidney function.[9,10]

Secondary study outcomes included changes in TKV (%) and body weight (kg) from 0 to 6 months during each trial. The TKV (cm^3) was calculated using either the ellipsoid volume equation or the stereology method from computed tomography or magnetic resonance imaging by third-party individuals.[11] Additional secondary endpoints included each trial's 6-month plasma vasopressin level (pg/ml) measured via radioimmunoassay using the AVP kit (Yamasa, Tokyo, Japan); office BP (mmHg); urine volume (ml), urine osmolarity (mOsm), and urine albumin (mg/d) assessed from 24-hour urine samples; and the liver-type fatty acid-binding protein levels (μg/gCr) evaluated using spot urine samples.

Exploratory variables included serum parameters that dapagliflozin use could affect, including hemoglobin (g/dl), hematocrit (%), fasting blood sugar (mg/dl), hemoglobin A1c (%), and uric acid (mg/dl). Other exploratory parameters included 6-month serum total protein (g/dl); albumin (g/dl); sodium (mEq/l); potassium (mEq/l); and lipid profiles, including serum total cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), low-density lipoprotein cholesterol (mg/dl), and triglyceride (mg/dl) levels.

Safety outcomes were systematically examined. In Supplementary Table S1, we show some prespecified and serious adverse events.

Statistical Analysis

The normality of continuous data distribution was assessed using the Shapiro–Wilk test. Normally distributed and skewed variables were presented as mean ± SD and median (interquartile range), respectively. Categorical variables were expressed as frequencies and percentages. Longitudinal changes in eGFR values were described using linear mix models including group (1 or 2), period (0–12 months), 0-month eGFR, and an interaction term; group × period was defined as a fixed effect, and the patient number was defined as a random effect.

The paired *t*-test or Wilcoxon signed-rank test was performed to compare continuous variables between the 2 trials, whereas the unpaired *t*-test or Mann–Whitney *U* test was used for within-group

comparisons between 2 sets of data divided by the sequence of dapagliflozin treatment, depending on the distribution of the parameters.

Linear mixed models were used to assess the impact of dapagliflozin on eGFR over time for sensitivity analysis. The model included fixed effects, such as the trial (with or without dapagliflozin), the period (1–6 months), and the 1-month eGFR, as well as an interaction term, period × trial, to assess the effect of dapagliflozin (model A). The patient number was a random effect. A separate model in which the period (1–6 months) and the 1-month eGFR were replaced with the period (0–6 months) and 0-month eGFR, respectively, was also analyzed (model B). Interim analyses were not performed.

Because this was a crossover trial, linear mixed models were used to analyze the carryover and order effects on the primary outcome, eGFR slope, and TKV change. Adjustments were performed for the group (1 or 2), trial (first or second), and treatment (with or without dapagliflozin) as fixed effects and for patient number as a random effect.[12,13] The effects of the group, trial, and treatment were regarded as carryover, order, and treatment effects, respectively.

Although there have been no trials evaluating the impact of SGLT2 inhibitors on eGFR in patients with ADPKD, based on the results of a previous trial that demonstrated the effect of dapagliflozin on the eGFR slope after the first 2 weeks (initial dip) or the "chronic" eGFR slope in patients with CKD,[14] we calculated that 25 patients were required to detect a 1.92 ml/min per 1.73 m^2 per year improvement in the chronic eGFR slope with an SD of 5.10 ml/min per 1.73 m^2 per year in trials with and without dapagliflozin and an intertrial correlation coefficient of 0.8 (paired t-test; $\beta = 0.20$; $\alpha = 0.05$).[4,15] Given a 20% estimated attrition rate, the calculated sample size was 30. SPSS software for Mac (ver. 27; IBM Corp., Armonk, NY) was used for all the statistical analyses. The threshold for statistical significance was set at $P < 0.05$.

RESULTS

Baseline Characteristics

Among the 50 patients with ADPKD who received tolvaptan for > 3 months and underwent the eligibility assessment, 42 met the inclusion criteria, and 30 consented to participate in the study (Figure 2). We randomized 30 participants in a crossover design to receive dapagliflozin first (group 1, $n = 15$) or continue usual care without an SGLT2 inhibitor (group 2, $n = 15$). However, 2 patients in group 1 and 1 patient in group 2 were lost to follow-up because of hospital transfer during their first trial period, making intertrial comparisons not feasible; consequently, 27 patients (13 and 14 patients in groups 1 and 2, respectively) were analyzed. Among these, 1 patient each from groups 1 and 2 refused to collect 24-hour urine samples; therefore, the parameters assessed from 24-hour urine samples were obtained from 25 patients (12 and 13 patients in groups 1 and 2, respectively). The median rate of treatment adherence (to dapagliflozin) was 100%.

The baseline features of all participants are outlined in Tables 1 and 2. They did not differ significantly between the 2 groups, whereas TKV and height-adjusted TKV (ml/m) tended to be higher in group 1 than in group 2 (1414 [993–2369] vs. 1012 [914–1126], $P = 0.08$ and 822 [575–1381] vs. 624 [516–675], $P = 0.07$, respectively).

Effect of Dapagliflozin on eGFR Change: The Primary Outcome

The longitudinal changes in eGFR values are shown in Figure 3. The slopes of $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ were significantly more moderate during the DAPA+ trial than those during the DAPA− trial (2.57 ± 7.88 vs. −5.65 ± 9.57 ml/min per 1.73 m^2 per year, $P = 0.002$; 3.91 ± 11.40 vs. −8.43 ± 13.44 ml/min per 1.73 m^2 per year, $P = 0.003$, respectively); the $eGFR_{cr}$ slope tended to be more moderate during the DAPA+ trial than during the DAPA− trial (1.03 ± 10.78 vs. −3.66 ± 8.88 ml/min per 1.73 m^2 per year, $P = 0.06$; Table 3).

The carryover effect was negligible for $eGFR_{cr\text{-}cys}$, $eGFR_{cys}$, and $eGFR_{cr}$ slopes ($P = 0.17$, 0.53, and 0.09, respectively). In addition, the order effect was absent for all slopes ($P = 0.59$, 0.64, and 0.30, respectively). The treatment effect persisted after these adjustments for all slopes ($P = 0.002$, 0.004, and 0.06, respectively).

The linear mixed model A confirmed that the $eGFR_{cr\text{-}cys}$ and $eGFR_{cys}$ with the estimated marginal mean during the DAPA+ trial were significantly higher than those during the DAPA− trial after 4 months (63.5 ± 0.9 vs. 59.5 ± 0.8 ml/min per 1.73 m^2, $P = 0.003$; 75.3 ± 1.4 vs. 69.2 ± 1.3 ml/min per 1.73 m^2, $P = 0.003$, respectively) and 6 months (62.5 ± 0.8 vs. 58.7 ± 0.8 ml/min per 1.73 m^2, $P = 0.003$; 73.7 ± 1.2 vs. 67.5 ± 1.2 ml/min per 1.73 m^2, $P = 0.002$, respectively; Figure 4a and b). In addition, after 5 months, $eGFR_{cr\text{-}cys}$ was significantly higher and $eGFR_{cr}$ tended to be higher during the DAPA+ trial than during the DAPA− trial (62.3 ± 0.9 vs. 59.5 ± 0.9 ml/min per 1.73 m^2, $P < 0.05$; 52.4 ± 0.7 vs. 50.3 ± 0.8 ml/min per 1.73 m^2, $P = 0.09$, respectively; Figure 4a and c).

In contrast, the linear mixed model B with 0-month as the baseline confirmed that the eGFR acutely declined after 1 month during the DAPA+ trial (initial dip), whereas it slightly increased during the DAPA− trial because of recovery from the initial dip in patients

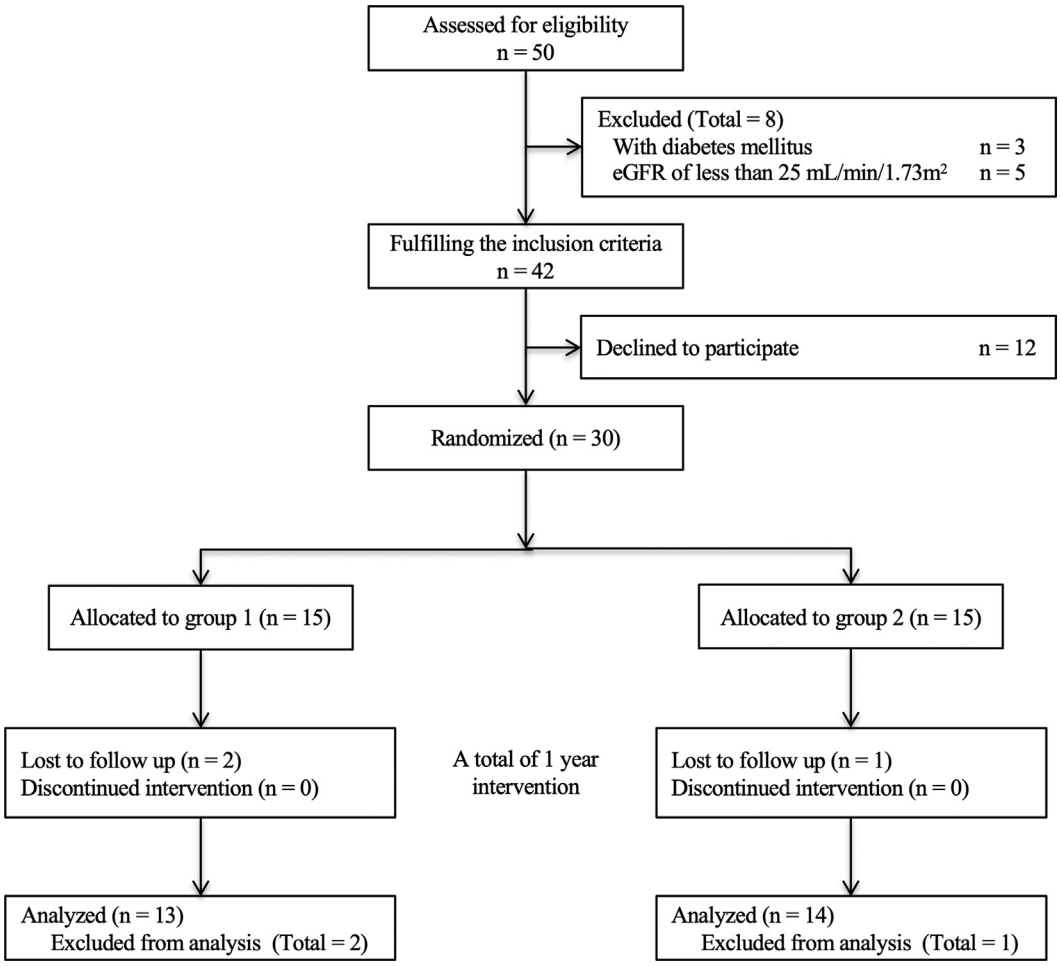

Figure 2. CONSORT flow diagram of patients through the various phases of the clinical trial.

in group 1 (Figure 5). Therefore, the eGFR was persistently and significantly lower from 1 to 6 months during the DAPA+ trial than during the DAPA− trial.

Effect of Dapagliflozin on Secondary Outcomes

The 6-month change in TKV was significantly attenuated during the DAPA+ trial compared with that during the DAPA− trial (−0.44 ± 4.91 vs. 5.04% ± 8.09%, $P = 0.01$; Table 4). Carryover and order effects were negligible for the TKV change ($P = 0.39$ and 0.27, respectively), and the treatment effect persisted after this adjustment ($P = 0.02$). The body weight change was significantly smaller during the DAPA+ trial than during the DAPA− trial (−0.69 ± 1.42 vs. 0.56 ± 1.49 kg, $P = 0.01$).

Among other secondary endpoints, the 6-month plasma vasopressin level was significantly higher during the DAPA+ trial than during the DAPA− trial (4.52 ± 2.02 vs. 3.58 ± 1.72 pg/ml, $P = 0.002$). Urinary osmolarity tended to be higher during the DAPA+ trial than during the DAPA− trial (184.4 ± 51.1 vs. 165.3 ± 47.9 mOsm, $P = 0.05$), whereas urinary volume did not differ significantly between the 2 trials (4472 ± 1389 vs. 4328 ± 1299 ml, $P = 0.51$). Whereas the systolic BP at 6 months was significantly lower (123.0 ± 13.1 vs. 128.4 ± 10.1 mmHg, $P = 0.04$) and pulse pressure tended to be lower (41.1 ± 9.2 vs. 44.3 ± 8.6 mmHg, $P = 0.08$) during the DAPA+ trial than during the DAPA− trial, the diastolic and mean BPs did not differ significantly between the trials, nor did urine albumin and liver-type fatty acid-binding protein.

Effect of Dapagliflozin on Exploratory Outcomes

Among serum parameters that may have been affected by dapagliflozin use, hemoglobin and hematocrit were significantly higher during the DAPA+ trial than during the DAPA− trial (14.1 ± 1.5 vs. 13.4 ± 1.3 g/dl, $P < 0.001$; 43.2% ± 3.6% vs. 40.4% ± 3.6%, $P < 0.001$, respectively; Table 5). Although fasting blood sugar tended to be lower during the DAPA+ trial than during the DAPA− trial (101.1 ± 17.5 vs. 110.2 ± 37.1 mg/dl, $P = 0.07$), hemoglobin A1c tended to be higher during the DAPA+ trial (5.64% ± 0.33% vs. 5.57% ± 0.39%, $P = 0.07$), probably because of the increase in hemoglobin levels during the trial. The uric acid level was significantly lower during the DAPA+ trial than during the DAPA− trial (5.09 ± 1.29 vs.

Table 1. Demographic and clinical characteristics of the study groups

Variables	All (n = 27)	Group 1 (n = 13)[a]	Group 2 (n = 14)[b]	P-value
Age (yr)	49.7 ± 12.1	49.2 ± 13.3	50.2 ± 11.4	0.84
Male/female (% male)	14/13 (52%)	5/8 (38%)	9/5 (64%)	0.26
Family history of ADPKD	4 (15%)	2 (15%)	2 (14%)	0.79
Hypertension (%)	22 (81%)	11 (85%)	11 (79%)	1
Use of RAS inhibitors (%)	18 (67%)	10 (77%)	8 (57%)	0.42
Tolvaptan (mg)	102.8 ± 24.2	95.2 ± 25.9	109.8 ± 21.1	0.12
Duration of tolvaptan treatment (years)	2.3 (0.5–6.2)	3.0 (0.3–6.1)	2.1 (1.2–5.8)	0.66
BMI (kg/m^2)	23.3 ± 2.9	24.0 ± 3.2	22.7 ± 2.5	0.25
Systolic BP (mmHg)	132.7 ± 12.5	131.8 ± 9.8	133.4 ± 14.7	0.77
Diastolic BP (mmHg)	84.2 ± 7.9	84.7 ± 6.3	83.8 ± 9.2	0.77
Mean BP (mmHg)	100.4 ± 8.5	100.4 ± 6.3	100.3 ± 10.3	0.97
Complications of ADPKD				
Liver cyst	23 (85%)	10 (77%)	13 (93%)	0.33
Brain aneurysm	2 (7%)	1 (8%)	1 (7%)	1
Valvular disease	7 (26%)	5 (38%)	2 (14%)	0.18
Mayo imaging classification, n (%)				0.36
1B	7 (26%)	2 (15%)	5 (36%)	
1C	15 (56%)	7 (54%)	8 (57%)	
1D	4 (15%)	3 (23%)	1 (7%)	
1E	1 (4%)	1 (8%)	0 (0%)	

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; BP, blood pressure; CCVD, cerebrovascular/cardiovascular disease; RAS, renin–angiotensin aldosterone system.
[a]Dapagliflozin treatment was initiated in group 1.
[b]Group 2 was initiated on treatment without dapagliflozin.

5.84 ± 1.19 mg/dl, $P < 0.001$). Among other exploratory parameters, serum total protein was significantly higher during the DAPA+ trial than during the DAPA− trial (7.22 ± 0.41 vs. 7.38 ± 0.42 g/dl, $P = 0.02$), whereas the other parameters did not differ significantly between the 2 trials.

Effect of Dapagliflozin on Safety Outcomes

These safety outcomes included 2 and 1 episodes of COVID-19 infection in the DAPA+ and DAPA− trials, respectively, and 1 episode of kidney cyst infection requiring hospitalization in the DAPA+ trial. However, pyuria was not observed during the infection, and a

Table 2. Biochemical and imaging data of the study groups

Variables	All patients (n = 27)	Group 1 (n = 13)[a]	Group 2 (n = 14)[b]	P-value
Kidney function				
$eGFR_{cr\text{-}cys}$ (ml/min per 1.73 m^2)	61.4 ± 25.3	59.7 ± 24.3	62.9 ± 27.0	0.76
$eGFR_{cr}$ (ml/min per 1.73 m^2)	53.8 ± 21.2	53.1 ± 22.9	54.5 ± 20.4	0.87
$eGFR_{cys}$ (ml/min per 1.73 m^2)	68.9 ± 30.2	66.4 ± 26.6	71.3 ± 34.0	0.68
Serum biochemical analyses				
AST level (IU/L)	21.6 ± 7.2	22.5 ± 5.5	30.8 ± 5.2	0.40
ALT level (IU/L)	20.2 ± 17.4	21.7 ± 11.7	16.8 ± 7.0	0.19
ALP level (U/L)	63.7 ± 23.1	60.1 ± 16.3	67.1 ± 28.2	0.44
γ-GTP level (IU/L)	40.9 ± 29.3	40.5 ± 33.9	41.4 ± 25.6	0.94
Sodium level (mEq/l)	140.8 ± 2.1	140.6 ± 1.5	141.0 ± 2.6	0.64
Potassium level (mEq/l)	4.18 ± 0.37	4.13 ± 0.29	4.23 ± 0.43	0.50
Albumin level (g/l)	4.29 ± 0.29	4.24 ± 0.30	4.34 ± 0.28	0.39
Fasting blood glucose level (mg/dl)	95.8 ± 11.9	97.1 ± 14.3	94.6 ± 9.4	0.59
LDL cholesterol level (mg/dl)	119.8 ± 31.0	130.4 ± 27.3	110.0 ± 31.8	0.09
HDL cholesterol level (mg/dl)	65.1 ± 19.1	65.2 ± 15.7	65.1 ± 22.5	0.98
Triglyceride level (mg/dl)	134.9 ± 99.8	107.1 ± 36.9	160.7 ± 131.0	0.17
Hemoglobin level (g/dl)	13.6 ± 1.4	13.8 ± 1.5	13.4 ± 1.3	0.39
Hematocrit level (%)	41.1 ± 3.5	42.0 ± 3.7	40.2 ± 3.2	0.18
Uric acid level (mg/dl)	6.19 ± 1.37	6.32 ± 0.84	6.38 ± 1.98	0.95
TKV (ml)	1400 (935–1480)	1414 (993–2369)	1012 (914–1126)	0.08
htTKV (ml/m)	838 (550–905)	822 (575–1381)	624 (516–675)	0.07

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; Cys, cystatin C; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; htTKV, height-adjusted total kidney volume; LDL, low-density lipoprotein; TKV, total kidney volume; γ-GTP, γ-glutamyl transpeptidase.
[a]Group 1 was initially treated with dapagliflozin.
[b]Group 2 was initially managed without dapagliflozin.

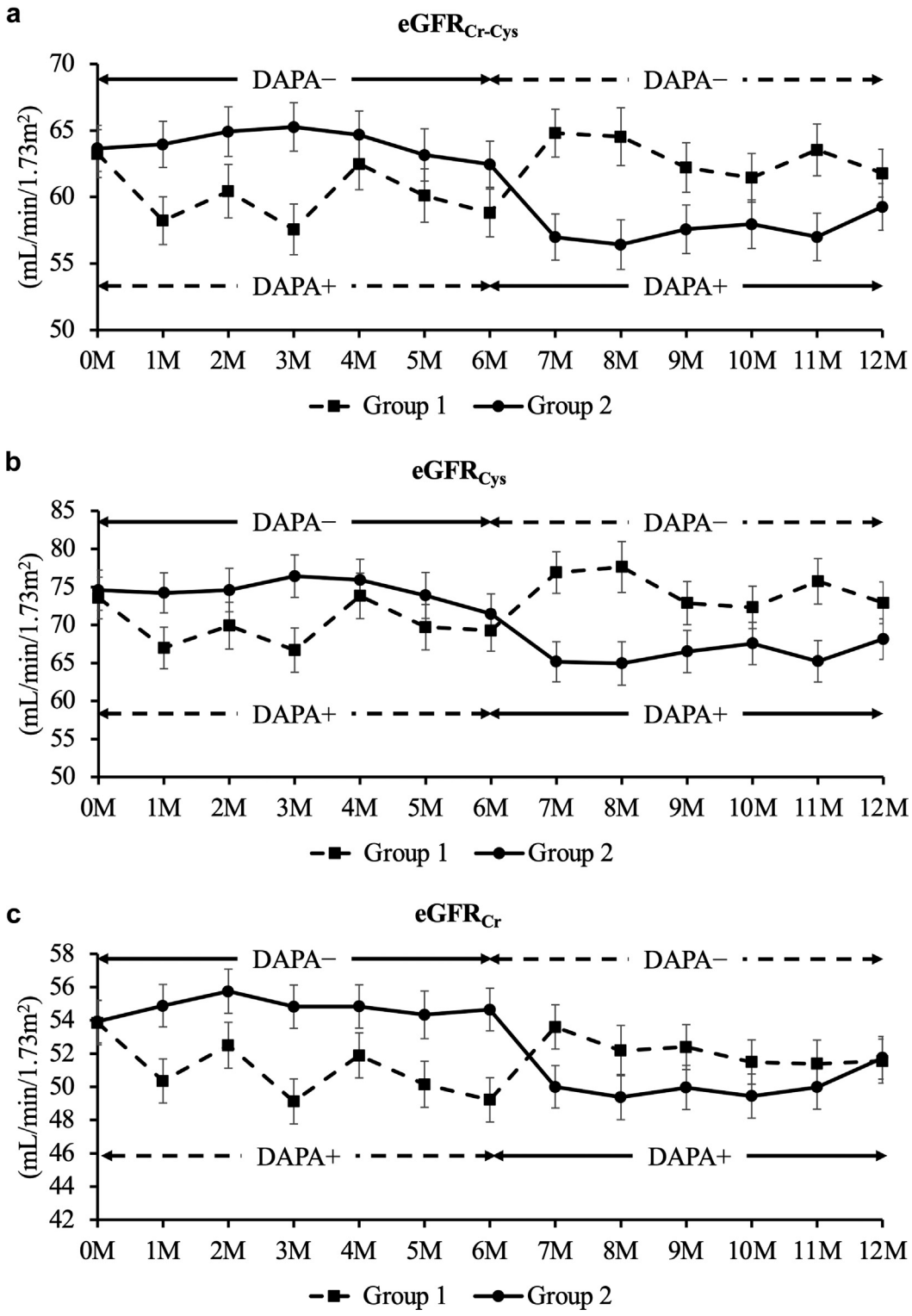

Figure 3. Mean change in the values of (a) $eGFR_{cr\text{-}cys}$, (b) $eGFR_{cys}$, and (c) $eGFR_{cr}$ during the whole study period in groups 1 and 2 from 0 to 12 months using linear mixed models. The model included fixed effects such as group (1 or 2), period (0–12 months), and 0-month eGFR, as well as an interaction term (period × group). Cr, creatinine; Cys, cystatin C; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate.

hematogenous route of infection was suspected. Thus, the causality between DAPA use and kidney cyst infection was considered less likely by the treating physician.

Although episodes of hypoglycemia were not systematically corrected, none of the patients developed hypoglycemia (blood glucose level $<$ 70 mg/dl) during routine blood sampling. A retrospective chart review

Table 3. Effect of dapagliflozin on eGFR slopes

Variables	Dapagliflozin+	Dapagliflozin−	*P*-value
$eGFR_{cr\text{-}cys}$ slope (ml/min per 1.73 m^2 per yr)	2.57 ± 7.88	−5.65 ± 9.57	0.002
$eGFR_{cr}$ slope (ml/min per 1.73 m^2 per yr)	1.03 ± 10.78	−3.66 ± 8.88	0.06
$eGFR_{cys}$ slope (ml/min per 1.73 m^2 per yr)	3.91 ± 11.40	−8.43 ± 13.44	0.003

Cr, creatinine; Cys, cystatin C; eGFR, estimated glomerular filtration rate.
These eGFR slopes were calculated by a linear regression model using eGFR values from 1 to 6 months of each trial, considering the initial decrease in eGFR observed with dapagliflozin administration.

revealed that renal cyst hemorrhage and subarachnoid hemorrhage were not recorded during the study period. Other events leading to hospitalization were also not recorded. In addition, 1 participant developed herpes simplex in the DAPA+ trial, 1 developed cystitis, and another developed epididymitis in the DAPA trial.

DISCUSSION

Although the underlying mechanism of SGLT2 inhibitor–associated renoprotection is still unknown, part of this effect has been attributed to a reduction in intraglomerular pressure because of glucose-induced osmotic diuresis and natriuresis associated with sodium delivery to the macula densa, resulting in afferent arteriolar constriction.[16] Clinically, SGLT2 inhibitors' renoprotective effect independent of diabetes has been reported primarily in patients whose urinary albumin-to-creatinine ratio is 200 to 5000,[4] whereas their impact on reducing the long-term eGFR slope has also been identified in patients with a urinary albumin-to-creatinine ratio < 30,[5] suggesting that there could be underlying mechanisms other than SGLT2 inhibitor–associated glomerular hyperfiltration attenuation.

In ADPKD, metabolic changes such as the switch to aerobic glycolysis and defective β-oxidation (the Warburg effect) have been implicated, resulting in decreased adenosine monophosphate-activated protein kinase activity and increased the mammalian target of rapamycin activity, in which hyperglycemia may promote cystogenesis and cyst growth.[17] Patients with ADPKD and type 2 diabetes have larger kidneys than those with ADPKD alone,[18] and obesity has been identified as an independent predictor of increased TKV growth and greater eGFR decline in the Halt Progression of Polycystic Kidney Disease Study A.[19] In addition, our analysis of the Japanese Polycystic Kidney Disease Registry revealed that a higher fasting blood sugar level was an independent predictor of a greater TKV change.[11] In these perspectives, ketosis-inducing interventions, including caloric restriction, intermittent fasting, and classic ketogenic diet consumption, may increase adenosine monophosphate-activated protein kinase activity and decrease mammalian target of rapamycin activity, leading to reduced cyst growth and kidney function amelioration in preclinical models.[20–24] Similarly, SGLT2 inhibitors induce ketosis and reductions in body weight and blood glucose levels, and these are likely to act synergistically to attenuate ADPKD progression.[25]

However, studies of SGLT2 inhibitors in animal models of ADPKD have yielded conflicting results. Although phlorizin, a competitive inhibitor of SGLT1 and SGLT2, hindered cyst epithelial proliferation in Han: Sprague–Dawley rats, dapagliflozin did not have such an effect.[26,27] In another study, dapagliflozin even worsened cyst volume growth and albuminuria in PCK rats.[28] In addition to the fact that neither model is based on PKD1 or PKD2 mutations, the vasopressin-stimulating effects of the SGLT2 inhibitors of concern may have led to the inconsistency of these findings.[6] Clinically, a single-arm retrospective study conducted in Japan revealed that dapagliflozin use was associated with a short-term decrease in eGFR and an increase in TKV in patients with ADPKD with or without tolvaptan.[29] Another single-arm observational study conducted in Japan suggested that dapagliflozin could be renoprotective while increasing the TKV.[30] Although they were both single-arm studies with small sample sizes and no control group, they still could not conclude a good or bad effect of dapagliflozin in patients with ADPKD. In contrast, the case of a patient with ADPKD receiving tolvaptan (at a maximum dose of 120 mg) in whom there was an additional renoprotective effect of dapagliflozin was described in a Japanese case report.[31]

In this regard, dapagliflozin was only administered in patients with ADPKD on tolvaptan (a V2 receptor antagonist), which may minimize the impact of vasopressin stimulation in this trial. Furthermore, the effect of dapagliflozin on patients was evaluated in an RCT (the most plausible design) in which the period without dapagliflozin was the control. Consequently, our trial indicated a possible beneficial effect of dapagliflozin on the eGFR slope and TKV change in patients with ADPKD receiving tolvaptan, although plasma vasopressin levels significantly increased with dapagliflozin use.

Several combined mechanisms were suspected in the beneficial effect of dapagliflozin that was demonstrated in our trial. First, dapagliflozin significantly reduced body weight and tended to decrease fasting blood sugar, which may benefit "metabolic reprograming" in patients with ADPKD, as described above. However, the level of albuminuria in our study participants was mild because of the nature of ADPKD; the effect of

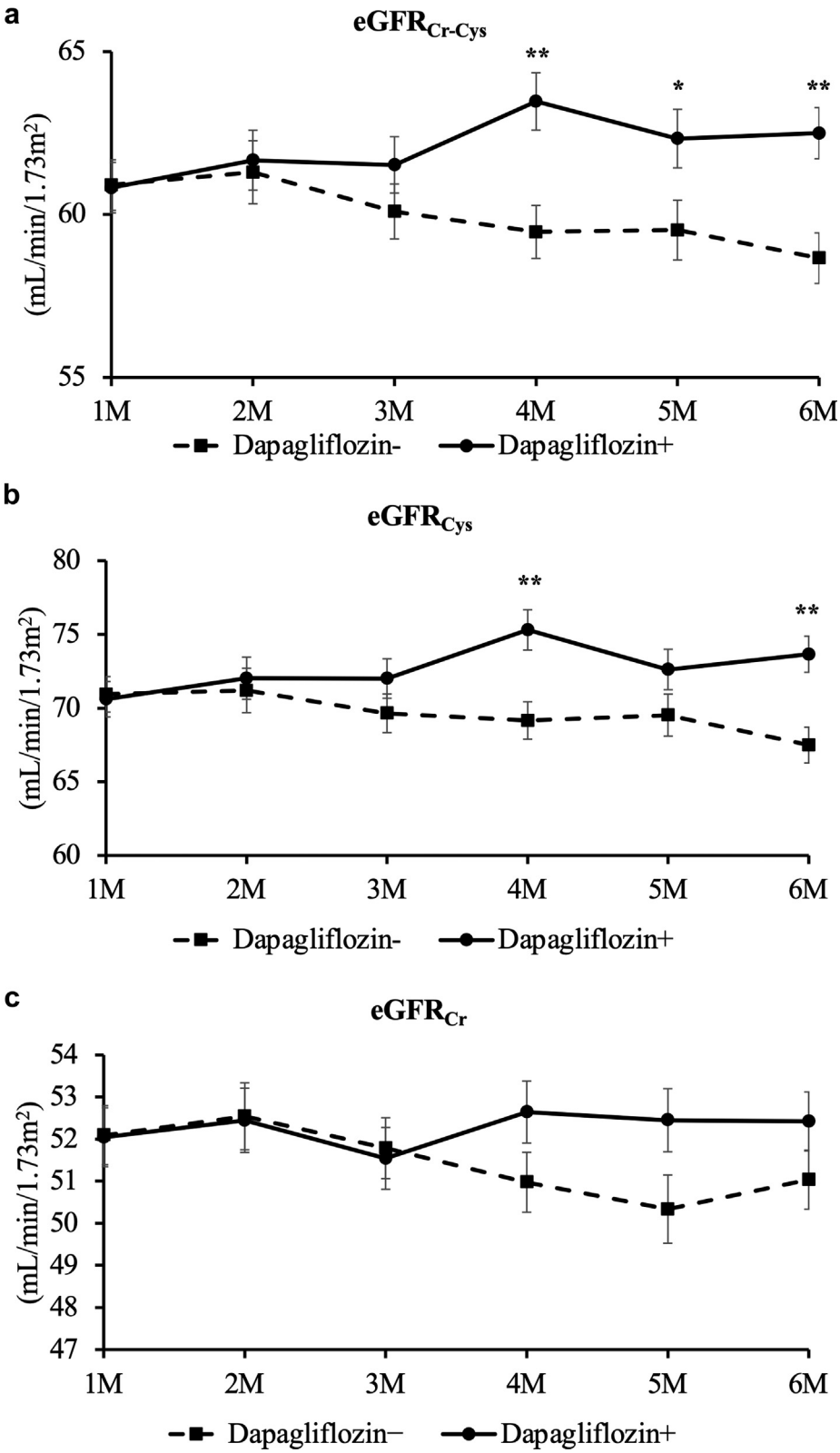

Figure 4. Mean change in the values of (a) $eGFR_{cr-cys}$, (b) $eGFR_{cys}$, and (c) $eGFR_{cr}$ during trials with and without dapagliflozin from 1 month to 6 months using linear mixed models. The model included fixed effects such as trial (with or without dapagliflozin), period (1–6 months), and 1-month eGFR, as well as an interaction term (period × trial). *P< 0.05; **P< 0.01 versus the trial without dapagliflozin. Bar represents mean ± SEM. cr, creatinine; cys, cystatin C, eGFR, estimated glomerular filtration rate.

dapagliflozin on albuminuria reduction was not observed in our trial, suggesting that the impact of dapagliflozin's attenuation of glomerular hyperfiltration on the overall beneficial effect of dapagliflozin observed in this study may be minimal. Second, dapagliflozin significantly increased serum

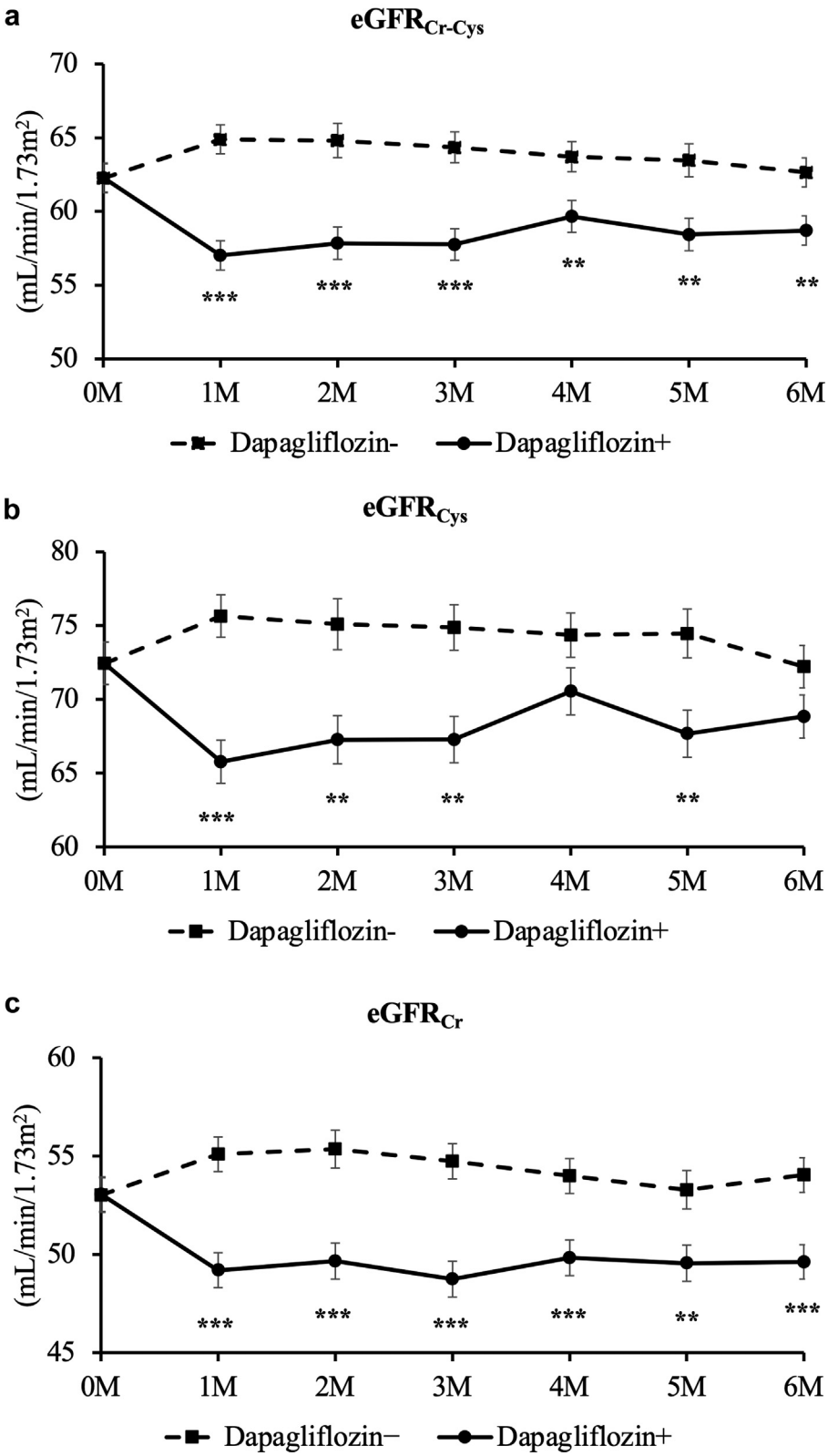

Figure 5. Mean change in the values of (a) $eGFR_{cr\text{-}cys}$, (b) $eGFR_{cys}$, and (c) $eGFR_{cr}$ during trials with and without dapagliflozin from 0 to 6 months using linear mixed models. The model included fixed effects, such as trial (with or without dapagliflozin), period (0–6 months), and 0-month eGFR as well as an interaction term, period × trial. $^{**}P< 0.01$; $^{***}P< 0.001$ versus the trial without dapagliflozin. Bar represents mean ± SEM. Cr, creatinine; Cys, cystatin C, eGFR, estimated glomerular filtration rate.

hemoglobin and hematocrit levels, which is important because anemia has been associated with CKD progression in patients with ADPKD.[32] Third, dapagliflozin use led to a significant reduction in serum uric acid levels, whereas high uric acid levels have been identified as independent predictors of kidney

Table 4. Effect of dapagliflozin on secondary outcomes

Variables	Dapagliflozin+	Dapagliflozin−	*P*-value
TKV change (%/6 mo)	−0.44 ± 4.91	5.04 ± 8.09	0.01
BW change (kg/6 mo)	−0.69 ± 1.42	0.56 ± 1.49	0.01
Urine volume (ml)	4,472 ± 1,389	4,328 ± 1,299	0.51
Urinary osmolarity (mOsm)	184.4 ± 51.1	165.3 ± 47.9	0.05
Urine albumin (mg/d)	36.4 ± 90.1	44.5 ± 86.0	0.62
L-FABP (μg/gCr)	5.25 ± 6.09	4.96 ± 5.92	0.39
Plasma vasopressin (pg/ml)	4.52 ± 2.02	3.58 ± 1.72	0.002
Systolic BP (mmHg)	123.0 ± 13.1	128.4 ± 10.1	0.04
Diastolic BP (mmHg)	81.9 ± 7.7	84.1 ± 7.7	0.31
Mean BP (mmHg)	95.6 ± 8.8	98.9 ± 7.6	0.13
Pulse pressure (mmHg)	51.9 ± 9.9	57.3 ± 5.8	0.08

BP, blood pressure; BW, body weight; L-FABP, liver-type fatty acid-binding protein; TKV, total kidney volume.
For variables, the values at 6 months of each trial were obtained.

function decline in patients with ADPKD.[33,34] Finally, given that hypertension is a universal risk factor for progression to ADPKD[35,36] and CKD, dapagliflozin significantly reduced systolic BP in this trial.

Nevertheless, this study had several limitations. First, this was a pilot trial with only a few participants who were followed-up for a short period, although an initial decrease in dapagliflozin was considered. In addition, although this study was an RCT, the crossover design may have introduced certain limitations, including the order and carryover effects, although both effects were statistically avoided. Considering these limitations, future large-scale, long-term RCTs with parallel designs are warranted. Second, because of the open-label design of this trial, the effects of several biases, including placebo effect and observer bias, could not be excluded, although the parameters assessed in this trial, including eGFR and TKV measured by third-party physicians, were relatively objective. Third, TKV or height-adjusted TKV was imbalanced between groups, although the difference was not significant. This might have affected the results, including eGFR slope and TKV change between the DAPA+ and DAPA− trials. However, the impact of this imbalance on the results was considered minimal because this was a crossover RCT, and all patients participated equally in the DAPA+ and DAPA− trials. In addition, the Mayo imaging classification, which predicts the progression of ADPKD, did not differ significantly between the groups. Fourth, as a prognostic tool of ADPKD, the PRO-PKD score was not evaluated. This is because genetic testing for patients with ADPKD is not covered by the health insurance in Japan and is not generally performed in clinical practice, and none of the participants had undergone genetic testing. Finally, although the dose of tolvaptan was maintained during the trial, other drugs, including antihypertensives, were adjusted by the treating physicians, which may have influenced the effect of dapagliflozin on participants' outcomes.

Table 5. Effect of dapagliflozin on exploratory outcomes

Variables	Dapagliflozin+	Dapagliflozin−	*P*-value
Hemoglobin (g/dl)	14.1 ± 1.5	13.4 ± 1.3	<0.001
Hematocrit (%)	43.2 ± 3.6	40.4 ± 3.6	<0.001
Fast blood sugar (mg/dL)	101.1 ± 17.5	110.2 ± 37.1	0.07
Hemoglobin A1c (%)	5.64 ± 0.33	5.57 ± 0.39	0.07
Uric acid (mg/dl)	5.09 ± 1.29	5.84 ± 1.19	<0.001
Total protein (g/dl)	7.38 ± 0.42	7.22 ± 0.41	0.02
Albumin (g/dl)	4.27 ± 0.27	4.20 ± 0.26	0.14
Sodium (mEq/l)	141.3 ± 2.0	140.5 ± 2.8	0.14
Potassium (mEq/l)	4.16 ± 0.39	4.20 ± 0.31	0.46
Total cholesterol (mg/dl)	213.6 ± 35.7	206.4 ± 31.3	0.13
HDL cholesterol (mg/dl)	65.9 ± 19.0	63.9 ± 17.2	0.2
Triglyceride (mg/dl)	135.8 ± 63.9	122.4 ± 57.8	0.18
LDL cholesterol (mg/dl)	120.6 ± 29.1	118.0 ± 27.2	0.53

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
For variables, the values at 6 months of each trial were obtained.

In conclusion, to the best of our knowledge, this is the first RCT to demonstrate the potential beneficial effects of dapagliflozin, an SGLT2 inhibitor, on the attenuation of ADPKD progression without compromising the tolerability to tolvaptan in patients with ADPKD. However, our results should be interpreted with caution given the aforementioned limitations. Notably, the results of this trial showed the additive efficacy and safety of dapagliflozin alone as co-therapy with tolvaptan. However, this trial did not evaluate the efficacy of dapagliflozin as monotherapy for ADPKD. Therefore, future parallel RCTs with larger sample sizes and longer follow-up periods are warranted to definitively demonstrate the effect of dapagliflozin on disease outcomes in patients with ADPKD receiving tolvaptan.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The authors would like to thank all participants for their dedication to this research project. The authors acknowledge Dr. Shigeaki Ohtsuki for technical and statistical assistance.

DATA AVAILABILITY STATEMENT

All data requests are submitted to the corresponding author for consideration. Access to anonymized data can be granted after a review.

AUTHOR CONTRIBUTIONS

The research idea and study design was developed by KU. Data acquisition was by KU, DK, T. Nag, EYH, RSh, RSu, EK, TKi, RT, TKa, TT, KH, TA, SY, JY, JI, MH and TKa. Data analysis/interpretation was done by KU and TNak.

Statistical analysis was done by KU and AY. Supervision or mentorship was done by TKa, YI, NW, IH and KH.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Safety outcomes systematically assessed during the trial.

CONSORT Checklist.

REFERENCES

1. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet*. 2019;393:919–935. https://doi.org/10.1016/S0140-6736(18)32782-X
2. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367:2407–2418. https://doi.org/10.1056/NEJMoa1205511
3. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med*. 2017;377:1930–1942. https://doi.org/10.1056/NEJMoa1710030
4. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446. https://doi.org/10.1056/NEJMoa2024816
5. The EMPA-KIDNEY Collaborative Group, Herrington WG, Staplin N, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–127. https://doi.org/10.1056/NEJMoa2204233
6. Marton A, Kaneko T, Kovalik JP, et al. Organ protection by SGLT2 inhibitors: role of metabolic energy and water conservation. *Nat Rev Nephrol*. 2021;17:65–77. https://doi.org/10.1038/s41581-020-00350-x
7. Gansevoort RT, van Gastel MDA, Chapman AB, et al. Plasma copeptin levels predict disease progression and tolvaptan efficacy in autosomal dominant polycystic kidney disease. *Kidney Int*. 2019;96:159–169. https://doi.org/10.1016/j.kint.2018.11.044
8. Kimura T, Washida N, Ohtsuki S, et al. A multi-center randomized controlled trial to investigate potential effects of exercise therapy on renal function stratified by renal disorders and renal pathology: beneficial or harmful effect in immunoglobulin A nephropathy. *Clin Exp Nephrol*. 2024;28:539–546. https://doi.org/10.1007/s10157-024-02461-2
9. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992. https://doi.org/10.1053/j.ajkd.2008.12.034
10. Horio M, Imai E, Yasuda Y, et al. GFR estimation using standardized serum cystatin C in Japan. *Am J Kidney Dis*. 2013;61:197–203. https://doi.org/10.1053/j.ajkd.2012.07.007
11. Uchiyama K, Mochizuki T, Shimada Y, et al. Factors predicting decline in renal function and kidney volume growth in autosomal dominant polycystic kidney disease: a prospective cohort study (Japanese Polycystic Kidney Disease registry: J-PKD). *Clin Exp Nephrol*. 2021;25:970–980. https://doi.org/10.1007/s10157-021-02068-x
12. Grizzle JE. The two-period change-over design and its use in clinical trials. *Biometrics*. 1965;21:467–480. https://doi.org/10.2307/2528104
13. Uchiyama K, Morimoto K, Washida N, et al. Effects of a remote patient monitoring system for patients on automated peritoneal dialysis: a randomized crossover controlled trial. *Int Urol Nephrol*. 2022;54:2673–2681. https://doi.org/10.1007/s11255-022-03178-5
14. Greene T, Ying J, Vonesh EF, et al. Performance of GFR slope as a surrogate end point for kidney disease progression in clinical trials: a statistical simulation. *J Am Soc Nephrol*. 2019;30:1756–1769. https://doi.org/10.1681/ASN.2019010009
15. Uchiyama K, Kitayama C, Yanai A, Ishibashi Y. The effect of trichlormethiazide in autosomal dominant polycystic kidney disease patients receiving tolvaptan: a randomized crossover controlled trial. *Sci Rep*. 2021;11:17666. https://doi.org/10.1038/s41598-021-97113-w
16. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int*. 2018;94:26–39. https://doi.org/10.1016/j.kint.2017.12.027
17. Chebib FT, Nowak KL, Chonchol MB, et al. Polycystic kidney disease diet: what is known and what is safe. *Clin J Am Soc Nephrol*. 2024;19:664–682. https://doi.org/10.2215/CJN.0000000000000326
18. Reed B, Helal I, McFann K, et al. The impact of type II diabetes mellitus in patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2012;27:2862–2865. https://doi.org/10.1093/ndt/gfr744
19. Nowak KL, You Z, Gitomer B, et al. Overweight and obesity are predictors of progression in early autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2018;29:571–578. https://doi.org/10.1681/ASN.2017070819
20. Warner G, Hein KZ, Nin V, et al. Food restriction ameliorates the development of polycystic kidney disease. *J Am Soc Nephrol*. 2016;27:1437–1447. https://doi.org/10.1681/ASN.2015020132
21. Nowak KL, Hopp K. Metabolic reprogramming in autosomal dominant polycystic kidney disease: evidence and therapeutic potential. *Clin J Am Soc Nephrol*. 2020;15:577–584. https://doi.org/10.2215/CJN.13291019
22. Torres JA, Kruger SL, Broderick C, et al. Ketosis ameliorates renal cyst growth in polycystic kidney disease. *Cell Metab*. 2019;30:1007–1023. https://doi.org/10.1016/j.cmet.2019.09.012
23. Hopp K, Catenacci VA, Dwivedi N, et al. Weight loss and cystic disease progression in autosomal dominant polycystic kidney disease. *iScience*. 2022;25:103697. https://doi.org/10.1016/j.isci.2021.103697
24. Oehm S, Steinke K, Schmidt J, et al. RESET-PKD: a pilot trial on short-term ketogenic interventions in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2023;38:1623–1635. https://doi.org/10.1093/ndt/gfac311
25. Patel DM, Dahl NK. Examining the role of novel CKD therapies for the ADPKD patient. *Kidney360*. 2021;2:1036–1041. https://doi.org/10.34067/KID.0007422020
26. Wang X, Zhang S, Liu Y, et al. Targeting of sodium-glucose cotransporters with phlorizin inhibits polycystic kidney disease progression in Han: SPRD rats. *Kidney Int*. 2013;84:962–968. https://doi.org/10.1038/ki.2013.199
27. Rodriguez D, Kapoor S, Edenhofer I, et al. Inhibition of sodium-glucose cotransporter 2 with dapagliflozin in Han: SPRD rats with polycystic kidney disease. *Kidney Blood Press Res*. 2015;40:638–647. https://doi.org/10.1159/000368540

28. Kapoor S, Rodriguez D, Riwanto M, et al. Effect of sodium-glucose cotransport inhibition on polycystic kidney disease progression in PCK rats. *PLoS One*. 2015;10:e0125603. https://doi.org/10.1371/journal.pone.0125603

29. Morioka F, Nakatani S, Uedono H, et al. Short-term dapagliflozin administration in autosomal dominant polycystic kidney disease-A retrospective single-arm case series study. *J Clin Med*. 2023;12:6341. https://doi.org/10.3390/jcm12196341

30. Yoshimoto M, Sekine A, Suwabe T, et al. Dapagliflozin treatment in patients with chronic kidney disease associated with autosomal dominant polycystic kidney disease. *Clin Kidney J*. 2024;17:sfae186. https://doi.org/10.1093/ckj/sfae186

31. Minatoguchi S, Hayashi H, Umeda R, et al. Additional renoprotective effect of the SGLT2 inhibitor dapagliflozin in a patient with ADPKD receiving tolvaptan treatment. *CEN Case Rep*. 2024;13:419–424. https://doi.org/10.1007/s13730-024-00859-1

32. Ushio Y, Kataoka H, Sato M, et al. Association between anemia and renal prognosis in autosomal dominant polycystic kidney disease: a retrospective study. *Clin Exp Nephrol*. 2020;24:500–508. https://doi.org/10.1007/s10157-020-01856-1

33. Torres VE, Grantham JJ, Chapman AB, et al. Potentially modifiable factors affecting the progression of autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:640–647. https://doi.org/10.2215/CJN.03250410

34. Kim H, Koh J, Park SK, et al. Baseline characteristics of the autosomal-dominant polycystic kidney disease sub-cohort of the KoreaN cohort study for outcomes in patients with chronic kidney disease. *Nephrology (Carlton)*. 2019;24:422–429. https://doi.org/10.1111/nep.13407

35. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective change in renal volume and function in children with ADPKD. *Clin J Am Soc Nephrol*. 2009;4:820–829. https://doi.org/10.2215/CJN.02810608

36. Schrier RW, Abebe KZ, Perrone RD, et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371:2255–2266. https://doi.org/10.1056/NEJMoa1402685