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Euglycemic diabetic ketoacidosis: A rare but serious side effect of sodium-glucose co-transporter 2 inhibitors

Lakušić N *et al.* Diabetic ketoacidosis and SGLT2 inhibitors

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Abstract

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication and from recently established therapy in chronic heart failure patients. A rare, but potentially life-threatening complication of SGLT2 inhibitor use is euglycemic diabetic ketoacidosis. We described a case of a middle-aged male patient with type 2 diabetes who developed metabolic ketoacidosis after a few days of empagliflozin administration. SGLT2 inhibitor related ketoacidosis presents with euglycemia or only modestly elevated glucose blood concentrations, which causes delayed detection and treatment of ketoacidosis. There are multiple possible risk factors and mechanism that might contribute to the pathogenesis of ketoacidosis. It is implied that SGLT2 inhibitor use and prescription by non-diabetologists (cardiologists, nephrologists, family physicians, *etc.*) will continue to grow in the future. It is important to inform the general cardiac public about this rare but serious side effect of SGLT2 inhibitors.

Key Words: Sodium-glucose co-transporter 2 inhibitors; Euglycemic diabetic ketoacidosis; Chronic heart failure

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Core Tip: Sodium-glucose co-transporter 2 inhibitors have recently become an established treatment for most chronic heart failure (CHF) patients (with and without diabetes), and it is important for the cardiologist to know their side effects, including those that are rare, but serious, like euglycemic ketoacidosis. In this way, an unwanted outcome of CHF treatment can be avoided.

TO THE EDITOR

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are an insulin-independent class of oral antihyperglycemic medication which decrease the reabsorption of glucose in the renal tubules, causing urinary glucose excretion and thereby modestly lowering elevated blood glucose levels in patients with type 2 diabetes. The SGLT2 receptors are expressed in the proximal tubule of the kidney and mediate reabsorption of 90% of the filtered glucose load. By their mechanism of action, SGLT2 inhibitors also modestly decrease blood pressure (osmotic diuresis) and weight (reduction in adipose tissue as well as calorie loss through glycosuria)^[1].

According to the latest European Society of Cardiology guidelines on chronic heart failure (CHF)^[2], SGLT2 inhibitors (empagliflozin, dapagliflozin) are equally used along with other established therapy for CHF. They can be used in patients with reduced, but also preserved (empagliflozin) ejection fraction of left ventricle, with or without diabetes^[3]. The SGLT2 inhibitors achieve beneficial effects by lowering blood pressure, stimulation of natriuresis and diuresis, neurohormonal effect, improvement of cardiac energy metabolism, reduction in inflammation, *etc.*^[4]. SGLT2 inhibitors improve cardiovascular outcomes and have a similar effect as a group of drugs in preventing HF and chronic kidney disease progression (class effect), efficacy in secondary prevention of atherosclerotic cardiovascular disease events (empagliflozin and canagliflozin) and in preventing cardiovascular mortality (empagliflozin)^[5].

Euglycemic diabetic ketoacidosis^[6] is a known and rare complication of SGLT2 inhibitor use and can potentially lead to a life-threatening situation, especially if not recognized in time^[7]. Shortly, we would like to describe a case of middle-aged male

patient with type 2 diabetes, without CHF, who developed metabolic ketoacidosis after a few days of empagliflozin administration.

⁷ The patient is a 42-year-old male with a history of type 2 diabetes treated with metformin for three years, which he took very irregularly. One week before hospitalization, he was administered the combination ¹⁴ of empagliflozin 12.5 mg/metformin 1000 mg twice daily. Two days after starting the medication he reported nausea and diarrhea, then vomiting with a feeling of fatigue and malaise. Diabetic ketoacidosis (ketonuria 8 mmol/L, arterial blood gas (ABG) analysis-pH 7.23, glucose 9.7 mmol/L) was diagnosed and the patient was urgently hospitalized. Parameters of renal function and serum kalium level were within referent range. Metabolic acidosis was successfully managed after two days of standard treatment (prompt fluid resuscitation with crystalloid solutions and monitoring of electrolyte and ketones, low-dose intravenous insulin) and omission of empagliflozin from further therapy. ¹² On the third day of treatment, the patient was discharged from the hospital with new recommended therapy-basal and fast-acting insulin and metformin.

⁴ Diabetic ketoacidosis is a complex metabolic disorder characterized by hyperglycemia, acidosis, and ketonuria, which usually develops in patients with diabetes when insulin levels are too low (absolute or relative insulin deficiency that is accompanied by an increase in counter-regulatory hormones, *i.e.*, glucagon, cortisol, *etc.*). In the absence of insulin, lipolysis is stimulated instead of glycogenolysis for energy production, consequently increasing ⁸ ketone levels followed by their accumulation in the blood leading to acidosis. Diabetic ketoacidosis most commonly occurs in patients with type 1 diabetes and is usually accompanied by high blood glucose levels^[8]. Increased risk of ketoacidosis was described among SGLT2 patients and several mechanisms might contribute to the pathogenesis-SGLT2 inhibitors ² decrease glucose level by an insulin-independent mechanism, ² increase the rates of lipolysis in adipose tissue and ketogenesis in the liver (increasing circulating ketone body levels), ² increase plasma glucagon levels, increase preproglucagon gene expression by acting directly upon pancreatic α -cells, and also SGLT2 inhibitors could decrease

renal clearance of ketone bodies (e.g., phlorizin-a nonselective inhibitor of SGLT1 and SGLT2, which increase renal tubular reabsorption of acetoacetate), etc^[9]. Ketone body levels are elevated in patients receiving SGLT2 inhibitor treatment (and in patients with HF) so it is important to emphasize that failing myocardium in diabetic heart and in HF patients is unable to optimally use traditional substrates (free fatty acid, glucose) but can effectively use ketone bodies as an alternative for energy production. Changes that may include critical effects of SGLT2 inhibitors are those in shifting metabolism from fat/glucose oxidation to ketone bodies and thereby improving myocardial and renal function^[10].

The incidence of ketoacidosis in patients using SGLT2 inhibitors is about 2 per 1000 treated patients^[11]. It is important to emphasize that SGLT2 inhibitor-associated ketoacidosis presents with euglycemia or only modestly elevated glucose blood concentrations, which causes delayed detection and treatment of ketoacidosis. Some of the risk factors for developing ketoacidosis in patients treated with SGLT2 inhibitors are prior diabetic ketoacidosis, hemoglobin A1C above 10%, recent hypoglycemia, low baseline serum bicarbonate levels, use of digoxin and medications for dementia^[11] or concomitant therapy with pioglitazone^[12]. Given that thiazolidinediones, including pioglitazone, can cause fluid retention, as such are contraindicated in patients with NYHA class III and IV heart failure, and are not recommended in patients with symptomatic heart failure^[2].

Patients with CHF are a complex group of patients with numerous comorbidities that require specific and differentiated treatment and close monitoring^[13]. Since SGLT2 inhibitors have recently become an established treatment for most CHF patients with and without diabetes^[2], and their use and prescription by non-diabetologists (cardiologists, nephrologists, and family physicians, etc.) will continue to grow in the future. Indeed, there are recommendations and suggestions that SGLT2 inhibitors and beta-blockers might be the first line of treatment for patients with CHF with reduced ejection fraction of left ventricle^[14].

Therefore, the main purpose of this letter is to inform and warn the general cardiac public about this ¹⁷ rare but serious side effect of SGLT2 inhibitors. In case of ⁵ nausea, vomiting, or malaise in patients taking SGLT2 inhibitors, prompt response and diagnostic screening are necessary. Serum ketones and ABG analysis should be obtained in any patient presenting these symptoms, ⁵ and SGLT2 inhibitors should be discontinued if acidosis is confirmed. In this way, serious side effects and an unwanted outcome of CHF treatment can be avoided.

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