**Name of Journal:** *World Journal of Cardiology*

**Manuscript NO:** 78704

**Manuscript Type:** LETTER TO THE EDITOR

**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

Nenad Lakušić, Ivana Sopek Merkaš, Ana Marija Slišković, Dora Cerovec

**Nenad Lakušić, Ivana Sopek Merkaš, Dora Cerovec,** Department of Cardiology, Special Hospital for Medical Rehabilitation Krapinske Toplice, Krapinske Toplice 49217, Croatia

**Nenad Lakušić,** Department of Clinical Medicine, Faculty of Dental Medicine and Health Osijek, Osijek 31000, Croatia

**Nenad Lakušić,** Department of Internal Medicine, Family Medicine and History of Medicine, Faculty of Medicine Osijek, Osijek 31000, Croatia

**Ana Marija Slišković,** Department of Cardiology, University Hospital Centre Zagreb, Zagreb 10000, Croatia

**Author contributions:** Lakušić N,Sopek Merkaš I, Slišković AM were responsible for the conception and design of the manuscript, literature review, and they wrote the first original draft; Lakušić N and Cerovec D contributed in acquisition of data, analysis and interpretation, literature review, and making critical revisions related to the important intellectual content of the manuscript; all authors gave final approval for the final version of the article to be published.

**Corresponding author: Ivana Sopek Merkaš, MD, Doctor,** Department of Cardiology, Special Hospital for Medical Rehabilitation Krapinske Toplice, 2 Gajeva, Krapinske Toplice 49217, Croatia. ivana.sopek@sbkt.hr

**Received:** July 10, 2022

**Revised:** August 29, 2022

**Accepted:** September 21, 2022

**Published online:**

**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

Lakušić N, Sopek Merkaš I, Slišković AM, Cerovec D. Euglycemic diabetic ketoacidosis: A rare but serious side effect of sodium-glucose co-transporter 2 inhibitors *World J Cardiol* 2022; In press

**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, SLGT2 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.

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 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. On the third day of treatment, the patient was discharged from the hospital with new recommended therapy*-*basal and fast-acting insulin and metformin.

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 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 decrease glucose level by an insulin-independent mechanism, increase the rates of lipolysis in adipose tissue and ketogenesis in the liver (increasing circulating ketone body levels), 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 rare but serious side effect of SGLT2 inhibitors. In case of 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, 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.

**REFERENCES**

1 **Clar C**, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open* 2012; **2** [PMID: 23087012 DOI: 10.1136/bmjopen-2012-001007]

2 **McDonagh TA**, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42**: 3599-3726 [PMID: 34447992 DOI: 10.1093/eurheartj/ehab368]

3 **Anker SD**, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 2021; **385**: 1451-1461 [PMID: 34449189 DOI: 10.1056/NEJMoa2107038]

4 **Lopaschuk GD**, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. *JACC Basic Transl Sci* 2020; **5**: 632-644 [PMID: 32613148 DOI: 10.1016/j.jacbts.2020.02.004]

5 **Täger T**, Atar D, Agewall S, Katus HA, Grundtvig M, Cleland JGF, Clark AL, Fröhlich H, Frankenstein L. Comparative efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i) for cardiovascular outcomes in type 2 diabetes: a systematic review and network meta-analysis of randomised controlled trials. *Heart Fail Rev* 2021; **26**: 1421-1435 [PMID: 32314085 DOI: 10.1007/s10741-020-09954-8]

6 **Razok A**, Ata F, Ahmed SMI, Al Mohanadi DHSH. Sodium-glucose co-transporter 2 inhibitors induced euglycemic diabetic ketoacidosis within four days of initiation. *World J Diabetes* 2022; **13**: 272-274 [PMID: 35432760 DOI: 10.4239/wjd.v13.i3.272]

7 **Liu J**, Li L, Li S, Wang Y, Qin X, Deng K, Liu Y, Zou K, Sun X. Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2020; **22**: 1619-1627 [PMID: 32364674 DOI: 10.1111/dom.14075]

8 **Gosmanov AR**, Kitabchi AE. Diabetic Ketoacidosis. In: Feingold KR, Anawalt B, Boyce A, editors. Endotext. South Dartmouth (MA): MDText.com, 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279146/

9 **Taylor SI**, Blau JE, Rother KI. SGLT2 Inhibitors May Predispose to Ketoacidosis. *J Clin Endocrinol Metab* 2015; **100**: 2849-2852 [PMID: 26086329 DOI: 10.1210/jc.2015-1884]

10 **Mudaliar S**, Alloju S, Henry RR. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. *Diabetes Care* 2016; **39**: 1115-1122 [PMID: 27289124 DOI: 10.2337/dc16-0542]

11 **Fralick M**, Redelmeier DA, Patorno E, Franklin JM, Razak F, Gomes T, Schneeweiss S. Identifying Risk Factors for Diabetic Ketoacidosis Associated with SGLT2 Inhibitors: a Nationwide Cohort Study in the USA. *J Gen Intern Med* 2021; **36**: 2601-2607 [PMID: 33564942 DOI: 10.1007/s11606-020-06561-z]

12 **Lin CW**, Hung SY, Chen IW. Relationship of concomitant anti-diabetic drug administration with sodium-glucose co-transporter 2 inhibitor-related ketosis. *J Int Med Res* 2022; **50**: 3000605221090095 [PMID: 35352579 DOI: 10.1177/03000605221090095]

13 **Sopek Merkaš I**, Slišković AM, Lakušić N. Current concept in the diagnosis, treatment and rehabilitation of patients with congestive heart failure. *World J Cardiol* 2021; **13**: 183-203 [PMID: 34367503 DOI: 10.4330/wjc.v13.i7.183]

14 **McMurray JJV**, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. *Circulation* 2021; **143**: 875-877 [PMID: 33378214 DOI: 10.1161/CIRCULATIONAHA.120.052926]

**Footnotes**

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** July 10, 2022

**First decision:** August 22, 2022

**Article in press:**

**Specialty type:** Cardiac and cardiovascular systems

**Country/Territory of origin:** Croatia

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** MP B, India; Papazafiropoulou A, Greece **S-Editor:** Chen YL **L-Editor:** A **P-Editor:** Chen YL