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A Cautionary Case of SGLT-2 Inhibitor-Induced Euglycemic Diabetic Ketoacidosis in a Patient with Foreseeable Risk Factors

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Abstract

Background: Euglycemic Diabetic Ketoacidosis (EDKA) is a rare but well-known adverse effect of sodium glucose transporter 2 (SGLT-2) inhibitors. This class of antidiabetic medications has ketogenic properties that predispose patients to develop EDKA, especially in the setting of intercurrent illnesses, major surgeries, increased alcohol intake, reduced insulin dosing, dehydration and reductions in carbohydrate intake. Case Presentation: A 68-year-old female with newly diagnosed metastatic adrenocortical carcinoma and adrenal insufficiency (AI) developed EDKA after palliative debulking that required ICU admission and intubation after being prescribed dapagliflozin by her outpatient provider. Conclusions: Healthcare providers must assess patient risk factors for developing EDKA prior to prescribing SGLT-2 inhibitors. This assessment requires an understanding of the inherent downstream metabolic effects of SGLT-2 inhibitor-induced glycosuria.

Keywords

Dapagliflozin, Empagliflozin, Euglycemic Diabetic Ketoacidosis, Ketosis, DKA, SGLT-2 Inhibitor, Type 1 Diabetes, Type 2 Diabetes, Endocrinology

1. Introduction

Sodium-glucose transporter 2 (SGLT-2) inhibitors are a relatively new class of antidiabetic medications that have been found to reduce mortality in patients with systolic heart failure as well as lower the risk of major adverse cardiovascular events in patients with established cardiovascular disease [1]. While unquestionably promising, SGLT-2 inhibitors have been linked to increased incidence of

euglycemic diabetic ketoacidosis (EDKA) since the Food and Drug Administration (FDA) released a warning in 2015 [2]. These concerns were supported by the findings of the EMPAREG [3], CANVAS [4], and DECLARE-TIMI 58 [5] trials, which demonstrated statistically significant increased risk of EDKA with the use of empagliflozin, canagliflozin, and dapagliflozin, respectively. SGLT-2 inhibitors were first approved for treating type 2 diabetes when the European Medicines Agency (EMA) approved Dapagliflozin in 2012 and the FDA approved Canagliflozin in 2013 [6] (**Figure 1**). Subsequent studies and trials would provide some convincing yet limited evidence to support its off-label use as adjunct therapy to insulin in type 1 diabetics [7]-[9]. The incidence of SGLT-2 inhibitor associated EDKA in type 2 diabetics has been found to be roughly 0.05% [10], whereas its incidence in type 1 diabetics has been found to be as high as 4.3% [11]. While the EMA approved dapagliflozin for adjunct therapy for type 1 diabetics with a BMI > 27 in 2019 [12], the FDA has yet to approve it for this purpose in the United States due to concerns for elevated risk of EDKA.

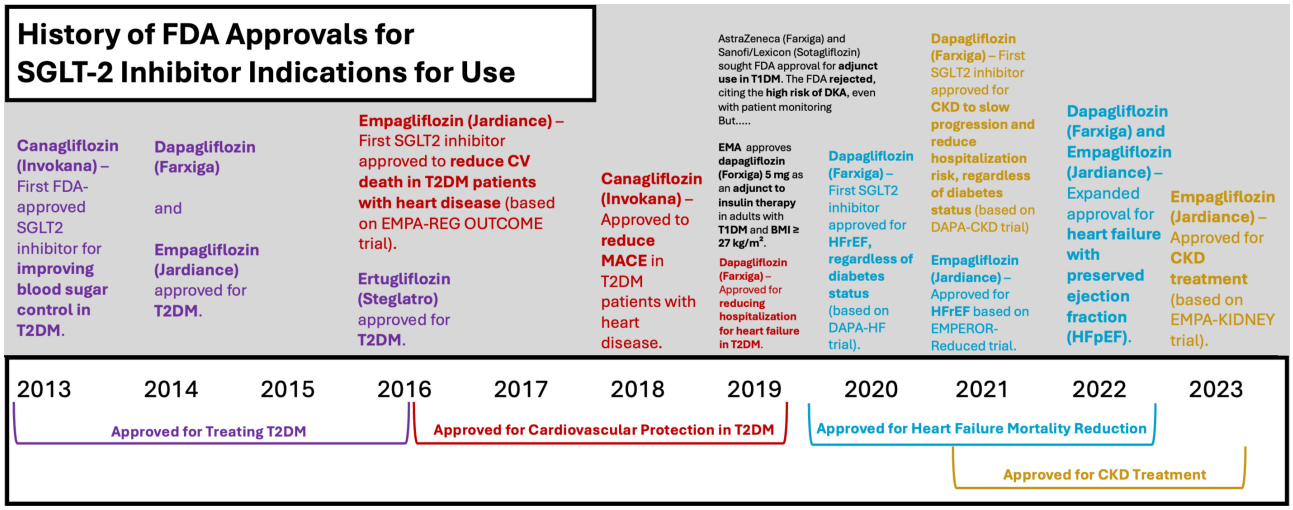

Figure 1. Timeline of SGLT-2 inhibitor FDA approvals for indications for use. CV (Cardiovascular), HFr/pEF (Heart failure with reduced/preserved ejection fraction), MACE (major adverse cardiovascular events), CKD (Chronic Kidney Disease).

EDKA is similarly defined as DKA (**Table 1**), but lacks its marked hyperglycemia, which can often conceal its ongoing manifestation and delay diagnosis. Significantly elevated blood glucose levels on initial point of care testing are often what set off alarm bells in providers' minds and lead to the timely administration of insulin and fluids. In addition, because EDKA patients are often spared the characteristic osmotic symptoms of polyuria, polydipsia, and/or mental status changes, EDKA can be quite insidious in its onset and presentation [13]. Therefore, providers must understand the risk factors for developing EDKA and educate patients on the signs and symptoms that can indicate its impending onset, such as nausea, vomiting, loss of appetite, fatigue, lethargy and abdominal pain [14].

Table 1. Laboratory Values in DKA vs EDKA.

Laboratory Value	DKA	EDKA
Blood glucose (70 - 100 mg/dL)	>250	<250
Arterial pH (7.35 - 7.45)	<7.3	<7.3
Serum Bicarbonate (24 - 32 mmol/L)	<18	<18
Anion Gap (4 - 12 mmol/L)	>12	>12
Serum Ketones (negative)	Present	Present
Urine Ketones (negative)	Present	Present

Risk factors for SGLT-2 inhibitor associated EDKA include low caloric intake or starvation, pregnancy, acute onset of infection, drug-induced intoxication, and surgery. Providers should assess whether these risk factors afflict their patients regularly before prescribing SGLT-2 inhibitors and counsel them on which clinical circumstances warrant the medication being withheld and for how long [15]. If a patient is prone to regularly having one or more of these risk factors, a thorough risk versus benefits discussion should take place with the patient prior to prescribing this class of medication. Alternative oral agents for patients deemed too high risk include older classes of medications such as biguanides, sulfonylureas, thiazolidinediones, and DPP4-inhibitors, as well as newer classes of medications, specifically, the GLP-1 receptor agonists, which also carry the beneficial cardiovascular effects that SGLT-2 inhibitors are often prescribed for [16].

While most healthcare providers are likely aware that EDKA is a rare but possible adverse effect of SGLT-2 inhibitors, do most also understand its underlying pathophysiology? Do they have a comprehensive understanding of the ketogenic metabolic compensations that inevitably occur after artificially lowering the total body glucose pool? Studies have shown that even non-diabetic patients without insulin deficiency who are on SGLT-2 inhibitors can have mild asymptomatic ketonemia at baseline [17]. Thus, perhaps the occurrence of EDKA can be mitigated by greater awareness among healthcare providers that SGLT-2 inhibitors inherently cause metabolic shifts towards greater reliance on fat oxidation and ketogenesis for energy production.

We report a case of a dapagliflozin-using patient with metastatic adrenocortical carcinoma (ACC) and adrenal insufficiency (AI) who developed EDKA after a palliative debulking procedure involving pancreatectomy. While this case may lack notable novel features or manifestations of rare phenomena, we felt it had concrete educational value in terms of highlighting the intrinsic ketogenic properties of SGLT-2 inhibitors and raising awareness among providers of the risk factors associated with EDKA. Informed consent was obtained posthumously from the patient's next of kin and this case received institutional approval.

2. Case Presentation

A 68-year-old female with type 2 diabetes who had recently been started on

dapagliflozin and recently diagnosed with pulmonary emboli on enoxaparin was brought to the emergency department due to gradually worsening abdominal pain for two weeks with generalized weakness, nausea, and vomiting. She had also reported difficulty maintaining her weight, losing 40 pounds unintentionally over the past several months. Her lab values were consistent with a high anion gap metabolic acidosis, presumed to be from a mild starvation ketosis as imaging would reveal a large left retroperitoneal adrenal mass with suspected metastatic lesions throughout her abdomen. An adrenal biopsy would demonstrate ACC.

Table 2. Laboratory values on admission to intensive care unit.

Lab Study	Component	Result
CMP	Sodium (135 - 145 mmol/L)	150
	Potassium (3.5 -5.0 mmol/L)	2.9
	Chloride (98 - 110 mmol/L)	113
	Carbon Dioxide (24 - 32 mmol/L)	3
	BUN (5.0 - 25 mg/dL)	23
	Creatinine (0.60 - 1.20 mgl/dL)	0.46
	Glucose (70 - 100 mg/dL)	221
	Anion Gap (5 - 15 mmol/L)	34
	Albumin (3.20 - 5.5 g/dL)	3.4
	AST (5 - 46 U/L)	8
	ALT (4 - 51 U/L)	11
	Alk Phos (40 - 129 U/L)	223
	Total Bilirubin (0.10 - 1.50 mg/dL)	0.2
Ketones	Beta Hydroxybutyrate (0 - 0.2 mmol/L)	11.6
CBC	WBC (4.40 - 10.5 10*3/uL)	12
	Hemoglobin (12.6 - 16.7 g/dL)	16.7
	Platelets (139 - 361 10*3/uL)	316
ABG	pH (7.32 - 7.45)	7.11
	pCO2 (35 - 45 mmHg)	12.3
	pO2 (65 - 105 mmHg)	93
	pHCO3-(22 - 26 mmHg)	4
UA	Protein (Negative)	1+
	Glucose (Negative)	4+
	Ketones (Negative)	2+

The patient lacked any family history to suggest her malignancy was driven by a germline mutation or familial malignancy syndrome (*i.e.* Li-Fraumeni Syndrome, Lynch syndrome, Multiple Endocrine Neoplasia Type 1, etc.), which collectively, account for approximately 5% - 10% of all cases of ACC [18]. She subsequently underwent palliative debulking with a left adrenalectomy, distal pancreatectomy, splenectomy, and left nephrectomy. The patient then developed postoperative hyperglycemia that would require increased insulin dosing, likely secondary to a now superimposed pancreatogenic (Type 3c) diabetes. In addition,

she also developed postoperative adrenal insufficiency and was started on hydrocortisone 20 mg daily. However, at discharge, the patient was not sent with insulin to take at home, but rather, was re-started on dapagliflozin at her follow-up appointment a week later.

Several days after restarting her SGLT-2 inhibitor, the patient returned to the emergency department with altered mental status and significant lethargy. Her laboratory values were notable for a pure high anion gap metabolic acidosis with appropriate respiratory compensation, consistent with EDKA in the setting of significantly elevated plasma ketones and only mildly elevated blood glucose (**Table 2**). Due to her declining level of consciousness and concern over her ability to maintain her own airway, the patient was transferred to intensive care unit (ICU), intubated, and placed on mechanical ventilation.

The patient was fluid resuscitated with dextrose 5% and lactated ringers at 200 cc/hr, a 20 mEq potassium chloride drip at 50 cc/hr that was then followed by a continuous intravenous infusion of regular insulin, which she would remain on for four days. While current guidelines recommend administering up to 200 mg of intravenous hydrocortisone daily for patients with primary adrenal insufficiency who are experiencing conditions requiring ICU care [19], given this patient was in EDKA and requiring intravenous insulin, the critical care team opted to increase her home dose of hydrocortisone by 50%. While the patient recovered from this acute episode of EDKA and was downgraded from the ICU, she ultimately succumbed to her metastatic disease at home on hospice roughly a month later.

3. Discussion

It is important to understand the physiologic cascade by which SGLT-2 inhibitors promote ketosis and can precipitate EDKA. The glycosuria-induced reduction in the total body glucose pool is accompanied by lower plasma blood glucose levels, which expectedly precipitate lower insulin dosing in type 1 diabetics to prevent hypoglycemia or lead to reduced endogenous insulin production in pancreatic beta cells of type 2 diabetics (**Figure 2**). Lower insulin levels, however, lead to disinhibition of carnitine palmitoyltransferase-I (CPT-1), an enzyme responsible for the transport of fatty acids into mitochondria where they are oxidized [20]. This in turn increases the rate of lipolysis in adipose tissue, fostering a metabolic shift towards relying on fatty acid breakdown for energy expenditure [21].

Studies have also shown that SGLT-2 inhibitors paradoxically increase endogenous glucose production, which is mediated by the actions of elevated concentrations of glucagon [22] [23]. Increased levels of glucagon, along with lower levels of insulin, are well-known to stimulate ketogenesis in the liver. Lastly, background ketosis is facilitated by SGLT-2 inhibitor use due to increased rates of ketone body (*i.e.* acetoacetate) reabsorption in the kidney tubules. This theory has been supported by animal studies using phlorizin, a naturally occurring compound in fruit tree bark that competes with glucose to bind SGLT-1 and SGLT-2 receptors and inhibit them [24].

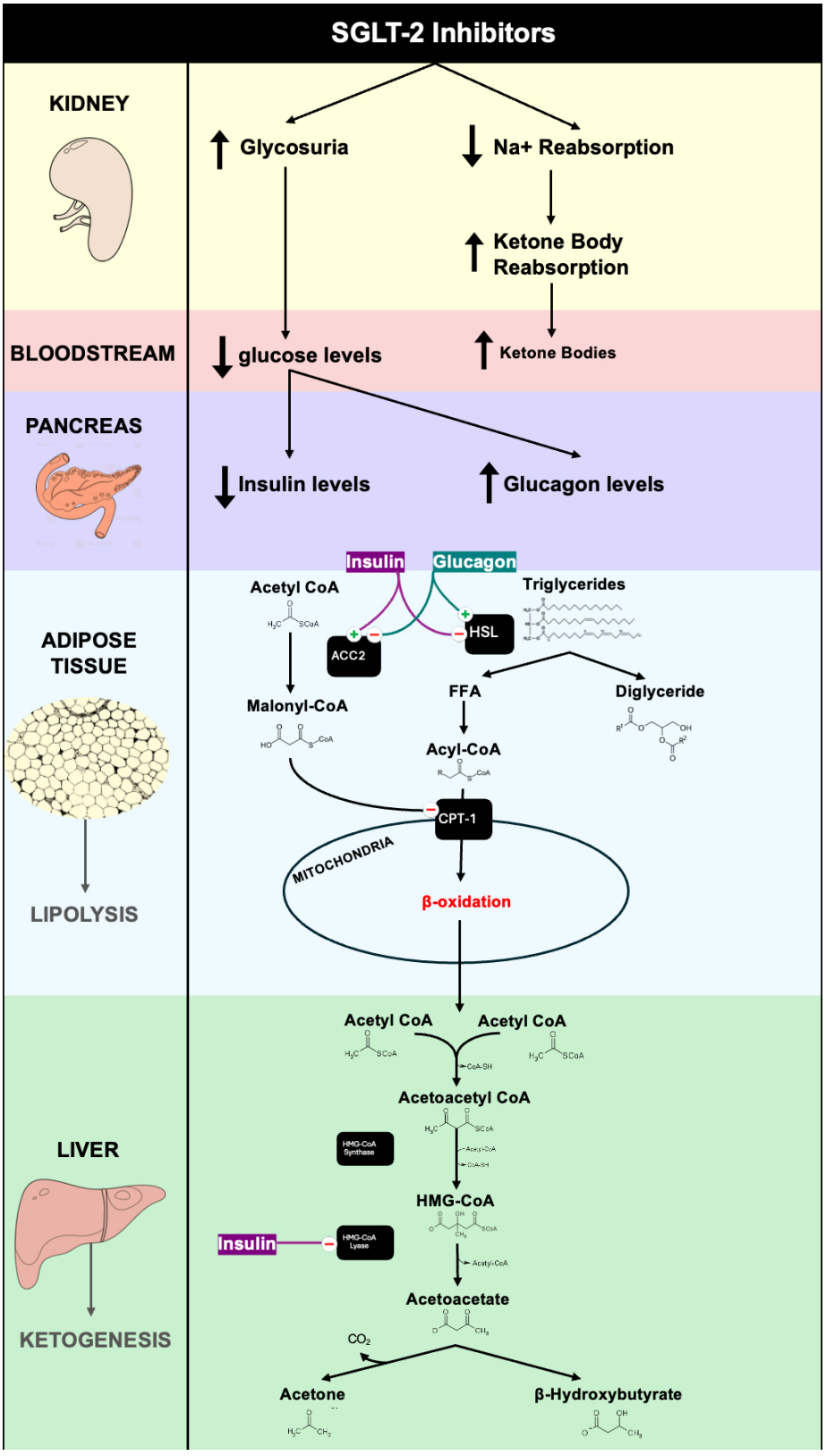

Figure 2. Graphic demonstrates how SGLT-2 inhibitors promote lipolysis and ketogenesis. Legend: Acetyl CoA Carboxylase-2 (ACC2), carnitine palmitoyltransferase-I (CPT-1), Hormone Sensitive Lipase (HSL), Free Fatty Acid (FFA).

Understanding the downstream ketogenic effects of SGLT-2 inhibitors can possibly allow providers some degree of *predictability* when assessing whether a patient may be at increased risk of shifting from asymptomatic ketonemia to a full-blown episode of EDKA [25]. Episodes of EDKA are typically precipitated by a triggering event or physiologic insult. Intercurrent illnesses, major surgeries, alcohol intake, reduced insulin dosing, dehydration and reductions in carbohydrate intake are the most common inciting factors of SGLT-2 inhibitor-induced EDKA identified in the relevant literature [26]. The common theme these factors share is that they all drive a patient's metabolism towards a state of relative or absolute starvation [13].

The patient described in this report had several of these risk factors, including metastatic cancer that caused frailty and reduced caloric intake. Following this diagnosis, the patient then underwent major surgery that led to the development of postoperative adrenal insufficiency and most likely pancreatogenic (Type 3c) diabetes, for which she was not started on home insulin for. This sequalae of clinical events likely resulted in the patient developing a severe absolute insulin deficiency after her pancreatectomy, which was then likely compounded by re-initiating her SGLT-2 inhibitor outpatient. This in turn likely increased the patient's metabolic rates of lipolysis and ketogenesis, driving her into DKA.

While this case report provides anecdotal evidence that highlights the importance of understanding the ketogenic properties of SGLT-2 inhibitors and clinical scenarios that may increase its risk of precipitating EDKA, its design has several limitations. First, the insights derived from this case report are predominantly theoretical and remain hypothesis-generating. Establishing a causal relationship between this patient's dapagliflozin use and her episode of EDKA would have demanded serial laboratory monitoring and clinical examination both before and after re-initiating her SGLT-2 inhibitor outpatient. In addition, the majority of data for this case report was collected posthumously from a review of the electronic records, and possible confounding variables may have not been documented and thus overlooked.

Lastly, and perhaps most importantly, the SGLT-2 inhibitor's indication for use should always be consistent with the patient's goals of care. This class of medication is commonly used for stricter diabetes control and/or long-term cardiovascular risk reduction, which in many cases may not be appropriate for patients afflicted by advanced malignancies with limited life expectancies. While SGLT-2 inhibitors show promising benefits beyond diabetes control, they must be used cautiously in patients who are prone to long periods of poor oral intake or who experience recurrent stressful psychologic or physiologic events. Greater awareness of the ketogenic properties of SGLT-2 inhibitors among healthcare providers could have the potential to mitigate the rate of EDKA occurrence.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Patel, S.M., Kang, Y.M., Im, K., Neuen, B.L., Anker, S.D., Bhatt, D.L., *et al.* (2024) Sodium-glucose Cotransporter-2 Inhibitors and Major Adverse Cardiovascular Outcomes: A SMART-C Collaborative Meta-Analysis. *Circulation*, **149**, 1789-1801. https://doi.org/10.1161/circulationaha.124.069568

[2] FDA Revises Labels of SGLT2 Inhibitors for Diabetes to Include Warnings about Too Much Acid in the Blood and Serious Urinary Tract Infection. https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious

[3] Zinman, B., Wanner, C., Lachin, J.M., Fitchett, D., Bluhmki, E., Hantel, S., *et al.* (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*, **373**, 2117-2128. https://doi.org/10.1056/nejmoa1504720

[4] Neal, B., Perkovic, V., Mahaffey, K.W., de Zeeuw, D., Fulcher, G., Erondu, N., *et al.* (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*, **377**, 644-657. https://doi.org/10.1056/nejmoa1611925

[5] Wiviott, S.D., Raz, I., Bonaca, M.P., Mosenzon, O., Kato, E.T., Cahn, A., *et al.* (2019) Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*, **380**, 347-357. https://doi.org/10.1056/nejmoa1812389

[6] Chao, E.C. (2014) SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. *Clinical Diabetes*, **32**, 4-11. https://doi.org/10.2337/diaclin.32.1.4

[7] Cheng, S.T.W., Chen, L., Li, S.Y.T., Mayoux, E. and Leung, P.S. (2016) The Effects of Empagliflozin, an SGLT2 Inhibitor, on Pancreatic B-Cell Mass and Glucose Homeostasis in Type 1 Diabetes. *PLOS ONE*, **11**, e0147391. https://doi.org/10.1371/journal.pone.0147391

[8] Henry, R.R., Rosenstock, J., Edelman, S., Mudaliar, S., Chalamandaris, A., Kasichayanula, S., *et al.* (2014) Exploring the Potential of the SGLT2 Inhibitor Dapagliflozin in Type 1 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. *Diabetes Care*, **38**, 412-419. https://doi.org/10.2337/dc13-2955

[9] Perkins, B.A., Cherney, D.Z.I., Partridge, H., Soleymanlou, N., Tschirhart, H., Zinman, B., *et al.* (2014) Sodium-glucose Cotransporter 2 Inhibition and Glycemic Control in Type 1 Diabetes: Results of an 8-Week Open-Label Proof-Of-Concept Trial. *Diabetes Care*, **37**, 1480-1483. https://doi.org/10.2337/dc13-2338

[10] Wang, Y., Desai, M., Ryan, P.B., DeFalco, F.J., Schuemie, M.J., Stang, P.E., *et al.* (2017) Incidence of Diabetic Ketoacidosis among Patients with Type 2 Diabetes Mellitus Treated with SGLT2 Inhibitors and Other Antihyperglycemic Agents. *Diabetes Research and Clinical Practice*, **128**, 83-90. https://doi.org/10.1016/j.diabres.2017.04.004

[11] Rosenstock, J., Marquard, J., Laffel, L.M., Neubacher, D., Kaspers, S., Cherney, D.Z., *et al.* (2018) Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials. *Diabetes Care*, **41**, 2560-2569. https://doi.org/10.2337/dc18-1749

[12] European Medicines Agency (2019) First Oral Add-On Treatment to Insulin for Treatment of Certain Patients with Type 1 Diabetes. https://www.ema.europa.eu/en/news/first-oral-add-treatment-insulin-treatment-certain-patients-type-1-diabetes#:~:text=1%20February%202019,below%2027%20kg/m2

[13] Chow, E., Clement, S. and Garg, R. (2023) Euglycemic Diabetic Ketoacidosis in the Era of SGLT-2 Inhibitors. *BMJ Open Diabetes Research & Care*, **11**, e003666.

https://doi.org/10.1136/bmjdrc-2023-003666

[14] Plewa, M.C., Bryant, M. and King-Thiele, R. (2023) Euglycemic Diabetic Ketoacidosis. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK554570/

[15] Matthew, D., Kimberley, E. and Elsen, J. (2021) Management of Euglycemic Diabetic Ketoacidosis. *U.S. Pharmacist*, **46**, HS1-HS6. https://www.uspharmacist.com/article/management-of-euglycemic-diabetic-ketoacidosis

[16] Marso, S.P., Daniels, G.H., Brown-Frandsen, K., Kristensen, P., Mann, J.F.E., Nauck, M.A., *et al.* (2016) Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*, **375**, 311-322. https://doi.org/10.1056/nejmoa1603827

[17] Yurista, S.R., Silljé, H.H.W., Oberdorf-Maass, S.U., Schouten, E., Pavez Giani, M.G., Hillebrands, J., *et al.* (2019) Sodium-Glucose Co-Transporter 2 Inhibition with Empagliflozin Improves Cardiac Function in Non-Diabetic Rats with Left Ventricular Dysfunction after Myocardial Infarction. *European Journal of Heart Failure*, **21**, 862-873. https://doi.org/10.1002/ejhf.1473

[18] Petr, E.J. and Else, T. (2018) Adrenocortical Carcinoma (ACC): When and Why Should We Consider Germline Testing? *La Presse Médicale*, **47**, e119-e125. https://doi.org/10.1016/j.lpm.2018.07.004

[19] Bornstein, S.R., Allolio, B., Arlt, W., Barthel, A., Don-Wauchope, A., Hammer, G.D., *et al.* (2016) Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*, **101**, 364-389. https://doi.org/10.1210/jc.2015-1710

[20] Ogawa, W. and Sakaguchi, K. (2015) Euglycemic Diabetic Ketoacidosis Induced by SGLT2 Inhibitors: Possible Mechanism and Contributing Factors. *Journal of Diabetes Investigation*, **7**, 135-138. https://doi.org/10.1111/jdi.12401

[21] Taylor, S.I., Blau, J.E. and Rother, K.I. (2015) SGLT2 Inhibitors May Predispose to Ketoacidosis. *The Journal of Clinical Endocrinology & Metabolism*, **100**, 2849-2852. https://doi.org/10.1210/jc.2015-1884

[22] Ferrannini, E., Muscelli, E., Frascerra, S., Baldi, S., Mari, A., Heise, T., *et al.* (2014) Metabolic Response to Sodium-Glucose Cotransporter 2 Inhibition in Type 2 Diabetic Patients. *Journal of Clinical Investigation*, **124**, 499-508. https://doi.org/10.1172/jci72227

[23] Merovci, A., Solis-Herrera, C., Daniele, G., Eldor, R., Fiorentino, T.V., Tripathy, D., *et al.* (2014) Dapagliflozin Improves Muscle Insulin Sensitivity but Enhances Endogenous Glucose Production. *Journal of Clinical Investigation*, **124**, 509-514. https://doi.org/10.1172/jci70704

[24] Cohen, J.J., Berglund, F. and Lotspeich, W.D. (1955) Renal Tubular Reabsorption of Acetoacetate, Inorganic Sulfate and Inorganic Phosphate in the Dog as Affected by Glucose and Phlorizin. *American Journal of Physiology-Legacy Content*, **184**, 91-96. https://doi.org/10.1152/ajplegacy.1955.184.1.91

[25] Rosenstock, J. and Ferrannini, E. (2015) Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern with SGLT2 Inhibitors. *Diabetes Care*, **38**, 1638-1642. https://doi.org/10.2337/dc15-1380

[26] Burke, K.R., Schumacher, C.A. and Harpe, S.E. (2017) sglt2 Inhibitors: A Systematic Review of Diabetic Ketoacidosis and Related Risk Factors in the Primary Literature. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, **37**, 187-194. https://doi.org/10.1002/phar.1881