SCIENTIFIC LETTER

# Postoperative Euglycemic Ketoacidosis Associated with Sodium-Glucose Cotransporter-2 Inhibitors Following Cardiovascular Surgery: A Case Series

*Cetoacidosis euglucémica por iSGLT2 en el postoperatorio cardiovascular: serie de casos*

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Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have revolutionized the treatment of diabetes mellitus and heart failure across the entire spectrum of ventricular function. However, their use has been associated with a rare but potentially life-threating complication: euglycemic ketoacidosis (EKA). This condition is characterized by metabolic acidosis and ketosis despite normal blood glucose levels. (1) The profound metabolic stress associated with cardiovascular surgery may precipitate this condition. (2)

The aim of this report is to describe four cases of EKA associated with dapagliflozin therapy in the postoperative period following cardiovascular surgery and to discuss the underlying pathophysiological mechanisms. (Table 1)

Case 1. Coronary artery bypass grafting and aortic valve replacement in a patient with insulin-dependent type 2 diabetes mellitus

A 55-year-old male patient with hypertension, dyslipidemia, obesity (body mass index [BMI], 37.2 kg/m$^2$), and a sedentary lifestyle had a long-standing history of insulin-dependent type 2 diabetes mellitus with poor glycemic control. He underwent combined aortic valve replacement with a 23-mm bioprosthetic valve and coronary artery bypass grafting using the left internal mammary artery (LIMA) to the left anterior descending artery (LAD) and a saphenous vein to a lateral branch of the left circumflex artery. His preoperative glycated hemoglobin (HbA1c) was 9.5%. His chronic medication included dapagliflozin 10 mg once daily, metformin, and both human insulin and insulin glulisine. The procedure was performed using cardiopulmonary bypass (CPB), with a 101-min CPB time and an 80-min aortic cross-clamp time. On postoperative day 1, the patient developed EKA (blood glucose, 179 mg/dL; pH, 7.30; bicarbonate, 8.6 mEq/L), requiring intravenous insulin infusion.

Case 2. Aortic valve replacement in a patient with non-insulin-dependent type 2 diabetes mellitus

A 60-year-old male patient, a former smoker, with overweight. His main cardiovascular condition was severe symptomatic aortic stenosis. He had non-insulin-dependent type 2 diabetes mellitus and was chronically treated with dapagliflozin and metformin 850 mg twice daily. He underwent surgical aortic valve replacement with a 25-mm bioprosthetic valve, with a 64-min CPB time and a 54-min aortic cross-clamp time. In the immediate postoperative period, he developed metabolic acidosis and his blood glucose was 189 mg/dL. The condition was interpreted as SGLT2i-associated ketoacidosis, which resolved after initiation of intravenous insulin infusion.

Case 3. Coronary artery bypass grafting (CABG) in a patient with heart failure and non-insulin-dependent type 2 diabetes mellitus

A 77-year-old female patient with a history of acute myocardial infarction (AMI), severe left ventricular dysfunction, and a 25% left ventricular ejection fraction (LVEF). She had non-insulin-dependent type 2 diabetes mellitus ($HbA_{1c}$, 6.2%). Her treatment regimen included dapagliflozin 10 mg, sacubitril/valsartan, and sitagliptin. She underwent off-pump CABG with a left internal mammary artery (LIMA) to the left anterior descending (LAD) artery and a saphenous vein to the right coronary artery (RCA). The patient developed postoperative EKA (blood glucose, 197 mg/dL; pH, 7.28; bicarbonate, 16.1 mEq/L) associated with surgical stress and prior SGLT2 inhibitor use.

Case 4. Aortic valve replacement in a patient with heart failure without diabetes mellitus

A 78-year-old male patient with a history of severe aortic stenosis and heart failure with preserved left ventricular ejection fraction (LVEF, 65%). Importantly, the patient did not have diabetes mellitus; he was receiving dapagliflozin 10 mg once daily for the treatment of his heart failure. He underwent a surgical aortic valve replacement with a 23-mm bioprosthetic valve using cardiopulmonary bypass, with a 69-

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**Table 1.** Clinical and laboratory parameters of the 4 cases

| Parameter | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Age / Sex | 55, M | 60, M | 77, F | 78, M |
| SGLT2i indication | Insulin-dependent diabetes mellitus | Non-insulin dependent diabetes mellitus | Diabetes + HF | HF |
| HbA1c (%) | 9.5 | 7.3 | 6.2 | Not available |
| Creatinine (mg/dL) / ClCr | 1.37 / 57 | 1.0 / 81.4 | 2.29 / 57 | 1.65 / 40.7 |
| LVEF (%) | 62 | 41–49 | 25 | 60–69 |
| Initial blood glucose | 179 mg/dL | 189 mg/dL | 197 mg/dL | 102 mg/dL |
| pH | 7.30 | 7.28 | 7.28 | 7.25 |
| Bicarbonate (mEq/L) | 8.61 | 16.3 | 16.15 | 16.97 |
| BE / Anion Gap | -14.4 / Elevated | -6.9 / Elevated | -8.2 / Elevated | -10.3 / Elevated |
| Lactate (mEq/L) | 1.7 | 2.8 | 2.57 | 6.42 |
| Ketonemia | Positive | Positive | Positive | Positive |

BE: base excess; CrCl: creatinine clearance; F: female; HbA1c: glycated hemoglobin; HF: Heart failure; LVEF: left ventricular ejection fraction; M: male; SGLT2i: sodium-glucose cotransporter-2 inhibitor

min CPB time and a 53-min aortic cross-clamp time. Postoperatively, he developed shock with refractory hypotension and severe metabolic acidosis (pH, 7.25; bicarbonate,16.9 mEq/L) with a normal blood glucose level (102 mg/dL). Positive ketonemia confirmed the diagnosis of EKA. (1,2)

Diabetic ketoacidosis is defined as a metabolic acidosis (pH ≤7.3; bicarbonate ≤18 mEq/L) with an increased anion gap, hyperglycemia (blood glucose level >250 mg/dL) and positive ketone bodies (beta-hydroxybutyrate ≥3 mmol/L), according to the American College of Endocrinology. (1,2)

In SGLT2i associated diabetic ketoacidosis, the criteria described above are met, with the characteristic feature of euglycemia (usually blood glucose level <250 mg/dL). (2)

Pathophysiologically, gliflozins induce persistent glycosuria by blocking glucose reabsorption in the proximal tubule, which persists even during fasting or metabolic stress. In addition, the reduction in plasma glucose levels decreases endogenous insulin secretion; at the same time, SGLT2i directly stimulate pancreatic ć-cells, increasing glucagon secretion. This hypoinsulinemic and hyperglucagonemic state promotes lipolysis and massive hepatic ketogenesis. Furthermore, SGLT2i may reduce renal ketone body clearance, exacerbating ketone accumulation in the blood. (3)

The postoperative period following cardiac surgery represents a precipitating factor, as surgical stress increases cortisol, epinephrine, and norepinephrine levels, thereby promoting insulin resistance. Additionally, cardiopulmonary bypass may perpetuate and amplify this effect through activation of the systemic inflammatory response. Preoperative fasting further reduces circulating insulin levels.

To prevent this complication, preoperative discontinuation of SGLT2i for at least 3 to 4 days before scheduled major surgery is recommended. In patients previously receiving these agents, pH and ketones (in blood or urine) should be measured in the presence of nausea, vomiting, general malaise, or persistent metabolic acidosis, regardless of whether blood glucose level is normal. Treatment requires insulin administration with glucose-containing solutions to suppress ketone production, along with aggressive fluid replacement. (1,4)

All four patients were receiving dapagliflozin 10 mg once daily. In all cases, following the metabolic stress of cardiovascular surgery, they developed high anion gap metabolic acidosis requiring insulin infusion despite the absence of hyperglycemia (blood glucose levels approximately 180–200 mg/dL). This report underscores the importance of close metabolic monitoring in patients receiving gliflozins who undergo coronary artery bypass grafting or surgical valve replacement, in accordance with the American Association of Clinical Endocrinology and the American College of Endocrinology (AACE/ACE) safety recommendations.

Importantly, patient 4 was receiving dapagliflozin for heart failure (HF) and did not have diabetes mellitus. This finding raises the question of whether postoperative EKA following cardiovascular surgery should be attributed to perioperative stress or represents a pharmacological effect of gliflozins.

Traditionally, EKA has been associated almost exclusively with absolute or relative insulin deficiency in diabetic patients. However, it may seem paradoxical that this condition can occur in non-diabetic patients, as observed in patient 4. As previously mentioned, by promoting glucosuria, these agents reduce the insulin-to-glucagon ratio even in euglycemic individuals. In the context of cardiac surgery, where counterregulatory hormones (cortisol and catecholamines) reach

peak levels, this imbalance is amplified, promoting lipolysis and hepatic ketogenesis regardless of the patient's prior insulin reserve. (5)

It could be argued that the stress of cardiac surgery (particularly with cardiopulmonary bypass) may contribute to acidosis. While a typical surgical patient may develop stress-induced hyperglycemia or lactic acidosis due to hypoperfusion, the metabolic shift toward ketone body production characteristic of EKA levels represents a specific biochemical hallmark of SGLT2 use, making it an adverse drug event triggered by surgical trauma. (6)

Finally, all four patients were referred directly for cardiac surgery without prior cardiovascular evaluation; therefore, SGLT2i therapy was not discontinued before surgery.

### Ethical considerations

Not applicable.

### Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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