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Letters to the Editor

Diuretic effects of sodium–glucose cotransporter 2 inhibitor in patients with type 2 diabetes mellitus and heart failure

Tetsushiro Takeuchi [a], Kaoru Dohi [a,*], Taku Omori [a], Keishi Moriwaki [a], Yuichi Sato [a], Shiro Nakamori [a], Naoki Fujimoto [b], Eitaro Fujii [a], Norikazu Yamada [a], Masaaki Ito [a]

[a] Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Japan
[b] Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, Tsu, Japan

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The prevalence of type 2 diabetes mellitus (T2DM) in the heart failure (HF) population is 15% to 25% [1,2], and T2DM plays an important role in the pathogenesis, prognosis, and response to treatment of HF [3]. Loop diuretics are prescribed to the vast majority of patients with symptomatic HF, but they directly upregulate renin gene expression by blocking sodium chloride uptake at the macula densa, which activates the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS), both of which are known to have adverse effects in heart failure [4–6]. Recently, a new class of oral glucose-lowering agents that inhibit renal sodium–glucose cotransporter 2 (SGLT2) has been approved. SGLT2 is present in the brush border of epithelial cells in the S1 and S2 segments of proximal renal tubules. Inhibition of SGLT2 leads to reduced glucose and sodium reabsorption in the proximal tubule [7,8], which has the potential for a diuretic effect without stimulating RAAS and SNS activation via the macula densa mechanism. Therefore, the aim of this study was to assess the short-term diuretic effects of ipragliflozin, an oral SGLT2 inhibitor, and their influences on neurohumoral activation in patients with T2DM and HF.

We prospectively and consequently enrolled a total of 20 Japanese patients with T2DM (HbA1c >6.0%) and HF between July 2014 and April 2015. They were admitted to hospital because of decompensated HF and appropriately treated by receiving intravenous inotropic agents, vasodilators and/or diuretic therapy. At enrollment, all patients were hemodynamically stabilized. The main exclusion criteria included severe decompensated HF with New York Heart Association (NYHA) class IV, advanced renal disease with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, small body size with a body weight <30 kg, presence of severe ketosis, diabetic coma, genitourinary tract infection, and pregnancy. The present study was conducted in accordance with the Declaration of Helsinki and all of the patients gave written informed consent to participate after receiving a written explanation of the study objectives and procedures.

All patients underwent blood and 24-hour urine tests including neurohumoral assessment before ipragliflozin therapy. Ipragliflozin was administered at a dose of 50 mg once daily after breakfast for at least 4 consecutive days. Background diuretics and other cardiac medications were maintained and water intake was not restricted during the treatment period. Vital signs and urine volume were measured at day 0 and every 24 h subsequently. Body weight was measured on days −1 through 3 after urination and before breakfast to the nearest 0.1 kg. Blood and urine samples were collected every 24 h all through the study period. All patients underwent repeated neurohumoral assessment and 24-hour urine tests on day 4. Continuous variables are expressed as the mean and standard deviation, and were compared using a paired t-test before and after ipragliflozin treatment. Discrete variables are expressed as numbers (percentages). Time-related comparisons of body weight and urine volume were analyzed by one-way analysis of variance. P values <0.05 were considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS Japan Institute, Tokyo, Japan).

Table 1 shows the clinical characteristics of the study subjects. Nine (45%) patients were diagnosed with ischemic cardiomyopathy. All of the 20 patients had already been receiving loop or thiazide diuretics and mean serum creatinine was 0.97 mg/dL at baseline. Daily urine volume increased on days 1 through 3 ($P < 0.05$ vs. baseline, Fig. 1). Body weight began to decrease on day 1, and continued to decrease gradually throughout the treatment period, showing a mean of -0.7 ± 0.7 kg on day 3 compared with day 0 (Fig. 1). Comparisons of vital signs, and blood and urine parameters before and after ipragriflozin treatment are shown in Table 2. Systolic blood pressure and heart rate remained unchanged. The 24-hour urine sugar excretion increased and urine sodium excretion tended to increase, resulting in increased urine

* Corresponding author at: Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu 514-8507, Japan.
E-mail address: dohik@clin.medic.mie-u.ac.jp (K. Dohi).

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Table 1
Baseline clinical characteristics.

Number of patients	20
Male, n (%)	12 (60)
Age, years	69.5 ± 13.4
Body mass index, kg/m^2	23.5 ± 6.8
NYHA functional class	
II, n (%)	13 (65)
III, n (%)	7 (35)
Ischemic cardiomyopathy, n (%)	9 (45)
Dilated cardiomyopathy, n (%)	2 (10)
Valvular heart disease, n (%)	4 (20)
Others, n (%)	5 (25)
HbA1c, %	7.1 ± 0.94
LV ejection fraction, %	44 ± 11
Medications	
β-blockers, n (%)	18 (90)
ACEI/ARB, n (%)	18 (90)
Digoxin, n (%)	2 (10)
Oral inotropic agents, n (%)	3 (15)
Loop diuretics, n (%)	19 (95)
Thiazide diuretics, n (%)	1 (5)
Aldosterone antagonists, n (%)	13 (65)
Anti-diabetic treatment	
Sulfonylureas, n (%)	6 (30)
DPP-4 inhibitors, n (%)	7 (35)
α-glucosidase inhibitors, n (%)	4 (20)
Biguanides, n (%)	2 (10)
Thiazolidinediones, n (%)	1 (5)
Insulin, n (%)	3 (15)

NYHA, New York Heart Association; LV, left ventricular; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4.

Table 2
Comparisons of clinical parameters at baseline and after ipragliflozin treatment.

	Baseline	After ipragliflozin treatment	P value
Vital signs			
Systolic blood pressure (mm Hg)	118 ± 27	114 ± 28	0.205
Diastolic blood pressure (mm Hg)	68 ± 15	65 ± 13	0.184
Heart rate (bpm)	73 ± 15	72 ± 10	0.437
Blood test			
Hematocrit (%)	36.0 ± 5.2	36.4 ± 4.9	0.077
Serum albumin (g/dL)	3.9 ± 0.3	4.1 ± 0.2	0.009
Creatinine clearance (mL/min)	54.9 ± 18.2	58.5 ± 15.0	0.387
Serum sodium (mEq/L)	139 ± 5	138 ± 5	0.139
Serum potassium (mEq/L)	4.1 ± 0.4	4.1 ± 0.3	0.759
Serum chloride (mEq/L)	101 ± 5	101 ± 5	0.213
Serum magnesium (mg/dL)	2.2 ± 0.2	2.4 ± 0.2	<0.001
Fasting blood glucose (mg/dL)	119 ± 30	103 ± 15	0.002
Plasma ANP (mg/dL)	127.9 ± 118.2	81.4 ± 56.6	0.004
Plasma BNP (mg/dL)	326.6 ± 225.7	271.4 ± 217.5	0.023
Plasma renin activity (ng/mL/h)	4.8 ± 5.5	5.8 ± 5.7	0.020
Plasma angiotensin II (pmol/L)	20 ± 24	20 ± 17	0.575
Plasma aldosterone (pmol/L)	130 ± 79	179 ± 213	0.376
Plasma noradrenaline (pg/mL)	463 ± 322	463 ± 321	0.852
24-hour urine test			
Urine sugar (g/day)	0.3 ± 0.6	24.5 ± 18.3	<0.001
Urine urea nitrogen (mg/dL)	440 ± 167	424 ± 125	0.015
Urine sodium (mEq/day)	75 ± 32	96 ± 40	0.051
Urine potassium (mEq/day)	27 ± 11	35 ± 12	0.004
Urine chloride (mEq/day)	71 ± 36	90 ± 42	0.086
Urine osmolality (mOsm/kg H_2O)	318 ± 102	411 ± 116	<0.001

osmolality. However, serum sodium concentration remained unchanged after ipragliflozin treatment. The 24-hour urine potassium quantity increased but serum potassium concentrations remained unchanged after ipragliflozin treatment. Creatinine clearance remained unchanged after ipragliflozin treatment. Although plasma renin activity mildly increased, plasma angiotensin II, aldosterone and noradrenaline levels remained unchanged. Plasma brain and atrial natriuretic peptide levels decreased after ipragliflozin treatment.

This, to our knowledge, is the first study to investigate the diuretic effects of SGLT2 and their influences on neurohumoral activation in patients with T2DM and HF. In the present study, short-term ipragliflozin treatment at a dose of 50 mg per day increased urine volume and decreased body weight. SGLT2 inhibition led to increases of glucose as well as sodium excretion without influencing serum sodium concentrations. These results indicate that ipragliflozin has great potential as a novel and effective diuretic agent. Ipragliflozin treatment also increased potassium excretion without influencing serum potassium concentration, probably due to the increased delivery of sodium to the distal nephron, which activates sodium reabsorption and potassium secretion in the distal convoluted tubule and in the connecting tubule [9]. To prevent rehospitalization, patients with HF generally require chronic oral loop diuretic treatment [10], but it can worsen renal function and activate the RAAS and SNS, all of which play fundamental roles in HF progression [4–6]. In the present study, short-term ipragliflozin therapy in patients on chronic oral diuretics decreased plasma natriuretic peptide levels without influencing plasma angiotensin II, aldosterone and noradrenaline levels. These results indicate that SGLT2 inhibition ameliorates cardiac load with minimal effects on RAAS and SNS activation via the macula densa mechanism.

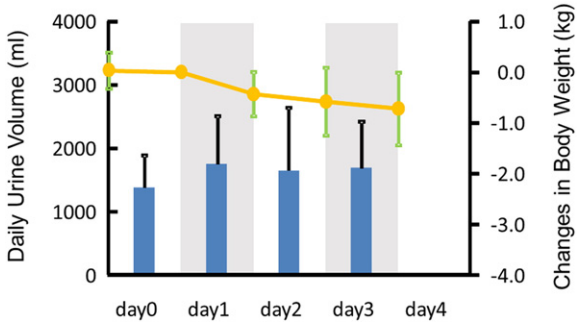

Fig. 1. Daily urine volume and changes in body weight from baseline over a 3-day period of ipragliflozin treatment. Blue bar indicates daily urine volume. Orange circles indicate changes in body weight. Data are expressed as mean ± SD. *P < 0.05 vs. baseline.

Several limitations need to be considered in this single-center study with a small patient population. There was no control group, and the long-term effects of ipragriflozin were not tested.

In conclusion, the present study demonstrated that short-term SGLT2 inhibition promotes diuresis and ameliorates cardiac load without affecting electrolyte balance and renal function, and minimally influencing RAAS and SNS in patients with T2DM and HF, so it has great potential as a novel strategy in the treatment of HF.

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Potential conflicts of interest

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