

## Euglycemic Diabetic Ketoacidosis When Reducing Insulin Dosage in Patients Taking Sodium Glucose Cotransporter 2 Inhibitor

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Sodium glucose cotransporter 2 (SGLT2) inhibitor has been recently reported of diabetic ketoacidosis due to accumulation of ketone bodies in patients with severe dehydration caused from such like diarrhea even though the patient had normal glucose level. This is a case of ketoacidosis in normal glucose level as production of ketone bodies is stimulated in liver with increased secretion of glucagon by stimulation of  $\alpha$  cells in pancreas due to increase of lipolysis caused from reducing insulin and by SGLT2 inhibitor among patients who are under concurrent insulin and SGLT2 inhibitor. Thus, insulin dosage reduction requires caution in order to control blood glucose level on combined treatment of SGLT2 inhibitor in a patient who is administering insulin because the patient may be caused ketoacidosis in normal blood glucose level. (Ewha Med J 2017;40(1):55-58)

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### Key Words

Diabetic ketoacidosis; Sodium glucose cotransporter 2

### Introduction

Diabetes is a disease that poses difficulty in controlling glucose as period of treatment becomes longer despite the concomitant administration of multiple drugs including insulin [1]. Due to such facts, recently drugs of various mechanisms are being developed, contributing in controlling glucose level. However, precaution is necessary as side effects of the drugs are being reported as well. Such side effects can be diverse depending on the individual traits and American Diabetes Association recommends customized antidiabetic strategy according to individual trait of patients (hyperlipidemia, hypertension, insulin resistance, etc.) [2]. Furthermore, understanding characteristics of various drugs and minimizing occurrence of side effects are crucial.

Recently released sodium glucose cotransporter 2 (SGLT2) inhibitor controls glucose by blocking reabsorption of glucose

in kidney and is known to lower body weight as well as blood pressure [3,4]. However, other than genital infection anticipated from such mechanism, death due to dehydration or diabetic ketoacidosis (DKA) is being reported as side effect, requiring caution when prescribed [5].

While general diabetic ketosis is accompanied by hyperglycemia, ketosis can occur in normal glucose when taking SGLT2 inhibitor. Therefore, ketosis must not be overlooked even in low or normal glucose level in patient taking SGLT2 inhibitor.

The authors experienced euglycemic DKA during the reduction of insulin dose due to the possibility of hypoglycemia because there was hypoglycemia during glucose control by multiple daily injection (MDI) insulin therapy and SGLT2 inhibitors and report it along with literature review.

## Case

The patient was 39-year-old female who had been diagnosed with type 2 diabetes 14 years ago. The patient did not receive any treatment for her diabetes and not sufficiently manage her blood glucose, but she started MDI insulin therapy since diabetic retinopathy was diagnosed in an examination 5 years ago. She had been treated with subcutaneous injection of 22 units of insulin glargine after dinner and 10 units of insulin glulisine before every meal until 8 months ago. The patient also took 1,000 mg of metformin, an oral antidiabetic drug, additionally. But the hemoglobin A1c was not controlled below 8.6%, and she additionally took 10 mg of dapagliflozin 8 months ago, and after taking dapagliflozin, the hemoglobin A1c was decreased to 6.4% on monitoring after 3 months of taking dapagliflozin. There was no sign of dehydration or genital infection after taking dapagliflozin, and body weight increased in 3 months after treatment from 66.4 kg to 68.9 kg, but showed decrease afterwards. After taking dapagliflozin, the patient sporadically felt hypoglycemia in fasting state before meal and glucose level in self-monitoring glucose test taken 1 hour after meal was 130 mg/dL, so the patient was reduced of her dosage to 20 units of insulin glargine and 8 units of insulin glulisine (Table 1).

Afterwards, there had been no other specific signs and the patient was followed up, but 9 days ago when the patient ingested meat, the patient experienced vomiting 3–4 times. The symptom alleviated, but during follow-up, the patient again

showed pain in left side of abdomen, nausea, and vomiting 3 days ago and visited emergency room. Self-measured glucose level before visit was about 100 mg/dL in fasting state, 150 mg/dL in 2 hours after meal. Other drugs the patient was taking other than antidiabetic drug was pregabalin, naloxone, and oxycodone for diabetic neuropathy and magnesium for constipation.

Upon arrival to emergency room, her blood pressure was 120/80 mmHg, pulse rate 110/min, respiratory rate 25/min, body temperature 36.8°C and her consciousness was clear. Though her oral mucosa was dry, but there was no odor of acetone. Lung, cardiac, and bowel sound were normal, and there was no edema. The patient complained of pain in her left side of abdomen, but not costovertebral angle tenderness. There was no observation of fever or increase of C-reactive protein which may be considered as symptoms of special external injuries or infections, and she has experienced no surgery. The patient's height was 160 cm, body weight, 62.5 kg, and body mass index (BMI) 24.4 kg/m<sup>2</sup>. As for family history, mother of the patient was receiving treatment for diabetes and had history of caesarian deliveries, 12 and 9 years ago.

In peripheral blood test conducted in emergency room, her white blood cell (WBC) was 12,150/mm<sup>3</sup> (polymorphonuclear neutrophils 89.6%, lymphocyte 9.1%, monocyte 1.1%), plasma glucose 178 mg/dL. In arterial blood gas analysis, her blood showed pH of 7.256, HCO<sub>3</sub><sup>-</sup> 13.3 mEq/L, pCO<sub>2</sub> 30.6 mmHg, pO<sub>2</sub> 105.3 mmHg, anion gap 22.4 mEq/L, with blood ketone body of 3.4 mmol/L (reference <0.6 mmol/L), lactate, 1.6

**Table 1.** Changes in hemoglobin (Hb) A1c and body weight by treatment method

| Date          | Hb A1c (%) | Treatment  | BW (kg) | BMI (kg/m <sup>2</sup> ) |
|---------------|------------|--|---------|--------------------------|
| 20 mo ago     | 8.9        | IG 20 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID                                | -       | -                        |
| 17 mo ago     | 9.1        | IG 22 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID                                | 66.4    | 25.7                     |
| 14 mo ago     | 8.3        | IG 22 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID                                | -       | -                        |
| 11 mo ago     | 7.8        | IG 22 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID                                | -       | -                        |
| 8 mo ago      | 8.6        | IG 22 unit on AL + IGL 10 unit on EBM + metformin 500 mg BID + SGLT2 inhibitor 10 mg start | 63.9    | 27.3                     |
| 5 mo ago      | 6.4        | IG 20 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID + SGLT2 inhibitor 10 mg        | 68.9    | 27.1                     |
| 2 mo ago      | 6.6        | IG 20 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID + SGLT2 inhibitor 10 mg        | 67.2    | 26                       |
| At admission  | -          | IG 20 unit on AL + IGL 8 unit on EBM   | 62.5    | 24.4                     |
| After 12 days | -          | IG 20 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID + vildagliptin 50 mg BID       | 62.5    | 24.4                     |
| After 1 mo    | 7.2        | IG 20 unit on AL + IGL 8 unit on EBM + metformin 500 mg BID + vildagliptin 50 mg BID       | -       | -                        |

BW, body weight; BMI, body mass index; IG, insulin glargine; AL, after lunch; IGL, insulin glulisine; EBM, every before meals; BID, bis in die; SGLT2, sodium glucose cotransporter 2.

nmol/L, and creatinine 0.56 mg/dL. In ketone body fraction test conducted after admission, her acetoacetate 2,532.1  $\mu$ mol/L, total ketone, 3,982.6  $\mu$ mol/L, and  $\beta$ -hydroxybutyric acid, 1,450.5  $\mu$ mol/L. Her fasting C-peptide was 0.72 ng/mL and fasting insulin, 12.97  $\mu$ U/mL. Fasting C-peptide and insulin which were measured before occurring diabetic ketoacidosis were 0.62 ng/mL and 19.76  $\mu$ U/mL, respectively.

Though her glucose level was not significantly high at the time of visit, with 178 mg/dL, as she showed ketoacidosis with pH 7.256, anion gap 22.4 mEq/L, and blood ketone body 3.4 mmol/L (reference <0.6 mmol/L), normal saline was continuously infused for treatment. In the test conducted in 24 hours after the visit, the patient showed deterioration with pH, 7.176 and anion gap, 24.3 mEq/L, but since her chief complaint of nausea and vomiting was alleviated, the patient started having her meal along with saline treatment and intensive insulin therapy. Early dose of insulin was 20 units of insulin glargine after dinner and 8 units of insulin glulisine before each meal. Daily administration of 3 L normal saline was maintained. Then, in 36 hours after visit, the patient's acidosis was corrected with pH, 7.406 and anion gap, 18 mEq/L. The patient was followed up while she maintained MDI therapy and started taking 100 mg of vildagliptin from the fourth day of her admission and 1,000 mg of metformin from the fifth day. Currently, the patient is on follow-up and hemoglobin A1c taken 1 month after discharge was 7.2%, with no other abnormal findings.

## Discussion

Unlike drugs that lower glucose level by increasing sensitivity on insulin or its secretion, SGLT2 inhibitor blocks glucose reabsorption, independent of insulin, to lower glucose. Therefore, calorie is removed as well, creating additional merit of body weight reduction and urine creation is increased, which reduces blood pressure as well [4]. Also, as it is independent of insulin secretion, there is lower risk of hypoglycemia [3]. However, with excessive renal excretion of glucose, urinary or genital infection may occur. Genital infection is more common in women and more common than urinary infection. Other than bacterial infection, risk of fungal infection increases, but in most cases, it has been treated with standard antifungal medication and has not reoccurred [6]. Furthermore, dehydration due to loss of hydration from osmotic diuresis due to excessive excretion of

glucose in urine is reported as common side effect [6].

DKA can occur in diabetic patients due to increase of counter regulatory hormones in stress condition such as insulin deficiency, trauma, and surgery. Increase of counter regulatory hormones like glucagon, catecholamine, cortisol, and growth hormone leads to glycogenolysis and gluconeogenesis, which ultimately result in hyperglycemia. Hyperglycemia is accompanied by osmotic diuresis, dehydration, reduced glomerular filtration and as decrease of glucose transporter4 due to reduced insulin amounts in peripheral muscles, gluconeogenesis and increased lipolysis to compensate for deficient glucose usage cause increased free fatty acids, acetoacetic acid and ketogenesis which result in metabolic acidosis. [7].

Diagnostic criteria for DKA were plasma glucose >250 mg/dL, arterial blood pH <7.3, plasma  $\text{HCO}_3^-$  <15 mEq/L and existence of moderate ketosis or ketonuria [8]. As the above diagnostic criteria, increase of blood glucose is generally observed when occurring DKA, however, it has been recently reported that euglycemic DKA can be occurred at normal blood glucose level if a SGLT2 inhibitor-taking patient has on dehydration caused by such like diarrhea [9]. This study considers a case which is somewhat similar to existing cases but this case is caused by increase of ketone bodies as reducing insulin on no-dehydration. It is difficult to determine the mechanism of ketoacidosis; however, it could be considered that ketoacidosis may be caused by increasing concentration of blood ketone body as stimulating ketone production in liver due to increase of glucagon secretion as stimulating  $\alpha$  cells of pancreas by SGLT2 inhibitor and as increasing synthesis of ketone in liver due to increase of lipolysis if a SGLT2 inhibitor administering patient reduces the insulin dose. In addition, for renal tubule in kidney, ketoacidosis may be caused by increase of blood ketone bodies as decrease clearance of ketone bodies in kidney by more reabsorbing negatively charged ketone bodies from formation of electrochemical gradient which is caused by increase of sodium concentration in renal tubular fluid as inhibiting reabsorption of sodium. In addition, sodium gradient in renal tubular due to SGLT2 inhibitor induces ketoacidosis by promoting reabsorption of monocarboxylate anions such as acetate and  $\beta$ -hydroxybutyrate through the sodium-monocarboxylate transporter existing in the apical membrane of renal tubular epithelium [10]. Therefore, it is more important to examine ketonuria rather than blood ketone body for screening of ketoacidosis among patients

who are taking SGLT2 inhibitor.

Thus, patients taking SGLT-2 inhibitor may have ketoacidosis despite their euglycemic state, and in case the patients complain of symptoms such as nausea and abdominal pain, it is required to confirm blood or urine ketone bodies. Besides, the patients with concurrent insulin medication should be paid more attention than other patients.

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