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RESEARCH LETTER

Glomerular Hypertrophy and Initial Dip in Estimated Glomerular Filtration Rate Following Dapagliflozin Administration

Akihiro Shimizu[1], Nobuo Tsuboi[2], Takaya Sasaki[2,3], Kotaro Haruhara[1], Kei Matsumoto[2], Hiroyuki Ueda[2], Shinya Yokote[2,3], Masahiro Okabe[4], Saeko Hatanaka[5], Masato Ikeda[1] and Takashi Yokoo[2]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University Kashiwa Hospital, Chiba, Japan; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [3]Division of Nephrology, Kawaguchi Municipal Medical Center, Kawaguchi, Japan; [4]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University Daisan Hospital, Tokyo, Japan; and [5]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University Katsushika Medical Center, Japan

Correspondence: Akihiro Shimizu, Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University Kashiwa Hospital, 163-1, Kashiwashita, Kashiwa 277-8567, Japan. E-mail: akihiro@jikei.ac.jp

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INTRODUCTION

The renoprotective effects of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, independent of their hypoglycemic actions, have attracted considerable attention in recent years.[1-4] Treatment with SGLT-2 inhibitors is accompanied by an acute reduction in the estimated glomerular filtration rate (eGFR), called the initial eGFR "dip," which may result from a decrease in intraglomerular pressure via inhibition of excessive action of tubuloglomerular feedback.[5,6] In clinical trials of SGLT-2 inhibitors, the initial eGFR dip was followed by long-term stabilization of kidney function decline.[1-4] One study showed that patients with a greater initial dip had a reduced GFR slope during the long-term clinical course.[7] However, the association between the initial dip after SGLT-2 inhibitor administration and the histopathological or morphometrical findings identified in kidney biopsy specimens has not been analyzed in the clinical setting.

Glomerular enlargement is an important adaptive response that ensures an optimal surface area of the glomerular capillaries and maintains the filtration function of the kidney. However, conditions such as obesity, diabetes, and chronic kidney disease (CKD) can compromise this regulatory system because of various underlying mechanisms.[8,9,S1,S2]

Dapagliflozin is an SGLT-2 inhibitor that can improve the long-term kidney outcomes in patients with CKD with or without diabetes.[2] This study investigated whether morphometric nephron-level parameters (i.e., glomerular volume and glomerular density) are associated with the initial eGFR dip after dapagliflozin administration in patients with non–diabetic kidney disease with CKD who have undergone kidney biopsy. The details of study methods are shown in the Supplementary Methods and Supplementary Figure S1.

RESULTS

The selection for patients is shown in Supplementary Figure S2. The study included 60 patients (mean age, 52 years; 71.7% male; median eGFR, 52.0 ml/min per 1.73 m^2; median urinary protein excretion rate was 1.13 g/day or g/g Cr). The initial visit took place a median of 49 days after dapagliflozin administration (Supplementary Table S1). In all, 57 patients (95.0%) had been treated with renin-angiotensin-aldosterone system inhibitors before dapagliflozin administration. The median duration from kidney biopsy to initiation of dapagliflozin was 651 days. Clinical findings at the time of biopsy and before dapagliflozin administration are compared in Supplementary Table S2. IgA nephropathy was the most common kidney biopsy diagnosis, affecting 28 patients (47%). Supplementary Table S3 shows a comparison of the clinical data at the time of dapagliflozin administration and at the first

Table 1. Comparisons of clinical findings among quartiles subdivided according to glomerular volume

Characteristics	Overall	Glomerular volume				*P* value
		Q1	Q2	Q3	Q4	
Number of patients, *n*	60	15	15	15	15	
Duration from start of DAPA, days	49 (28–63)	49 (28–63)	56 (28–70)	42 (35–77)	56 (28–63)	0.93
Male sex	43 (72)	9 (60)	9 (60)	11 (73)	14 (93)	0.03
Age, yr	52 ± 15	49 ± 14	56 ± 16	49 ± 17	54 ± 17	0.52
BMI, kg/m^2	25.2 (22.9–29.8)	22.9 (21.3–27.7)	24.8 (22.4–34.4)	28.0 (24.1–31.5)	26.6 (24.9–27.5)	0.14
Hypertension	43 (72)	10 (67)	11 (73)	8 (53)	14 (93)	0.25
Diabetes	8 (13)	1 (7)	3 (20)	2 (13)	2 (13)	0.73
Systolic BP, mm Hg	125 (119–134)	125 (116–132)	130 (120–139)	123 (113–131)	125 (123–133)	0.50
Diastolic BP, mm Hg	78 (70–84)	76 (69–82)	75 (70–84)	78 (65–84)	80 (68–86)	0.89
Hemoglobin, g/dl	14.1 ± 2.0	13.6 ± 1.9	14.0 ± 2.7	14.1 ± 1.7	14.6 ± 1.4	0.57
Serum Cr, mg/dl	1.17 (0.88–1.51)	1.32 (0.77–1.71)	1.11 (0.79–1.35)	1.04 (0.77–1.57)	1.25 (1.12–1.44)	0.50
eGFR, ml/min per 1.73 m^2	52.0 (37.6–66.1)	43.9 (34.7–68.6)	52.3 (38.0–63.1)	60.8 (36.1–78.9)	51.7 (37.6–59.2)	0.78
Proteinuria, g/g Cr or g/day	1.13 (0.62–2.18)	1.10 (0.84–2.00)	0.84 (0.26–2.00)	2.01 (0.76–3.28)	1.41 (0.49–3.83)	0.21
Uric acid, mg/dl	6.2 (5.5–7.4)	6.3 (5.6–7.3)	6.0 (5.3–7.2)	5.8 (5.3–7.2)	7.2 (5.5–7.6)	0.60
HbA1c, %	5.8 (5.7–6.3)	5.7 (5.3–5.8)	5.8 (5.7–7.2)	5.9 (5.8–6.3)	5.8 (5.6–7.0)	0.13
DAPA initial dose of 10 mg/day	46 (77)	12 (80)	12 (80)	12 (80)	10 (67)	0.41
RAAS inhibitor use	57 (95)	15 (100)	14 (93)	13 (87)	15 (100)	0.79
Diuretic use	7 (12)	1 (7)	2 (13)	1 (7)	3 (20)	0.37
Time from kidney biopsy to initiation of DAPA, days	651 (246–1385)	475 (328–1056)	489 (190–1448)	560 (384–1311)	1024 (239–1546)	0.92

Data are presented as median (interquartile range), *n* (%), or mean ± standard deviation.
BMI, body mass index; BP, blood pressure; Cr, creatinine; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; Q, quartile; RAAS, renin-angiotensin-aldosterone system.

outpatient visit after dapagliflozin administration. Seventeen patients (28.3%) showed an initial eGFR dip, defined as a decrease from the baseline value ≥10%. The initial dip in eGFR was significantly correlated with the rate of proteinuria reduction (Supplementary Figure S3).

Clinical findings (Table 1) and histopathological and morphometric data (Supplementary Table S4) were compared among quartiles of patients subdivided according to glomerular volume. As glomerular volume increased, glomerular density decreased. Figure 1 shows comparisons of the frequency of an initial eGFR dip after dapagliflozin administration among quartiles of patients subdivided according to glomerular volume and glomerular density. As volume increased, the percentage of patients with an initial eGFR dip increased. Among the glomerular density quartiles, there were no differences in the percentages of patients with an eGFR dip. Quartiles of patients subdivided by global glomerulosclerosis and interstitial fibrosis/tubular atrophy showed no significant differences in the frequency of an initial dip (Supplementary Figure S4).

Supplementary Table S5 shows the results of univariate and multivariate logistic analyses of the association between the initial dip and the glomerular volume quartiles. In univariable analysis, glomerular volume was associated with the initial dip after dapagliflozin administration. In multivariable analyses of 2 models consisting of different confounding factors, glomerular volume was still an independent variable associated with the initial dip.

Sensitivity analyses were performed in patients with a cortical area ≥ 4 mm^2 in the biopsy specimen ($n = 53$), those with a ≤ 4 year duration from kidney biopsy to dapagliflozin administration ($n = 49$), and those without diabetes ($n = 52$). The results were similar to those identified in the original study population (Supplementary Figure S5, Supplementary Tables S6–S8).

DISCUSSION

We investigated the association between glomerular volume and the initial eGFR dip in patients with CKD treated with the SGLT-2 inhibitor dapagliflozin. Patients with a larger glomerular volume had a higher frequency of an initial eGFR dip ≥ 10% compared with the baseline value.

In a *post hoc* analysis of the DAPA-CKD trial,[7] the long-term kidney function decline in patients with an initial dip ≥ 10% after 2 weeks of dapagliflozin treatment was slower than that of patients who had an initial dip < 10%. Therefore, an initial dip ≥ 10% is considered a surrogate for a favorable long-term kidney prognosis. Notably, most patients enrolled in recent clinical trials of SGLT-2 inhibitors had previously been treated with renin-angiotensin-aldosterone

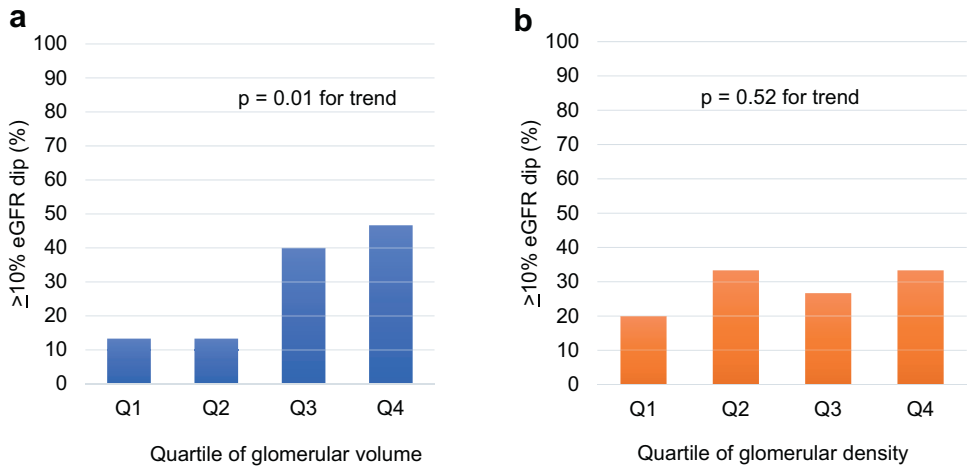

Figure 1. Frequency of patients with an initial eGFR dip ≥ 10% following dapagliflozin administration. Comparisons of frequency of patients with an initial eGFR dip ≥ 10% following dapagliflozin administration among quartiles of patients subdivided according to (a) glomerular volume and (b) glomerular density. eGFR, estimated glomerular filtration rate.

system inhibitors,[7,S3–S5] and SGLT-2 inhibitors may therefore improve glomerular hyperfiltration through tubuloglomerular feedback in concert with the intraglomerular pressure lowering effects of renin-angiotensin-aldosterone system inhibitors.[S6] Our results are in line with this series of findings, as most patients had received renin-angiotensin-aldosterone system inhibitors before dapagliflozin. In addition, the initial eGFR dip was greater in patients with a large glomerular volume whose intraglomerular pressure was considered relatively high. These results indicate that patients with glomerular hypertrophy may receive greater benefit from treatment with SGLT-2 inhibitors.

By contrast, chronic histopathological lesions of the kidney, such as global glomerulosclerosis and interstitial fibrosis/tubular atrophy, were not associated with an increased incidence of an initial dip after dapagliflozin administration. These differences imply that global glomerulosclerosis and interstitial fibrosis/tubular atrophy arise from a variety of kidney injury mechanisms other than hyperfiltration and that glomerular hypertrophy, which may directly reflect hyperfiltration, is more closely associated with the initial dip than these lesions representing chronic renal scarring.

In this study, the glomerular density in kidney biopsy specimens was also analyzed as a candidate parameter. Recent literature suggests that glomerular density may indicate both the total nephron count and nephron hypertrophy.[S7–S12] Notably, we did not find an association between glomerular density and the initial eGFR dip. Furthermore, multivariate analysis showed that the relationship between glomerular volume and the initial dip was independent of glomerular density. These results imply that glomerular volume is a more suitable surrogate marker than glomerular density with respect to the initial eGFR dip after administration of SGLT-2 inhibitors.

This study had several important limitations. First, the sample size was small, which may have influenced the statistical power. Second, the data from only 2 time points were analyzed; we therefore cannot prove a causal relationship between the initial dip and subsequent long=term kidney functional outcomes. Third, the patient population was not homogeneous. Fourth, we cannot exclude the possibility that the changes in the eGFR were due to individual differences in disease progression. Lastly, the use of needle biopsy specimens for this analysis have introduced a sampling bias.[S13]

In conclusion, our results demonstrate that glomerular volume measurement before SGLT-2 inhibitor administration may be useful to predict the subsequent initial eGFR dip. Our findings imply that patients presenting with glomerular hyperfiltration may benefit from treatment with SGLT-2 inhibitors. To confirm our present results, further studies with larger cohorts that allow for appropriate multivariate adjustment for confounding factors are needed.

DISCLOSURES

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Representative light microscopy findings from kidney biopsies.

Figure S2. Flowchart of patient selection.

Figure S3. Correlation between initial dip in eGFR and the change in proteinuria after starting of dapagliflozin.

Figure S4. Frequency of an initial eGFR dip $\geq$ 10% following dapagliflozin administration.

Figure S5. Sensitivity analysis on the frequency of an initial eGFR dip $\geq$ 10% following dapagliflozin administration among different glomerular volume quartiles.

Table S1. Baseline clinical characteristics of patients before dapagliflozin administration.

Table S2. Comparison of variables at the time of biopsy diagnosis and immediately before dapagliflozin administration.

Table S3. Comparison of clinical findings at baseline and at the first outpatient visit following dapagliflozin administration ($n = 60$).

Table S4. Comparison of histopathological and morphometric findings among quartiles divided according to glomerular volume.

Table S5. Univariable and multivariable logistic regression analyses of glomerular volume quartiles or continuous variables associated with >10% initial eGFR dip following dapagliflozin administration.

Table S6. Univariate and multivariate logistic regression analyses of quartiles or continuous variables of glomerular volume associated with an initial eGFR dip $\geq$ 10% following dapagliflozin treatment in patients with a cortical area $\geq$ 4 mm^2 ($n = 53$).

Table S7. Univariate and multivariate logistic regression analyses of glomerular volume quartiles or continuous variables associated with an initial eGFR dip $\geq$ 10% following dapagliflozin treatment in patients with a duration from kidney biopsy to dapagliflozin administration $\leq$ 4 years ($n = 49$).

Table S8. Univariate and multivariate logistic regression analyses of glomerular volume quartiles or continuous variables associated with an initial eGFR dip $\geq$ 10% following dapagliflozin treatment in patients without diabetes ($n = 52$).

STROBE Checklist

REFERENCES

1. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–127. https://doi.org/10.1056/NEJMoa2204233
2. 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
3. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306. https://doi.org/10.1056/NEJMoa1811744
4. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334. https://doi.org/10.1056/NEJMoa1515920
5. Thomson SC, Rieg T, Miracle C, et al. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. *Am J Physiol Regul Integr Comp Physiol*. 2012;302:75–83. https://doi.org/10.1152/ajpregu.00357.2011
6. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129:587–597. https://doi.org/10.1161/CIRCULATIONAHA.113.005081
7. Jongs N, Chertow GM, Greene T, et al. Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor dapagliflozin in patients with CKD. *J Am Soc Nephrol*. 2022;33:2094–2107. https://doi.org/10.1681/ASN.2022030306
8. Denic A, Elsherbiny H, Mullan AF, et al. Larger nephron size and nephrosclerosis predict progressive CKD and mortality after radical nephrectomy for tumor and independent of kidney function. *J Am Soc Nephrol*. 2020;31:2642–2652. https://doi.org/10.1681/ASN.2020040449
9. Kataoka H, Ohara M, Honda K, Mochizuki T, Nitta K. Maximal glomerular diameter as a 10-year prognostic indicator for IgA nephropathy. *Nephrol Dial Transplant*. 2011;26:3937–3943. https://doi.org/10.1093/ndt/gfr139