



Effects of SGLT2 Inhibitor on Neurohormonal Activity and Electrolyte Management in an Elderly Patient with Type 2 Diabetes Mellitus and Acute Heart Failure: A Case Report

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Abstract

Introduction: Effects of a sodium-glucose cotransporter-2 inhibitor (SGLT2i) on changes in the neurohormonal activity were investigated in an 85-year-old patient with Type 2 Diabetes Mellitus (T2DM) and acute Heart Failure (HF).

Case presentation: While maintaining the background medications constant, we started her on the SGLT2i empagliflozin 10 mg/d to treat the worsening HF and diabetic derangement. One week later, her body weight was markedly reduced by 3.6 kg, and HF-related physical signs were ameliorated, but serum b-type natriuretic peptide concentration was only slightly reduced. Despite attaining marked diuresis, the changes in the hemoglobin and hematocrit values from baseline were mild, indicating less vascular contraction after SGLT2i administration. Serum sodium and chloride concentrations were increased on day 7 and further increased on day 28 under SGLT2i treatment. Treatment induced a marked reduction in the plasma renin activity on day 7, which was further reduced to a near normal level on day 28.

Conclusion: According to the “chloride theory” for HF pathophysiology, reduced activation of the renin-angiotensin-aldosterone system by an SGLT2i could be expected by (1) preserving or enhancing chloride ions supplied to the macula densa and (2) retaining the vascular volume as a result of the enhanced serum chloride concentration.

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Keywords: Heart Failure; SGLT2 Inhibitor; Chloride; Renin-angiotensin-aldosterone system; Diuretic.

Introduction

Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i) is an anti-hyperglycemic drug with accompanying diuretic action [1,2]. Its pharmacologic properties of diuretic action are not yet fully clarified. Recent clinical study [3] reported that an SGLT2i diuretic enhances or regains serum chloride concentrations in patients with Type 2 Diabetes Mellitus (T2DM)/Non-Heart Failure (HF). Accordingly, “chloride-regaining” diuretics, such as SGLT2i, might preserve vascular volume and induce excessive

extravascular fluid to drain into the vascular space via enhanced vascular “tonicity” caused by the increased serum chloride concentration [4]. The “chloride theory” for HF pathophysiology [4] predicts that such a “chloride-regaining” diuretic would not exaggerate the activity of Renin-Angiotensin-Aldosterone System (RAAS) [5]. The mechanisms of SGLT2i treatment for HF via effects on RAAS activity, however, are unclear. The present report describes the case of a patient with T2DM and acute HF who



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was prescribed diuretic treatment with SGLT2i add-on therapy, in whom specific SGLT2i effects via the “chloride-regaining” diuretic action on the plasma volume and RAAS activity were investigated from the viewpoint of the “chloride theory” [4].

Case presentation

An 85-year-old woman, who was treated for T2DM and chronic HF (NYHA functional class III) due to hypertension, pacemaker implantation, and rheumatic valvular heart disease at another hospital, began to visit to my outpatient clinic regularly 1 year prior to the present emergent admission for a chief complaint of progressive dyspnea (NYHA functional class IV) and systemic edema over the preceding 2 weeks. The patient was uneventful for 1 year before the present admission, and she was being treated at the time with a daily dose of glucose-lowering agents (sitagliptin 50 mg and repaglinide 0.5 mg), a blood pressure-lowering agent (amlodipine 5 mg), and diuretics (azosemide 30 mg and spironolactone 25 mg). Her habitus at clinical stability 1 month before the present admission was 143 cm tall and weighing 48.1 kg (body mass index 23.5 kg/m²). She consistently took her prescribed medications. There were no apparent precipitating factors for the present worsening HF event but she was undergoing orthopedic rehabilitation at the time.

Table 1 shows the changes in various clinical tests before and after initiating the SGLT2i (empagliflozin 10mg daily) treatment. Laboratory tests included peripheral blood and urine tests, measurement of B-Type Natriuretic Peptide (BNP), diabetic-related tests, and neurohormonal tests. The background use of glucose-lowering agents, an anti-hypertensive agent, and diuretics described above was kept constant before beginning the SGLT2i treatment and throughout the evaluation period. At the initial presentation of worsening HF (day 1), her blood pressure was 129/84 mmHg, heart rate was irregular at 107 beats/min, temperature 36.5°C, and oxygen saturation 96% on ambient air. Physical examination revealed HF-related physical signs of neck vein distension, severe peripheral edema with weight gain of 1.5 kg over 1 month, and bilateral pulmonary rales. A 12-lead electrocardiogram revealed atrial fibrillation with an irregular heart rate of 107 beats/min and a conducted narrow QRS complex. Cardiac ultrasonography showed preserved left ventricular ejection fraction (54%) and non-dilated diastolic volume (92cc), but a narrowed mitral valve area (0.5 cm²) due to a severely calcified mitral valve and a moderately enlarged left atrium. Doppler echocardiogram showed a moderate degree of tricuspid regurgitation and a raised estimated pulmonary arterial pressure (45 mmHg). Thoracic and abdominal ultrasound

revealed moderate pleural effusion and an expanded inferior vena cava with minimal respiratory change. Blood examination revealed an increased serum BNP concentration (from 87 to 203 pg/ml) and HbA1c (9.8% to 10.3%) compared with that at a clinic visit during relative clinical stability 1 month before. Plasma renin activity was markedly enhanced (20.8 ng/mL/h), but plasma aldosterone (267 pg/mL) and anti-diuretic hormone (3.3 pg/mL) levels were only slightly elevated.

Treatment with an SGLT2i (empagliflozin 10 mg daily) was initiated for worsening HF and diabetic derangement. One week later (day 7), the patient's body weight had markedly decreased by 3.6 kg, and HF-related physical signs and pleural effusion on thoracic ultrasound were ameliorated, but the serum BNP concentration was only slightly reduced. The hemoglobin (+0.5 g/dL) and hematocrit (+0.8%) values changes only slightly from baseline despite marked diuresis, indicating less vascular contraction after SGLT2i administration. The same trends were noted 4 weeks later (day 28).

The serum sodium and chloride concentrations gradually increased on days 7 and 28 under the SGLT2i treatment (sodium from 136 mEq/L before treatment to 137 and 139 mEq/L, and chloride from 100 mEq/L at baseline to 101 and 104 mEq/L, respectively). The serum blood urea nitrogen and creatinine concentrations were mildly increased after treatment. After treatment, plasma renin activity was markedly reduced to 13.1 ng/mL/h on day 7, and further reduced to a near normal level of 3.4 ng/mL/h on day 28. The plasma aldosterone level was reduced to 90.4 pg/mL on day 28 and anti-diuretic hormone levels did not change during the observation period. Two weeks later, the patient was discharged in an acceptable HF status (day 43; Table 1).

Thus, the observations in this patient included preservation of the plasma volume (estimated by monitoring the hemoglobin/hematocrit) and reduced RAAS activity despite the massive diuresis induced by add-on SGLT2i mono-therapy.

Discussion

Diuretic treatment with an SGLT2i in a patient with T2DM and acutely decompensated HF lead to three important findings, as follows: SGLT2i diuretic 1) preserved or enhanced the serum chloride concentration, 2) preserved the vascular volume even after massive diuresis, and 3) reduced the exaggerated RAAS activity though RAAS activity is typically enhanced by conventional diuretics [4,5]. Figure 1 summarizes the possible effects caused by SGLT2i on the plasma volume and RAAS activity in the present T2DM/HF patient from the viewpoint of the “chloride theory” [4].

Table 1: Changes in physical and blood tests before and after sodium-glucose transporter-2 inhibitor (SGLT2i) treatment.

	Normal range	Admission to the hospital				
		Before treatment		After SGLT2i treatment		
		Before 1 month	day 1	day 7	day 28	day 43 (pre-discharge)
A. Heart failure-related examination						
Body weight (kg)		48.1	49.6	46	45.3	44.8
Blood pressure (mmHg)		142/74	129/84	115/85	86/46	112/65
Heart rate (bpm)		99	107	105	80	82
Heart failure-related signs						

Neck vein distention		No	Yes	No	No	No
Pulmonary rales		No	> basal 1/3	No	No	No
Leg edema		No	Up to knee	No	No	No
Pleural effusion by ultrasound		—	Massive	Minimal	No	No
B-type natriuretic peptide (pg/mL)	< 18.4	87.2	203	185	182	—
Neurohormonal test						
Adrenaline (ng/mL)	< 0.1	—	0.03	≅0.01	≅0.01	—
Noradrenaline (ng/mL)	0.1–0.5	—	1.14	0.58	0.28	—
Renin activity (ng/mL/h)	0.2–2.3	—	20.8	13.1	3.4	—
Aldosterone (pg/mL)	36–240	—	266.6	256.6	90.4	—
Anti-diuretic hormone (pg/mL)	< 2.8	—	3.3	3.1	2.9	—
B. Peripheral blood test						
Hemoglobin (g/dL)	11.6–14.8	11.5	10	10.5	10.2	10.3
Hematocrit (%)	35.1–44.4	35.3	31.5	32.3	32.2	32.9
Mean red blood cell volume (fL)	83.6–98.2	98.3	99.7	96.1	97	97
Albumin (g/dL)	4.1–5.1	—	4	—	3.7	—
Serum electrolytes						
Sodium (mEq/L)	138–145	136	136	137	139	138
Potassium (mEq/L)	3.6–4.8	4.8	4.6	4	4.2	4.3
Chloride (mEq/L)	101–108	98	100	101	104	103
Blood urea nitrogen (mg/dL)	8.0–20.0	19.2	25	31.7	26.2	27.1
Serum creatinine (mg/dL)	0.46–0.79	0.93	1.05	1.32	1.16	1.18
C. Urinary test (spot urine)						
Urinary electrolytes						
Sodium (mEq/L)		—	68	—	56	—
Potassium (mEq/L)		—	25	—	16.4	—
Chloride (mEq/L)		—	54.1	—	55.1	—
D. Diabetes-related test						
HbA _{1c} (%)	4.6–6.2	9.8	10.3	10	9.1	8.7
Fasting blood glucose (mg/dL)	73–109	412	297	175	86	97
LDL cholesterol (mg/dL)	63–163	123	84	—	88	—
HDL cholesterol (mg/dL)	48–103	50	60	—	40	—
E. Treatment (daily dose)						
Loop diuretic		Azosemide 30mg				
Mineralocorticoid receptor antagonist		Spironolactone 25mg				
SGLT2 inhibitor				Empagliflozin 10mg		

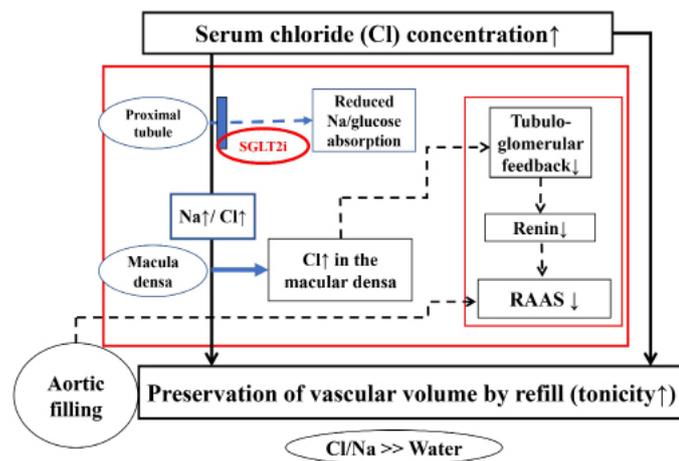


Figure 1: Effects of the diuretic action of an SGLT2 inhibitor on the renal tubular Na/Cl and the RAAS according to the “chloride theory”. Solid line indicates enhanced supply or excitatory effect, and dotted line indicates reduced supply or inhibitory effect. Large red square represents the kidney as an action place for the reabsorption of electrolytes and water, and the small red square represents the renin-angiotensin-aldosterone system. Cl: Chloride; Na: Sodium; RAAS: Renin-Angiotensin-Aldosterone System.

SGLT2 inhibitor as a possible “chloride-regaining” diuretic for HF treatment

According to my “chloride theory” for HF pathophysiology [4,5], manipulation of the serum chloride concentration could become an attractive therapeutic target for treating HF [6], such as by reducing the quantity and concentration of serum chloride using conventional diuretics for worsening HF, and preserving and enhancing the concentration of serum chloride with aquaresis using a V_2 -receptor antagonist [4,7] or acetazolamide [8,9]. On the basis of my recent observations in T2DM/non-HF patients [3], the use of an SGLT2i could be a suitable chloride-regaining diuretic for worsening HF due to its effects to preserve or enhance the serum chloride concentration, as similarly observed in the T2DM patient with acutely decompensated HF reported here. A recent experimental study provided evidence for the chloride-regaining effect of SGLT2i in a rat DM model [10]. Thus, according to the “chloride theory”, diuretic that restores chloride level, such as an SGLT2i, would drain excessive extravascular fluid into the vascular space and preserve vascular volume [11] via enhanced vascular tonicity caused by increased serum chloride concentration in acute decompensated HF [4,5]. The reduced RAAS activity induced by the SGLT2i would favor body fluid reduction in parallel with the osmotic diuretic action.

Diuretic therapy to preserve the serum chloride concentration may induce a residual cardiac volume overload in relation to cardiac function as previously indicated under treatment with a V_2 -receptor antagonist [4,7] or acetazolamide [8,9]. This concept could apply to the present case undergoing diuretic treatment with an SGLT2i because the vascular volume did not decrease, and thus the magnitude of the serum BNP reduction was so small even after massive diuresis under the SGLT2i diuretic treatment, in accordance with the recent clinical study [12]. Adjusting the combination of various diuretics and their dosages according to their effects on the serum chloride concentration might favorably reduce the vascular volume and contribute to cardiac unloading.

RAAS activity under SGLT2i treatment for worsening HF status

Conventional diuretics typically enhance RAAS activity [5], but in the present case the SGLT2i greatly reduced the RAAS activity (Table 1). The effect of SGLT2i on RAAS activity are controversial [2]. Enhanced RAAS activity could be expected from the effects of blood pressure-lowering and blood vessel contraction caused by the SGLT2i [13]. One report suggested that SGLT2i activates the RAAS by decreasing the chloride supply to the macula densa [14]. Several clinical studies reported enhancement of plasma renin activity [3,15]. Another report, however, indicated that SGLT2i therapy inhibits RAAS activity [16], including some experimental studies [17,18].

In this background, the “chloride theory” [4,5] predicts that SGLT2i therapy would have favoring an inhibitory effect on RAAS activity, as shown in Figure 1. Accordingly, reduced RAAS activity, angiotensin II in particular, may lead to the dilation of efferent glomerular arterioles, thereby reducing glomerular hydraulic pressure, and the glomerular filtration rate. Decreased glomerular hydraulic pressure induced by an SGLT2i would also result from afferent arteriolar constriction via tubuloglomerular feedback [16,19]. Preservation of the serum chloride concentration and plasma volume by the SGLT2i would, however, counterbalance these actions and prevent worsening of renal function [4]. Further studies are needed to investigate RAAS activity in T2DM/HF patients because complex and various changes in the RAAS activity could exist under different phases (e.g., acute, sub-acute, or chronic) of SGLT2i treatment among heterogeneous populations of T2DM patients with HF status of different degree of severity.

Conclusion

In conclusion, a glucose-lowering drug, an SGLT2i, may act as a “chloride-restoring” diuretic with concomitant RAAS activity not to be exaggerated under treatment for worsening HF. Additional studies are required to determine the effects of this agent on the pharmacologic, hemodynamic, neurohormonal, and prognostic aspects of HF pathophysiology in T2DM/HF patients, and the “chloride theory” is expected to provide a background framework for analytic investigation of the diuretic effects of SGLT2i in HF pathophysiology.

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Statement of Ethics

The ethics committee at Nishida Hospital approved the study protocol.

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