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Euglycemic diabetic ketoacidosis with SGLT2 inhibitors in lean type 2 diabetes

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Abstract

We experienced a case of euglycemic diabetic ketoacidosis after adding SGLT2 inhibitor to current medications in type 2 diabetes. She was 57 years old and DM duration was 3 years. She had low body mass index (< 18 mg/m^2) which may mean relative insulin deficiency state. Her ketone body levels and fasting serum glucagon levels were higher with SGLT2 inhibitors and decreased after stopping them. Their DKA were improved by stopping SGLT2 inhibitors, hydration with insulin treatment.

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are novel anti-hyperglycemic agents showed surprisingly significant reductions in cardiovascular mortality and all-cause mortality [1]. While the exact mechanisms why SGLT2 inhibitors dramatically improved CV outcome are not clear, one of explanations for them is that they lower not only glucose but also weight and blood pressure [2]. In terms of weight loss, SGLT2 inhibitors produce weight loss of ~2-3 kg, secondary to the 280-320 kcal/day loss because 70-80 g of glucose is excreted in the urine [3,4]. Since type 2 diabetes are usually more obese than non-diabetes, SGLT2 inhibitors may be the first medication after metformin for obese diabetic patients. But, weight loss could be a concern for patients with low body weight after SGLT2 inhibitors treatment.

We recently experienced a case of euglycemic diabetic ketoacidosis with SGLT2 inhibitors in lean type 2 diabetes.

Case reports

A 57-year-old woman was diagnosed with diabetes at the age of 54 years. Her height was 163 cm, body weight was 47 kg and body mass index was 17.7 kg/m^2. She had family history of diabetes. She did not have history of diabetic ketoacidosis. She received glimepiride (4 mg/day), metformin (2,000 mg/day) and sitagliptin (100 mg/day), but her HbA1c was 8.5%. She strongly refused insulin injection because she had skin reaction with several kinds of insulins. We added SGLT2 inhibitor, dapagliflozin (10 mg/day) to previous medications for 28 days before admission. After taking a SGLT2 inhibitor, epigastralgia progressively developed and dietary intake decreased. Nausea and vomiting were developed 2 days before admission. There were no infectious diseases evidenced by chest X-ray, electrocardiogram, and urinary sediments. We stopped dapagliflozin and continuous intravenous insulin, Ringer's solution and glucose infusion was initiated. Ketoacidosis was improved after 1 day. Table 1 shows her baseline characteristics checked before dapagliflozin medication. Her laboratory findings at admission and follow up are shown at table 2.

Discussion

We experienced a case of euglycemic diabetic ketoacidosis after adding SGLT2 inhibitor to current medications in type 2 diabetes. While she did not have history of DKA and any other evidence of insulin deficiency, she had low body mass index (< 18 mg/m^2) which may mean relative low beta cell mass. Her DKA was improved by hydration with insulin treatment.

SGLT2 inhibitors are one of the most promising and popular anti-diabetic medications these days. Their main adverse effects are increase of genital fungal infections and bacterial urinary tract infections, polyuria and volume depletion, particularly in patients taking loop diuretics and the elderly [3,5,6]. Recently, there are case reports of diabetic ketoacidosis in patients with type 1 diabetes or T2DM treated with SGLT2 inhibitors [7-9]. Diabetes ketoacidosis (DKA) is largely associated with type 1 diabetes and severe hyperglycemia is a cardinal feature. SGLT-2 inhibitor-associated DKA were also more common in type 1 diabetes than type 2 diabetes. Contrast to traditional DKA, they did not show severe hyperglycemia, so they are called euglycemic DKA

Table 1. Baseline characteristics of case. Ab: Antibody; GAD: Glutamic Acid Decarboxylase; IA-2: Insulin Autoimmune-2; NC: Not Checked.

FBS	198 mg/dL
HbA1c	8.5%
C-peptide	1.2 ng/mL
Anti-GAD Ab	<0.3 U/mL
Anti-IA2 Ab	<0.4 U/mL
Insulin Ab	<0.4 U/mL

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Table 2. Laboratory data at admission and follow up of case. ALT: Alanine Transferase; AST: Aspartate Aminotransferase; BUN: Blood Urea Nitrogen; Cr: Creatinine; Na: Sodium; K: Potassium.

	At admission	Day 3	Day 7
FBS (mg/dL)	199	168	161
HbA1c (%)	8.4	NC	NC
Na (mmol/L)	141	138	139
K (mmol/L)	4.3	4.1	4.2
AST (IU/L)	30	NC	22
ALT (IU/L)	26	NC	24
Amylase (IU/L)	51	49	50
Lipase (IU/L)	47	46	47
BUN (mg/dL)	21.3	14.0	10.1
Cr (mg/dL)	0.5	0.6	0.5
Ketone body (μmol/L)	7321	5313	4900
Blood gas analysis-pH	7.05	7.34	7.40
Glucagon (pg/mL)	309	250	135

or ketosis. The absence of significant hyperglycemia in these patients made their detection and treatment delayed by physicians and patients.

There are lots of questions and concerns about how SGLT2 inhibitors cause DKA. Insulin dose reduction is an important contributing factor associated with SGLT2 inhibitor-induced ketoacidosis. Because of the glucose-lowering property of SGLT2 inhibitors, doses of insulin were decreased to minimize the risk of hypoglycemia [10]. The resulting decrease in circulating insulin levels can cause to increase the lipolysis in adipose tissue and ketogenesis in the liver. These changes predicted to increase circulating ketone body levels. Elevated ketone body levels with SGLT2 inhibitors have another explanation. We checked ketone body levels of our case after admission and follow up, but did not check before SGLT2 inhibitor treatment. Her levels of ketone body were decreased after stopping SGLT2 inhibitors, which means SGLT2 inhibitor increased their ketone body levels.

One study showed that phlorizin (a nonselective SGLT1/SGLT2 inhibitor) promoted renal tubular reabsorption of acetoacetate [11]. Reabsorption of negatively charged ketone bodies would be accelerated by decrease of Na^+ reabsorption and subsequent increases the concentration of Na^+ in the renal tubular fluid. In addition to increased ketone body production, decreased renal clearance exert an additive effect to increase circulating ketone body levels. We did not check urine ketone body levels in our case. Human studies showed that SGLT-2 inhibitors are associated with an increase in plasma glucagon levels through uncertain mechanisms [12,13]. Hyperglucagonemia increases the propensity toward ketone production [14]. Recent one study showed SGLT2 is expressed on pancreatic α-cells and SGLT2 inhibitors directly increase glucagon synthesis and secretion from pancreatic alpha cells [15]. Our case showed that fasting serum glucagon levels were higher with SGLT2 inhibitor than without SGLT2 inhibitor.

Action mechanism of SGLT2 inhibitors is kidney tubular glucose reabsorption, so their effects have been suggested to be insulin-independent. These made physician use this novel drug for any stage of type 2 diabetes classified by degree of insulin deficiency. But, type 1 diabetes have higher chances of DKA with SGLT2 inhibitors than type 2 diabetes means severe insulin deficiency can be predisposing factor for SGLT2 induced DKA. Low body weight may mean relative insulin deficiency is more dominant pathophysiology than insulin resistance even in type 2 diabetes. While our case did not have very low c-peptide level like type 1 diabetes, insulin deficiency might be a risk factor for their DKA.

One study reported that tofogliflozin, one of SGLT2 inhibitors, caused a dose-dependent increase of total ketone body levels in type 2 diabetes, but the ranges of plasma levels were wide evidenced by large SD [16]. This can suggest that some individuals experienced a clinically relevant increase in ketone body levels, but not others. In terms of fuel energetics, SGLT2 inhibitors thereby can improve myocardial/renal work efficiency and function by elevation of ketone body [17]. They suggested that empagliflozin shifted myocardial fuel metabolism from fat/glucose oxidation to a more energy-efficient ketone bodies, which is beneficial CV event. These results may suggest that there are better way to individualize SGLT2 inhibitors for type 2 diabetes depending on degree of ketone body level elevations and insulin deficiency state.

In conclusion, we experienced a case of SGLT2 induced DKA in lean type 2 diabetes. Her ketone body levels and fasting serum glucagon levels were higher with SGLT2 inhibitors and decreased after stopping them. They were completely improved by quitting SGLT2 inhibitors and insulin and fluid treatment.

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