




Switching from low-dose thiazide diuretics to sodium–glucose cotransporter 2 inhibitor improves various metabolic parameters without affecting blood pressure in patients with type 2 diabetes and hypertension

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Keywords

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ABSTRACT

Aims/Introduction: Sodium–glucose cotransporter 2 (SGLT2) inhibitors function to increase urinary glucose excretion and improve glycemic control in individuals with type 2 diabetes mellitus. SGLT2 inhibitors, as well as diuretics, increase urinary volume, which leads to the reduction of blood pressure. The aim of the present study was to compare the effects of SGLT2 inhibitor and thiazide diuretic on blood pressure, metabolic parameters and body mass composition.

Materials and Methods: A total of 31 participants were enrolled in the present study. We switched from thiazide diuretics to an SGLT2 inhibitor, ipragliflozin, in participants with type 2 diabetes and hypertension whose blood pressure was controlled with thiazide diuretics. Three months after the switch, we evaluated the effects of such switching on blood pressure, various metabolic parameters and body mass composition.

Results: There was no significant difference in blood pressure from baseline to 3 months later. However, glycated hemoglobin, fasting plasma glucose and uric acid were significantly decreased after the switch. Body mass index and visceral fat area were also significantly reduced after the switch. Furthermore, urinary albumin excretion was also significantly decreased after the switch.

Conclusions: Switching from thiazide diuretic to an SGLT2 inhibitor, ipragliflozin, markedly improved various metabolic parameters and body mass composition without affecting blood pressure in participants with type 2 diabetes and hypertension.

INTRODUCTION

It is well known that both type 2 diabetes and hypertension lead to the onset of cardiovascular and cerebrovascular events through the progression of atherosclerosis¹, and that hypertension is very often complicated with type 2 diabetes². To control not only diabetes but also hypertension is extremely important in type 2 diabetes patients with hypertension. The American

Diabetes Association, the European Society of Hypertension and the Japanese Society of Hypertension recommend the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs) as a first choice for type 2 diabetes patients with hypertension^{3–5}. These drugs decrease not only the risk of macroangiopathy^{6–8}, but also other diabetic complications^{9–13}. Furthermore, these drugs also delay the onset of diabetes^{14–16}.

In the case of insufficient blood pressure control using these drugs, increasing the dose of each drug, or additional use of

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calcium channel blockers (CCBs) or a small amount of thiazide diuretic is recommended as a next step⁵. CCB has a relatively strong blood pressure-lowering effect and reduces the risk of cardiovascular disease^{14,17,18}. It has been reported that thiazide diuretics decrease cardiovascular events^{14,19,20}. However, thiazide diuretics worsen glucose and lipid metabolism, and they cause hypokalemia, hypomagnesemia and hyperuricemia^{14,19,21}. Some reports showed that thiazide diuretics did not decrease cardiovascular events because of exacerbated glucose and lipid metabolism²².

Sodium–glucose cotransporter 2 (SGLT2) inhibitor is a novel class of oral anti-hyperglycemic drug. SGLT2 is expressed primarily in the S1 segment of the proximal tubule and accounts for approximately 90% of reabsorbed glucose²³. Treatment with SGLT2 inhibitor leads to improved glycemic control, caloric loss and reduced bodyweight through an insulin-independent manner²⁴. This causes an osmotic diuresis and mild natriuresis, which leads to the reduction in plasma volume and visceral fat mass reduction, and the decrease of blood pressure. Clinical trials have shown a significant reduction from baseline in both systolic and diastolic blood pressure after administration of SGLT2 inhibitors^{25–28}. Although the blood pressure-lowering effects of SGLT2 inhibitors are already established²⁹, guidance is required on how to use these agents in patients already receiving the most commonly prescribed antihypertensive regimens.

In the present study, we switched from thiazide diuretics to an SGLT2 inhibitor, ipragliflozin, in participants with type 2 diabetes and hypertension whose blood pressure was controlled with thiazide diuretics, and evaluated the effects of such switching on blood pressure, glycemic control, other metabolic parameters and body mass composition.

METHODS

Study population and patient preparation

The present study was retrospectively carried out with outpatients in the division of Diabetes, Endocrinology and Metabolism in Kawasaki Medical School from January to September in 2016. Enrolled patients met the following criteria: (i) glycated hemoglobin (HbA1c) > 6.0%; and (ii) having already taken thiazide diuretics for hypertension with ARB or angiotensin-converting enzyme inhibitors and/or CCB in participants with type 2 diabetes. In addition, the participants were those who fulfilled the following criteria: (i) without severe renal dysfunction; (ii) without severe liver dysfunction; (iii) without infectious disease, malignancy or various endocrine diseases; and (iv) not using steroid drugs. We switched from only thiazide diuretics to 50 mg of the SGLT2 inhibitor, ipragliflozin. We compared the blood pressure, metabolic parameters and body composition using InBody770 (InBody Japan[®], Tokyo, Japan) before and after 3 months from switching. A total of 31 (22 men, 9 women) participants were enrolled in the present study. As it is well known that blood pressure is substantially influenced by temperature, and that there is seasonal variation in HbA1c

levels, as a control we used the data of individuals ($n = 19$) who used thiazide diuretics as an antihypertensive drug, but did not switch to an SGLT2 inhibitor in the same observation period as the switching group. In addition, the start month ratio of the non-switching group corresponded to that of the switching group using a random number table in order to avoid the possible influence of other factors. The registration number of UMIN was R000033348. The study protocol was approved by the institutional review board of Kawasaki Medical School (No. 2540), and the study was carried out in accordance with the Declaration of Helsinki, and we provided public information on the study via the Internet, instead of obtaining informed consent from each patient. We carried out data collection for variables such as type of medication and smoking status, as well as biochemical data.

Statistical analysis

All analyses were carried out by using JMP version 9 (SAS Institute Inc., Cary, NC, USA). The paired t -test and Wilcoxon signed-rank test were used for the comparison between two paired groups. Student's t -test and Mann–Whitney U -tests were used for the difference between the switching group and non-switching group with $P < 0.05$ regarded as significant. The results were expressed as mean \pm standard deviation. To examine which factors are associated with change in (Δ) blood pressure, we carried out Spearman's rank correlation coefficient test. Furthermore, to examine which factors independently determine Δ blood pressure, we carried out multiple regression analysis.

RESULTS

Clinical characteristics in the study participants

A total of 31 (22 men, 9 women) participants were enrolled in the present study. The characteristics of the study participants at baseline were as follows: age 68.9 ± 8.5 years old; body mass index (BMI) 27.7 ± 5.2 kg/m²; duration of diabetes 16.2 ± 9.4 years; HbA1c $7.1 \pm 1.0\%$; and fasting plasma glucose 141.2 ± 42.8 mg/dL. The frequencies of diabetic complications were as follows: neuropathy 51.6%; retinopathy 19.4%; and nephropathy (urinary albumin ≥ 30 mg/gCr) 51.6%. The frequencies of ischemic heart disease and stroke were 3.2 and 19.4%, respectively. The insulin and glucagon-like peptide-1 receptor agonist usage rate were both 9.7%, and usage rate of dipeptidyl peptidase-4 inhibitor, metformin, thiazolidine, sulfonyleurea, glinide and α -glucosidase inhibitor were 58.1, 64.5, 54.8, 29.3, 12.9 and 16.1%, respectively. The usage rate of angiotensin receptor blocker, calcium channel blocker, statin, fibrates and antihyperuricemics were 96.8, 71.0, 58.1, 12.9 and 12.9%, respectively. The breakdown and dosage of the thiazide diuretics were hydrochlorothiazide (67.7%, 7.7 ± 2.7 mg), indapamide (22.6%, 0.9 ± 0.2 mg) and trichlormethiazide (9.7%, 1.3 ± 0.6 mg). The ARB and CCB usage rates were 96.8 and 71.0%, respectively, and there were no dosage changes in any drugs for 3 months after switching.

Evaluation of various metabolic parameters after switching from thiazide diuretics to SGLT2 inhibitor ipragliflozin

The differences in all parameters from baseline to 3 months later are shown in Table 1. Surprisingly, 3 months after the switch, the mean systolic and diastolic blood pressure did not significantly change from baseline (from 131.2 ± 12.9 mmHg to 132.1 ± 13.2 mmHg; from 74.5 ± 9.9 mmHg to 75.8 ± 11.2 mmHg). Heart rate also did not change from baseline to 3 months later (from 71.0 ± 16.3 b.p.m. to 68.0 ± 11.8 b.p.m.; Table 1). HbA1c and fasting blood glucose levels were significantly improved 3 months later compared with baseline (from 7.1 ± 1.0% to 6.7 ± 0.9%, *P* < 0.0001; from 141.2 ± 42.8 mg/dL to 118.9 ± 26.5 mg/dL, *P* < 0.005), and

fasting insulin level was significantly reduced 3 months later compared with baseline (from 8.1 ± 5.5 μU/mL to 6.4 ± 4.4 μU/mL, *P* < 0.01). We believe that such phenomena were due to the increase of urinary glucose excretion by ipragliflozin, which led to the decline of insulin demand. A significant reduction was observed in BMI (from 27.7 ± 5.2 kg/m² to 27.2 ± 5.2 kg/m², *P* < 0.005). Switching from thiazides to an SGLT2 inhibitor also resulted in improvement of lipid profile. High-density lipoprotein cholesterol was significantly increased 3 months later compared with baseline (from 51.6 ± 13.8 mg/dL to 55.8 ± 15.9 mg/dL, *P* < 0.05). In contrast, there were no significant changes in low-density lipoprotein cholesterol and triglyceride from baseline to 3 months later (from

Table 1 | Comparison of various values between at baseline and 3 months later in the switching and non-switching group

Parameter	Baseline			3 months				
	Switching: A	Non-switching: B	<i>P</i> (A vs B)	Switching: C	Non-switching: D	<i>P</i> (C vs D)	<i>P</i> (A vs C)	<i>P</i> (B vs D)
Age (years)	68.9 ± 8.5	70.5 ± 8.9	NS	-	-	-	-	-
DM duration (years)	16.2 ± 9.4	19.2 ± 10.2	NS	-	-	-	-	-
BMI (kg/m ²)	27.7 ± 5.2	25.9 ± 3.9	NS	27.2 ± 5.2	25.6 ± 4.0	NS	<0.0005	<0.04
Bodyweight (kg)	74.5 ± 19.4	66.1 ± 9.4	NS	73.1 ± 19.4	65.2 ± 9.3	NS	<0.0001	<0.03
HR (b.p.m.)	71.0 ± 16.3	71.3 ± 13.6	NS	68.0 ± 11.8	76.0 ± 12.4	NS	NS	NS
SBP (mmHg)	131.2 ± 12.9	134.7 ± 14.7	NS	132.1 ± 13.2	132.6 ± 18.8	NS	NS	NS
DBP (mmHg)	74.5 ± 9.9	71.1 ± 8.7	NS	75.8 ± 11.2	69.7 ± 11.1	NS	NS	NS
Hemoglobin (g/dL)	12.9 ± 1.6	13.0 ± 1.8	NS	13.6 ± 1.8	12.7 ± 1.6	NS	<0.0001	<0.02
Hematocrit (%)	39.1 ± 4.3	40.0 ± 4.7	NS	41.7 ± 4.9	38.9 ± 4.3	NS	<0.0001	<0.02
HbA1c (%)	7.1 ± 1.0	6.6 ± 0.6	<0.05	6.7 ± 0.9	6.5 ± 0.7	NS	<0.0001	NS
FPG (mg/dL)	141.2 ± 42.8	-	-	118.9 ± 26.5	-	-	<0.005	-
Insulin (μU/mL)	8.1 ± 5.5	-	-	6.4 ± 4.4	-	-	<0.01	-
Serum Na (mEq/L)	139.5 ± 2.1	138.6 ± 1.8	NS	139.6 ± 2.1	138.8 ± 2.0	NS	NS	NS
Serum K (mEq/L)	4.2 ± 0.3	4.2 ± 0.3	NS	4.3 ± 0.5	4.3 ± 0.4	NS	<0.05	NS
UA (mg/dL)	6.0 ± 1.3	5.7 ± 1.3	NS	5.0 ± 1.1	5.9 ± 1.4	<0.05	<0.0001	NS
Cre (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	NS	0.9 ± 0.2	0.9 ± 0.2	NS	NS	NS
BUN (mg/dL)	18.3 ± 5.3	18.6 ± 6.9	NS	18.8 ± 5.4	17.7 ± 5.5	NS	NS	NS
eGFR (mL/min/1.73 m ²)	67.9 ± 14.4	67.3 ± 22.4	NS	66.31 ± 5.2	67.8 ± 26.3	NS	NS	NS
LDL-C (mg/dL)	92.0 ± 23.6	84.5 ± 24.1	NS	92.4 ± 23.5	91.2 ± 24.3	NS	NS	<0.01
HDL-C (mg/dL)	51.6 ± 13.8	53.8 ± 16.8	NS	55.8 ± 15.9	56.7 ± 20.5	NS	<0.05	NS
TG (mg/dL)	102.8 ± 51.4	-	-	89.5 ± 47.1	-	-	NS	-
Ketone body (μmol/L)	222.1 ± 234.0	-	-	292.0 ± 238.2	-	-	NS	-

Urinalysis	Switching (baseline)	Switching (3 months)	<i>P</i> -value
Urinary Na (mEq/L)	120.6 ± 42.3	114.6 ± 33.5	NS
Urinary Alb (mg/g.Cr)	165.2 ± 335.5	108.8 ± 190.4	<0.05
Urinary NAG (IU/L)	12.9 ± 14.1	8.6 ± 5.8	<0.05
Urinary glucose (mg/dL)	112.8 ± 330.5	2624.0 ± 1419.4	<0.0001

InBody	Switching (baseline)	Switching (3 months)	<i>P</i> -value
Body fat mass (kg)	25.5 ± 12.1	24.4 ± 12.4	<0.0005
Visceral fat area (cm ²)	121.1 ± 51.4	115.5 ± 49.6	<0.005
Skeletal muscle mass (kg)	26.9 ± 6.2	26.8 ± 6.4	NS

Data presented as mean ± standard deviation. BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; K, potassium; Na, sodium; NAG, N-acetyl-β-D-glucosaminidase; NS, not significant; SBP, systolic blood pressure; TG, triglyceride; UA, uric acid.

92.0 ± 23.6 mg/dL to 92.4 ± 23.5 mg/dL; from 102.8 ± 51.4 mg/dL to 89.5 ± 47.1 mg/dL). Furthermore, the dramatic improvement was observed in uric acid levels after the switching from thiazides diuretics to an SGLT2 inhibitor (from 6.0 ± 1.3 mg/dL to 5.0 ± 1.1 mg/dL, $P < 0.0001$). Amazingly, the amount of urinary sodium excretion was kept at the same level despite switching from thiazides diuretics (from 120.6 ± 42.3 mEq/L to 114.6 ± 33.5 mEq/L, not significant). The switching from thiazide diuretics to ipragliflozin led to the significant reduction of urinary albumin excretion (from 165.2 ± 335.5 mg/gCr to 108.8 ± 190.4 mg/gCr, $P < 0.05$). Urinary N-acetyl- β -D-glucosaminidase was also significantly reduced from 12.9 ± 14.1 U/L to 8.6 ± 5.8 U/L during 3 months ($P < 0.05$). Ketone bodies did not increase significantly after the switch (from 222.1 ± 234.0 μ mol/L to 292.0 ± 138.2 μ mol/L).

Evaluation of body mass composition after switching from thiazide diuretics to SGLT2 inhibitor ipragliflozin

In order to examine the change in body composition when switching from thiazide diuretics to ipragliflozin, we investigated it using InBody770. A significant reduction of body fat mass and percentage were observed 3 months later after the switch compared with baseline (from 25.5 ± 12.1 kg to 24.4 ± 12.4 kg, $P < 0.0005$; from 32.8 ± 7.9% to 31.7 ± 8.3%, $P < 0.005$). It seemed that body fat reduction was due to the reduction of visceral fat mass (from 121.1 ± 51.4 cm² to 115.5 ± 49.6 cm², $P < 0.005$). In contrast, there was no difference in the skeletal muscle mass between before and after SGLT2 inhibitor administration (from 26.9 ± 6.2 kg to 26.8 ± 6.4 kg; Table 1).

Comparison of various parameters between switching group from thiazide diuretics to SGLT2 inhibitor ipragliflozin and non-switching group

As a control, we used the data of participants ($n = 19$) who used thiazide diuretics as an antihypertensive drug without switching to SGLT2 inhibitor and did not change dosage in any other drugs in the same observation period as the switching group. First and most importantly, there were no significant differences in age and duration of diabetes between the switching group and non-switching group (Table 1). Next, there were no significant differences in Δ systolic and Δ diastolic blood pressure between the two groups (Table 2). These data show that the patients in both groups had similar characteristics. In addition, there was no significant difference in systolic blood pressure levels at baseline and 3 months later between the switching to SGLT2 inhibitor group and non-switching group (baseline 131.2 ± 12.9 mmHg vs 134.7 ± 14.7 mmHg; 3 months later 132.1 ± 13.2 mmHg vs 132.6 ± 18.8 mmHg). The same result was observed in diastolic blood pressure (baseline 74.5 ± 9.9 mmHg vs 71.1 ± 8.7 mmHg; 3 months later 75.8 ± 11.2 mmHg vs 69.7 ± 11.1 mmHg; Table 1). Δ HbA1c significantly decreased in the switching group compared with

the non-switching group ($P < 0.05$; Table 1). Although the HbA1c level in the switching group at baseline was significantly higher than that of the non-switching group (7.1 ± 1.0% vs 6.6 ± 0.6%, $P < 0.05$), there was no significant difference at 3 months later between the two groups (6.7 ± 0.9% vs 6.5 ± 0.7%). Furthermore, in the non-switching group, there were no significant changes in blood pressure, HbA1c, fasting blood glucose and uric acid during 3 months corresponding to the follow-up period in the switching group.

In addition, to examine in which individuals the SGLT2 inhibitor effectively exerted an antihypertensive effect, we carried out univariate analyses. There was no significant correlation between Δ blood pressure (both Δ systolic blood pressure and Δ diastolic blood pressure) and baseline values of BMI, bodyweight, visceral fat mass area, HbA1c, uric acid, age, sex and Δ visceral fat area, and Δ HbA1c and Δ bodyweight in the switching group (data not shown). Furthermore, to examine which factors contribute to the antihypertensive effect of SGLT2 inhibitors, we examined whether Δ blood pressure was influenced by taking ARB, pioglitazone, glucagon-like peptide-1 receptor agonists, insulin and smoking. However, there was no significant correlation between them. In addition, there was no significant correlation between Δ blood pressure and estimated salt intake, which was calculated with urinary Na excretion. We also examined whether Δ blood pressure was influenced by the type and amount of thiazide diuretics, but there was no significant correlation between them (data not shown).

DISCUSSION

In the present study, we switched from thiazide diuretics to the SGLT2 inhibitor, ipragliflozin, in participants with type 2 diabetes and hypertension. Three months after the switch, there was no significant difference in systolic and diastolic blood pressure from the baseline. Although it was known that SGLT2 inhibitors exerted beneficial effects on blood pressure, we believe that the data in the present study clearly show that there is no clear difference in blood pressure-lowering effects between thiazide diuretics and SGLT2 inhibitor. In this study, we encouraged the participants to measure blood pressure at home and obtained the data from 22 participants. Although there might be some problem in the point of accuracy in self-monitoring blood pressure, there was a significant improvement in the average systolic and diastolic blood pressure 3 months after the switch to ipragliflozin (average from -1 month to baseline 135.8 ± 11.5 mmHg, 73.5 ± 9.9 mmHg, average from 1 month to 3 months: 129.5 ± 10.3 mmHg, 70.9 ± 9.3 mmHg, $P < 0.05$, $P < 0.005$, respectively). These self-monitoring blood pressure data, as well as the blood pressure data obtained in our hospital, show that the blood pressure-lowering effects of SGLT2 inhibitor are, at least, not weak compared with those of thiazide diuretics.

In the present study, we set a control group that did not change to ipragliflozin from thiazide diuretics in order to exclude the influence of seasonal variation in various variables,

Table 2 | Comparison of the change amount for 3 months between the switching group and non-switching group.

Parameter	Switching group	Non-switching group	P-value
ΔSBP (mmHg)	0.9 ± 10.8	-2.1 ± 13.0	NS
ΔDBP (mmHg)	1.5 ± 7.7	-1.4 ± 8.2	NS
ΔHbA1c (%)	-0.3 ± 0.4	-0.1 ± 0.3	<0.05
ΔSerum K (mEq/L)	0.2 ± 0.4	0.1 ± 0.3	NS
ΔUA (mg/dL)	-1.0 ± 1.0	0.2 ± 0.7	<0.005
ΔBMI (kg/m ²)	-0.5 ± 0.7	-0.4 ± 0.6	NS
ΔBodyweight (kg)	-1.4 ± 1.7	-0.9 ± 1.5	NS

Data presented as mean ± standard deviation. BMI, body mass index; DBP, diastolic blood pressure; K, potassium; NS, not significant; SBP, systolic blood pressure; UA, uric acid.

such as blood pressure and HbA1c level, as much as possible. In addition, the start month ratio of the non-switching group corresponded to that of the switching group using a random number table in order to avoid the possible influence of other factors. BMI and bodyweight were decreased in the non-switching group, as well as the switching group (Table 2). This was probably due to the fact that switching to ipragliflozin mainly took place in winter, and thereby the season-matched control group was also allocated mainly in the winter season. Therefore, we cannot deny the possibility that BMI and bodyweight were decreased as a seasonal fluctuation due to change of lifestyle from winter to spring in the non-switching group.

Recently, it has been further established that SGLT2 inhibitors have the power to not only reduce blood pressure the same as thiazide diuretics, but also improve other metabolic parameters, such as high-density lipoprotein cholesterol and uric acid³⁰. Considering that the antihypertensive effect of thiazide diuretics is mainly based on the inhibition of Na⁺ reabsorption in the distal tubule, it was marvelous that the amount of urinary sodium excretion did not significantly change after switching to the SGLT2 inhibitor from thiazide diuretics. It was recently shown that the antihypertensive effect of SGLT2 inhibitor was considered to be, in large part, a loop diuretic effect³¹. It is known that thiazide diuretics worsen glucose and lipid metabolism, but that SGLT2 inhibitors ameliorate glucose and lipid metabolism. Fasting insulin level was significantly reduced after the switch to ipragliflozin. We believe that the main reason for the reduction of insulin secretion is the decline of insulin demand as a result of the marked increase of urinary glucose excretion by ipragliflozin. In addition, the serum potassium level was slightly, but significantly, increased after switching from thiazide diuretics to ipragliflozin. Therefore, although speculative, we believe it is possible that such an increase of serum potassium level was also involved in an increment of insulin secretion. We believe that such characteristics of these drugs contributed to the difference in the effects on various metabolic parameters. Taken together, it is likely that the switch from thiazide diuretics to SGLT2 inhibitor would improve various metabolic parameters without affecting blood pressure.

In addition, the switch from thiazide diuretics to an SGLT2 inhibitor, ipragliflozin, led to the reduction of body mass index and visceral fat area. It is well known that visceral fat secretes various inflammatory cytokines, and is very closely associated with the development of insulin resistance and glucose intolerance. In addition, it is known that SGLT2 inhibitors function to alter body mass composition and reduce visceral fat mass. We believe that such reduction of visceral fat mass contributed to the amelioration of glycemic control after the switch to ipragliflozin.

Furthermore, the switch from thiazide diuretics to an SGLT2 inhibitor, ipragliflozin, led to the reduction of urinary albumin and urinary N-acetyl-β-D-glucosaminidase excretion, which are known as markers for proximal tubular disorder. Much attention has recently been drawn to SGLT2 inhibitors exerting beneficial effects on renal function as well, although the precise mechanism remains unclear. However, as a part of the possible mechanism, it is considered that SGLT2 inhibitors suppress glucose reabsorption with NaCl at the proximal tubule, which leads to the increment of NaCl at the distal tubule and the decline of glomerulus internal pressure through improvement of afferent arteriole expansion. In addition, ARB expands the efferent arteriole more than the afferent arteriole, which leads to kidney function protection. For these reasons, we believe that combined use of a SGLT2 inhibitor and ARB would lead to further protection of renal function, although some clinical studies with larger numbers of participants would be necessary to strengthen this hypothesis. It is obviously very important to prevent various diabetic complications, such as diabetic nephropathy, and urinary albumin excretion is an established marker of diabetic nephropathy. Therefore, we believe that the reduction of proximal tubular disorder markers after the switch from thiazide diuretics to ipragliflozine would be very promising when we consider treatment for patients with type 2 diabetes and hypertension.

The data in the present study suggest that in patients with type 2 diabetes and hypertension using thiazide diuretics, it would be better to switch from thiazide diuretics to an SGLT2 inhibitor. It is likely that the switch from thiazide diuretics to an SGLT2 inhibitor would improve various metabolic parameters and body mass composition without affecting blood pressure. However, there were some limitations to the present study. First, this study had a small population. It was mainly because there were just 59 patients using thiazide diuretics for antihypertension, although >2,500 type 2 diabetes patients were treated in our hospital. It was thought that the attending doctors felt there could be potential problems of thiazide diuretics in view of patients' metabolism. Second, this research was a retrospective study, and we could not set the control in the accurate meaning. However, as a control, we used the data of participants who used thiazide diuretics as an antihypertensive drug without switching to an SGLT2 inhibitor, and did not change the dosage in any other drugs in the same observation period as the switching group. Indeed, there was no substantial

difference between them. Furthermore, in the case of obtaining insufficient blood pressure control using ARB and CCB, we strongly suggest that an SGLT2 inhibitor should be used rather than thiazide diuretics as a next step in patients with hypertension complicated with type 2 diabetes. The improvement of blood pressure, as well as metabolism (e.g., glycemic control), would lead to suppressing macroangiopathy in the future. Needless to say, in order to demonstrate our hypothesis in the present study, prospective trials should be carried out in which thiazide diuretics or SGLT2 inhibitors are added to the existing antihypertensive therapy in patients with type 2 diabetes.

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DISCLOSURE

HK has received honoraria for lectures, and received scholarship grants from Sanofi, Novo Nordisk, Lilly, Boehringer Ingelheim, MSD, Takeda, Ono Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Pfizer, Kissei Pharma, AstraZeneca, Astellas, Novartis, Kowa, Chugai and Taisho Pharma. KK has been an advisor to, received honoraria for lectures from and received scholarship grants from Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical Co., Ltd, MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim Co., Ltd, Chugai, Daiichi Sankyo, and Sanofi. The other authors declare no conflict of interest.

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