CASE REPORT

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Persistent Diuresis Associated Dapagliflozin Treatment

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ABSTRACT Diabetic ketoacidosis is a clinical entity characterized by high blood sugar, ketone positivity and high anion gap metabolic acidosis. In these patients; polyuria is commonly detected due to hyperglycemia. Polyuria-induced dehydration may even be seen, especially in elderly patients. Polyuria is not expected to continue after hyperglycemia has resolved. We reported in this article; a 55 years old man with type-2 diabetes mellitus who was treated with a sodium-glucose cotransporter 2 (SGLT2) inhibitor (dapagliflozin) who developed diabetic ketoacidosis and persistent diuresis in the post-treatment normoglycemic period.

Keywords: Diabetes mellitus; polyuria; sodium-glucose transporter 2

Sodium glucose cotransporter 2 (SGLT2) inhibitors are oral antidiabetic drugs that improve urinary excretion of glucose, in this way regulating glycemic control and promoting weight loss.[1] The mechanism of action of SGLT2 inhibitors is a blood sugar reduction independent of insulin.[2] Diabetic ketoacidosis (DKA) is most serious acute metabolic complication of diabetes.[3] The use of oral antidiabetic agents including SLGT-2 inhibitors in the treatment of diabetic ketoacidosis is rare.[4,5] In the literature, the case of euglycemic diabetic ketoacidosis associated with canagliflozine has been discussed. In this case; persistent diuresis is discussed after normoglisemia.[6] However, an article about dapagliflozin is not available in the literature. In this article we will present diabetic ketoacidosis developed during the use of dapagliflozin. Persistent diurezis was discussed after acidosis was treatment and normoglycemia was maintained.

CASE REPORT

55 years old male patient who had diabetes mellitus and HbA1c 15 mg/dL was recommended intensive insulin therapy by his internal medician doctor. The patient refused to use this treatment. Another doctor prescribed vildagliptin-metformin and dapagliflozin treatment to the patient. The patient used only dapagliflozin from this treatment regimen. The patient was brought back by his relatives due to nausea and vomiting after 4 months of starting oral antidiabetic treatment. The patient had nausea, vomiting and abdominal pain. On the day of admission to the hospital, the change of consciousness developed. He did smoke but didn't use alcohol.

Exemination on patient was at the agitation and delirium clinic. The patient's blood pressure was 90/50 mmHg, his heart rate was 107 beats/min, and his temperature was 36,3°C. A urinalysis detected leucocyturia, glycosuria, ketonuria; venous blood gas analysis showed high anion gap metabolic acidosis-pH: 6.92- and a normal lactate level (Lac: 1.1), HCO^3: 6.8, pCO^2: 17. The patient had severe metabolic acidosis. His biochemistry outcome showed electrolyte disturbance and hyperglycemia (300 mg/dL), creatinin: 1.5 mg/dL, urea: 85.3 mg/dL, sodium level is 132 mmol/L, potassium level is 4,9 mmol/L, clor level is 92 mmol/L, calcium level is 8,8 mg/dL, serum c-peptide level was measured 4 months prior, it was 2,48 ng/mL. His biochemical data is shown in Table 1. His blood count revealed neutrophil-induced leukocytosis. Empirical ceftriaxone therapy was started for urinary tract infections. No recurrence was detected in the urine culture from the patient. Daily glycosuria didn't follow up.

The patient's oral antidiabetic agent was discontinued cause of diabetic ketoacidosis. At first implemented isotonic saline added sodium bicarbonate and a continuous insulin infusion. Aggressive sodium bicarbonate therapy was given because the pH was at a level that was inconsistent with life. In the patient's follow up; 5% dextrose infusion was added to the patient because his acidosis did not improve even though his blood sugar was <200 mg/dL. The next day the urea and creatinin values declined to normal levels. The infusion of dextrose and saline with sodium bicarbonate continued because the patient had resistant acidosis. On the 2nd day of hospitalization metabolic acidosis improved, delirium clinic retreated and oral nutrition was initiated. Therefore the basal bolus regimen was switched from insulin infusion therapy. Excessive urination since the patient's hospitalization was continued despite the provision of normoglycemia. Therefore, oral fluid intake of the patient was restricted. Despite the restriction of oral fluid intake, the patient's polyuria continued and there was

TABLE 1: Laboratory values of the patient during hospitalization.

Parameters	1. day	2. day	3. day	4. day	5. day
Serum creatinin (mg/dL)	1.5	1.2	0.9	1.1	0.9
Serum glucose (mg/dL)	300	106	108	160	140
pH	6.91	7.21	7.26	7.30	7.34
HCO_3	6	14	17	19	23
Urine glucose	+++	+++	+++	+++	+++

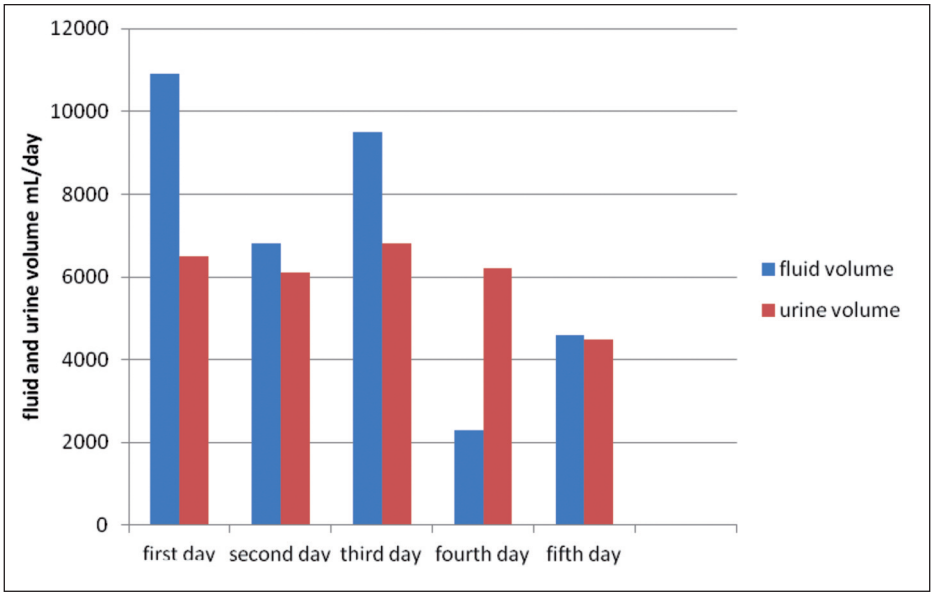

FIGURE 1: Patient's total fluid support and urine outflow chart during hospitalization.

7000 ml of urine output. In Figure 1, the patient's oral fluid intake and urine output were showed. Patient's oral fluid intake restricted on the fourth day of treatment cause of polyuria, even so urine output was not reduced. Glycosuria continued from the first day of hospitalization to discharge; although blood sugar decline to normal levels on second day. On the 10th day of hospitalization, the patient was discharged with basal bolus insulin regimen. The patient did not come to polyclinic control.

DISCUSSION

SGLT-2 inhibitors, the first member of dapagliflozin; have been widely used in the treatment of Type-2 diabetes mellitus. Various previous studies have shown that; the effect of blood sugar reducing of SGLT-2 inhibitors is due to inhibition of glucose reabsorption at the kidney level.[7,8]

Depending on this polyuria develops and may lead to dehydration. This effect is clearly demonstrated in a study of rats with dapagliflozin.[9] Canagliflozin is another member of SGLT-2 inhibitors. In a recent case report; patient has euglycemic acidosis and polyuria occurring whose receiving canagliplozin treatment has been discussed. According to this case report there is still ongoing polyuria even after the patient has had euglycemia.[6] In another previous study shown that, polyuria was continued even after 11 days of discontinuation of SGLT-2 inhibitors.[10]

In our case on the 7th day of treatment, the serum glucose measurement was 96 mg/dL, therefore the urine measurement showed +++ glycosuria. In our case that we have presented; there was a polyuria that did not respond to oral fluid restriction. polyuria that does not respond to oral fluid restriction; may be the effect of dapagliflozin due to nephrogenic or central diabetes insipidus enhancer. The findings of this case emphasize that; SGLT-2 inhibitors may cause severe diabetic ketoacidosis, persistant polyuria and dehydration.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ahmet Gülmez;* ***Design:*** *Ahmet Gülmez, Tuğba Kandemir Gülmez;* ***Inspection/Consultancy:*** *Ahmet Gülmez;* ***Data Collection and/or Processıng:*** *Ahmet Gülmez, Tuğba Kandemir Gülmez;* ***Analysis and/or Comment:*** *Ahmet Gülmez, Tuğba Kandemir Gülmez;* ***Welding Arrangements:*** *Ahmet Gülmez, Tuğba Kandemir Gülmez;* ***Complete Writing:*** *Ahmet Gülmez, Tuğba Kandemir Gülmez;* ***Critical Investigation:*** *Ahmet Gülmez, Tuğba Kandemir Gülmez;* ***Resources and Fund Provision:*** *Ahmet Gülmez; Materials: Ahmet Gülmez.*

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