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Short Communication

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# Comparison of Diuretic Effects between Empagliflozin, a Sodium-Glucose Co-Transporter 2 Inhibitor With Osmotic Diuresis, and Tolvaptan, a Water Diuretic, in Two Type 2 Diabetic Patients Taking Sodium Diuretics

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## ABSTRACT

Empagliflozin, one of sodium-glucose co-transporter 2 (SGLT2) inhibitors, has been demonstrated to have beneficial effects on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events. The mechanisms behind these benefits of empagliflozin are presumed to include osmotic diuresis, being rather close to water diuresis than sodium diuresis. Two cases are presented here, where distinct changes in urinary water and sodium excretion were seen immediately after replacing tolvaptan, a water diuretic, with empagliflozin. Case 1 with heart failure showed a large decrease in urinary sodium excretion with a slight decrease in urine volume. By contrast, Case 2 with nephrotic syndrome showed a large increase in urinary sodium excretion with an increase in urine volume. The differences were probably due to distinct diuretic effects of empagliflozin and tolvaptan in the presence of sodium diuretics as well as distinct pathological conditions. In addition, the amount of urine protein was reduced after the replacement in Case 2. SGLT2 inhibitors would be expected to have the potential to exert some beneficial effects other than lowering blood glucose levels by increasing urinary glucose excretion.

**KEYWORDS:** Sodium-glucose co-transporter 2 inhibitor (SGLT2 inhibitor); Empagliflozin; Osmotic diuresis; Tolvaptan; Water diuresis; Sodium diuresis.

## INTRODUCTION

The recent EMPA-REG OUTCOME trial has demonstrated that empagliflozin, one of sodium-glucose co-transporter 2 (SGLT2) inhibitors, in addition to standard care had beneficial effects on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events.[1] Moreover, the secondary microvascular outcome has revealed that the use of empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo.[2] It is suggested that the mechanisms behind these benefits of empagliflozin include osmotic diuresis, reductions in arterial stiffness and the rate pressure product, and direct renovascular effects through activating tubuloglomerular feedback.[2,3] Unlike strong osmotic diuretics such as intravenously administered mannitol,[4] SGLT2 inhibitors seem to be rather close to that of tolvaptan, a selective oral vasopressin $V_2$-receptor antagonist,[5] to promote water diuresis (excretion of electrolyte-free water).[6,7] Urinary sodium excretion was shown to slightly increase only early after the administration of SGLT2 inhibitors in experimental animals.[8,9] Two cases are presented in this short communication, where distinct changes in urinary water and sodium excretion were seen immediately after replacing tolvaptan with empagliflozin. Osmotic diuresis–related effects of SGLT2 inhibitors will be discussed.

## CASES

Case 1 (Table 1) was a 93-year-old woman with type 2 diabetes, hypertension and heart failure. She was hospitalized due to the worsening of heart failure. She was 141 cm in height and 48 kg in weight. Her HbA1c level was 5.8% on diet therapy alone. She was intermittently treated with tolvaptan in the presence of sodium diuretics. After the 3rd treatment with 7.5 mg tolvaptan for 7 days, it was replaced with 10 mg empagliflozin. Changes in urinary excretion of water, glucose and electrolytes are shown in Table 1. Since an indwelling urethral catheter was placed, urinary creatinine excretion was not measured to estimate the accuracy of 24-hour urine volume. After the replacement of tolvaptan with empagliflozin, urine volume was slightly decreased from 1650 to 1500 ml/day (mean value for two days; the ratio, 0.91), and urinary sodium excretion was apparently decreased from 72.6 to 47.8 mM/day (0.66). Before and after the 4-day measurement period, serum levels of albumin, urea nitrogen, creatinine, sodium and potassium were 2.9 and 2.6 g/dL, 30 and 33 mg/dL, 1.19 and 1.48 mg/dL, 139 and 140 mM/L, and 4.5 and 4.3 mM/L, respectively.

Case 2 (Table 2) was a 44-year-old man with type 2 diabetes, hypertension and nephrotic syndrome. He was referred and admitted to our hospital due to severe edema. He was 167 cm in height and 71 kg in weight. His HbA1c level was 6.5% under the treatment with a dipeptidyl peptide-4 inhibitor. After 20 days' treatment with 7.5 mg tolvaptan in the presence of sodium diuretics, it was replaced with 10 mg empagliflozin. Changes in urinary excretion of water, creatinine, glucose, electrolytes and protein are shown in Table 2. After the replacement of tolvaptan with empagliflozin, urine volume was increased from 1250 to 1550 ml/day (mean value for two days; the ratio, 1.24), and urinary sodium excretion was apparently increased from 66.9 to 107.1 mM/day (1.60). In addition, the amount of urine protein was decreased from 7.6 to 6.8 g/day (0.89). Before and after the 4-day measurement period, serum levels of albumin, urea nitrogen, creatinine, sodium and potassium were 1.9 and 2.6 g/dL, 24 and 28 mg/dL, 2.67 and 2.60 mg/dL, 142 and 139 mM/L, and 4.4 and 4.7 mM/L, respectively.

Case 3 as a reference case (Table 3) was a 67-year-old women with type 2 diabetes, hypertension and renal insufficiency. She was hospitalized due to shortness of breath caused by obesity and asthma. She was 155 cm in height and 102 kg in weight. Her HbA1c level was 7.4 % under the treatment with 500 mg metformin and a dipeptidyl peptide-4 inhibitor. Empagliflozin was added to her treatment in the absence of diuretics when her weight was 99 kg and serum levels of albumin, urea nitrogen, creatinine, sodium and potassium were 3.3 g/dL, 18 mg/dL, 1.64 mg/dL, 143 mM/L and 4.3 mM/L, respectively.

| Four consecutive hospital days | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Urine Volume (ml/day) | 1800 | 1500 | 1400 | 1600 |
| Urine Glucose (g/day) | <0.1 | <0.1 | 4.7 | 10.0 |
| Urine Sodium (mM/day) | 70.2 | 75.0 | 47.6 | 48.0 |
| Urine Chlorine (mM/day) | 59.4 | 64.5 | 40.6 | 43.2 |
| Urine Potassium (mM/day) | 21.6 | 18.6 | 18.5 | 22.1 |
| Tolvaptan | 7.5 mg | 7.5 mg | - | - |
| Empagliflozin | - | - | 10 mg | 10 mg |
| Furosemide | 10 mg | 10 mg | 10 mg | 10 mg |

**Table 1:** Urinary data and oral diuretics in Case 1 (see the section of Cases).

| Four consecutive hospital days | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Urine Volume (ml/day) | 1300 | 1200 | 1500 | 1600 |
| Urine Creatinine (g/day) | 0.93 | 1.07 | 0.90 | 0.93 |
| Urine Glucose (g/day) | 2.7 | 3.0 | 13.3 | 14.3 |
| Urine Sodium (mM/day) | 68.9 | 64.8 | 99.0 | 115.2 |
| Urine Chlorine (mM/day) | 49.4 | 40.8 | 87.0 | 99.2 |
| Urine Potassium (mM/day) | 19.4 | 20.5 | 23.3 | 25.8 |
| Urine protein (g/day) | 7.3 | 7.8 | 6.9 | 6.6 |
| Tolvaptan | 7.5 mg | 7.5 mg | - | - |
| Empagliflozin | - | - | 10 mg | 10 mg |
| Furosemide | 20 mg | 20 mg | 20 mg | 20 mg |
| Azosemide | 60 mg | 60 mg | 60 mg | 60 mg |
| Spironolactone | 25 mg | 25 mg | 25 mg | 25 mg |

**Table 2:** Urinary data and oral diuretics in Case 2 (see the section of Cases).

| Four consecutive hospital days | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Urine Volume (ml/day) | 2400 | 2300 | 2700 | 2900 |
| Urine Creatinine (g/day) | 0.92 | 0.75 | 0.77 | 0.86 |
| Urine Glucose (g/day) | 0.2 | 0.2 | 9.2 | 12.7 |
| Urine Sodium (mM/day) | 134.4 | 87.4 | 113.4 | 110.2 |
| Urine Chlorine (mM/day) | 100.8 | 57.5 | 75.6 | 69.6 |
| Urine Potassium (mM/day) | 22.6 | 16.1 | 18.9 | 20.3 |
| Empagliflozin | - | - | 10 mg | 10 mg |

**Table 3:** Urinary data in Case 3, a reference case with empagliflozin in the absence of diuretics (see the section of Cases).

Changes in urinary excretion of water, creatinine, glucose and electrolytes are shown in Table 3. After the addition of empagliflozin, urine volume was increased from 2350 to 2800 ml/day (mean value for two days; the ratio, 1.19), and urinary sodium excretion was very slightly increased from 110.9 to 111.8 mM/day (1.01). An increase in glycosuria (approximately 10 g/day) after the administration of empagliflozin was small because of renal insufficiency, and was similar to that seen in Cases 1 and 2.

## DISCUSSION

Because the effect of SGLT2 inhibitors on glycosuria is depending on glomerular filtration rate in its mechanism,[10,11] the amount of glycosuria induced by empagliflozin (approximately 10 g/day) in 3 patients with renal insufficiency presented here was small compared with that by SGLT2 inhibitors (approximately 50 to 100 g/day) reported in type 2 diabetic patients without renal insufficiency.[12-14] In Case 3, the administration of empagliflozin in the absence of diuretics caused an increase in urine volume with almost no change in urinary sodium excretion. Such osmotic diuresis as seen in familial renal glycosuria[5,15,16] seems to be close to water diuresis of tolvaptan,[6,7] which has been shown to be effectively used in patients with decompensated heart failure.[17,18] However, during two days after replacing tolvaptan with empagliflozin, Case 1 showed a large decrease in urinary sodium excretion with a slight descrease in urine volume. By contrast, Case 2 showed a large increase in urinary sodium excretion with a small increase in urine volume. The different changes in urinary water and sodium excretion were due probably to distinct diuretic effects of empagliflozin and tolvaptan in the presence of sodium diuretics as well as distinct pathological conditions.

SGLT2 mediates glucose reabsorption in the kidney by catalysing the active transport of glucose with sodium at 1:1 stoichiometry across the luminal membrane. The inward sodium gradient across the luminal epithelium is maintained by ATP-driven active extrusion of sodium ($Na^+/K^+$-ATPase) across the basolateral membrane into the blood.[19] Glucose and sodium molecules increased by the inhibition of SGLT2 (low affinity, high capacity) located in the early proximal tubule deliver to the later renal tubule. The excess of glucose can be partially reabsorbed by SGLT1 (high affinity, low capacity) located in the late proximal tubule, and that of sodium can be reabsorbed to a larger extent in the late proximal tubule, the loop of Henle, the distal tubule and the collecting tubule (Figure 1). Therefore, urinary sodium excretion is presumed not to be practically increased by the SGLT2 inhibition, as seen in Case 3 and elsewhere.[8,9,20] In the case of mannitol as an osmotic diuretic, mannitol filtered from glomerulus acts to retain water and to dilute sodium, and then decreases the numbers of sodium-absorbing sites of the tubular cells that are exposed to sodium, leading to urinary sodium loss.[4] Mannitol, a monosaccharide like glucose, is usually administered intravenously in a dose of ~100 g over ~60 min,[21] the urinary excretion of which is expected to be much larger than that of glucose induced by SGLT2 inhibitors. This is inferred to make a difference in their effects on urinary sodium excretion.

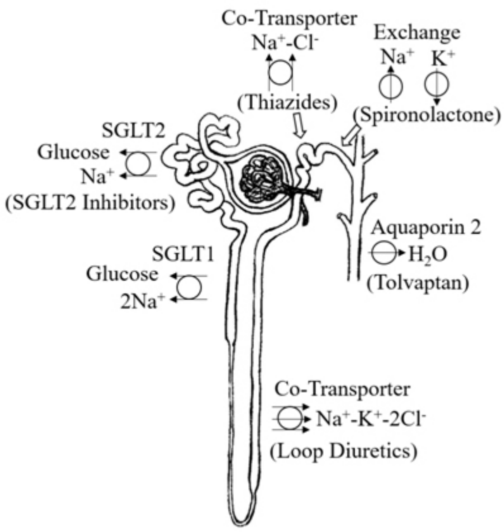


**Figure 1:** A diagram of nephron and action sites of diuretics in parentheses, including SGLTs (sodium-glucose co-transporters) 1 and 2.

Then, diuresis with SGLT2 inhibitors seems to be close to that with tolvaptan, a water diuretic. However, in the presence of sodium diuretics acting on the renal tubule later than the proximal tubule, SGLT2 inhibitors are considered to increase urinary sodium excretion greater than that increased by loop diuretics, thiazides, and/or spironolactone alone (Figure 1). Therefore, Cases 1 and 2 did not show similar urine data after the replacement of tolvaptan with empagliflozin. In Case 2 treated with stronger sodium diuretics, 10 mg empagliflizin appeared to be more potent than 7.5 mg tolvaptan as a diuretic. In addition, it was worthy of note that the amount of urine protein was

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reduced immediately after the replacement. Inhibiting SGLT2 might have saved energy inside the proximal tubular cells for other proximal tubular functions such as renal protein reabsorption. Canagliflozin, another SGLT2 inhibitor, has recently been reported to decrease urinary albumin-to-creatinine ratio independently of its glycemic effects from the early stage of the trial in type 2 diabetic patients with the baseline ratio more than 30 mg/g.[22] SGLT2 inhibitors would be expected to have the potential to exert some beneficial effects other than lowering blood glucose levels by increasing urinary glucose excretion.

## CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest.

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