Review Article

Sodium-glucose co-transporter-2 inhibitors and euglycemic ketoacidosis: Wisdom of hindsight

Awadhesh Kumar Singh[1,2]

[1]*Departments of Endocrinology, G.D. Hospital and Diabetes Institute, Kolkata, West Bengal,* [2]*Sun Valley Diabetes Hospital, Guwahati, Assam, India*

ABSTRACT

Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are newly approved class of oral anti-diabetic drugs, in the treatment of type 2 diabetes, which reduces blood glucose through glucouresis via the kidney, independent, and irrespective of available pancreatic beta-cells. Studies conducted across their clinical development program found, a modest reduction in glycated hemoglobin ranging from –0.5 to –0.8%, without any significant hypoglycemia. Moreover, head-to-head studies versus active comparators yielded comparable efficacy. Interestingly, weight and blood pressure reduction were additionally observed, which was not only consistent but significantly superior to active comparators, including metformin, sulfonylureas, and dipeptydylpeptide-4 inhibitors. Indeed, these additional properties makes this class a promising oral anti-diabetic drug. Surprisingly, a potentially fatal unwanted side effect of diabetic ketoacidosis has been noted with its widespread use, albeit rarely. Nevertheless, this has created a passé among the clinicians. This review is an attempt to pool those ketosis data emerging with SGLT-2i, and put a perspective on its implicated mechanism.

Key words: Ketoacidosis, ketonemia, ketonuria, ketosis, sodium -glucose co-transporter-2 inhibitors

Introduction

Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are newly approved second-line drug, after metformin, in the treatment of type 2 diabetes mellitus (T2DM). It can be used as monotherapy as well. This class of drugs has a unique mode of action through the kidney, independent of insulin secretion from the beta-cell of the pancreas. It reduces blood glucose, by inhibiting glucose reabsorption at sodium-glucose co-transporter-2 (SGLT-2) receptors in the proximal tubule of the kidney, by inducing glucosuria.[1] This unique mode of glucose lowering properties, independent of available beta-cell, also makes these agents a tempting possible option in treating type 1 diabetes mellitus (T1DM), although it is currently not recommended.

Currently, the three most advanced SGLT-2i in clinical trials; canagliflozin, dapagliflozin, and empagliflozin have been approved by Food Drug Administration (FDA) and European Medicine Agency (EMA). Few others such as ipragliflozin, tofogliflozin, and luseogliflozin are also approved in Japan. Of these six gliflozins, the most selective SGLT-2i, to the SGLT-2 receptor over SGLT-1 receptor, in decreasing order are tofogliflozin (1:3000), empagliflozin (1:2500), luseogliflozin (1:1770), dapagliflozin (1:1200), ipragliflozin (1:860), and canagliflozin (1:414).[2]

All the SGLT-2i have shown a modest glycated hemoglobin (HbA1c) reduction (−0.5 to −0.8%), without

Corresponding Author: Dr. Awadhesh Kumar Singh, Flat-1C, 3 Canal Street, Kolkata - 700 014, India.
E-mail: draksingh_2001@yahoo.com

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inducing significant hypoglycemia, during their phase 3 clinical trials.[3,4] Moreover, these once daily oral drugs can also be safely combined with other anti-diabetic drugs (metformin, sulfonylureas [SUs], pioglitazone, and dipeptydylpeptide-4 [DPP-4] inhibitors) including insulin, with an additional and significant glucose lowering properties. Furthermore, head-to-head studies versus active comparators, including metformin, SUs, and DPP-4 inhibitors, yielded comparable efficacy; while, in addition, SGLT-2i also demonstrated significant reduction in body weight and blood pressure.[5,6] Because of these additional advantages, apart from the modest glucose lowering, SGLT-2i currently appears as a promising oral anti-diabetic drugs in the treatment of T2DM.[7]

Sodium-Glucose Co-transporter-2 Inhibitors and Ketosis – Current Evidence

A recent alert from FDA on May 15, 2015 and a month later from EMA on June 10, 2015 suggested, new-onset diabetic ketoacidosis (DKA) with the use of SGLT-2i, based on the FDA Adverse Event Reporting System (FAERS) and EudraVigilance (EV) database, respectively.[8,9]

While the FDA reported 20 cases of DKA, ketoacidosis, and ketosis with SGLT-2i based on the data reported to FAERS from March 2013 to June 6, 2014; EMA found 147 case of DKA reported with SGLT-2i at EV database as of May 19, 2015.

FDA found DKA mostly in T2DM, although few cases were of T1DM and some cases did not specify the indication.[8] On the other hand, of the 147 case of DKA, EMA found 101 case in T2DM, and 46 cases in T1DM. Further breakout of 147 DKA cases from EMA, suggested 96 cases reported with canagliflozin, 46 cases with dapagliflozin, and 5 cases with empagliflozin. Of 101 cases of DKA in T2DM, 63 reported with canagliflozin, 34 with dapagliflozin, and 4 with empagliflozin. Overall, 69 cases (53 with canagliflozin and 16 with dapagliflozin) required hospitalization and recovered with intensive insulin supplementation.[9] Time of onset of DKA varied from 3 days to 1-year; however majority developed it within first 2 months of SGLT-2 inhibitors initiation.[9]

Interestingly, as several of these DKA cases had reasonably normal plasma glucose, in spite of high anion gap acidosis and increased plasma ketones; these were often termed as "euglycemic ketoacidosis" or euglycemic DKA (EuDKA). Indeed, the prognosis of EuDKA is similar to DKA, a potentially life-threatening condition, although, the presence of normoglycemia in EuDKA could mask its recognition and could be responsible for underreporting.

In view of these emerging data, the European Commission (EC) initiates a procedure under Article 20 of Regulation No: 726/2004 and request the Agency to assess the above concern and their impact on the benefit risk balance for these medicinal products. The EC request the EMA to give its opinion by May 31, 2016, on whether the marketing authorizations of these products should be maintained, varied, suspended, or revoked. In addition, the EC requests the Agency to give its opinion as to whether temporary measures are necessary to ensure the safe and effective use of these medicinal products. As the request is based on the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee (PRAC).

Nonetheless, this emerging EuDKA with SGLT-2i has caused a commotion among the clinicians and has created a passé. Taylor *et al.* have addressed this issue in a recent review.[10] Kalra *et al.* have also briefly communicated on this issue very recently, and proposed a pragmatic approach for the clinician.[11] The present review has collated further updates of data on ketosis reported with SGLT-2i and put a perspective on its putative mechanism.

Review Method

Boolean search in PubMed and Google engine was done using term ketosis, ketones, and ketoacidosis "AND" SGLT-2 inhibitors through July 2015. Relevant articles as well as the case reports which were presented in diabetes and endocrine international congress as an abstract, were retrieved until July 2015.

Euglycemic Diabetic Ketoacidosis with Sodium-glucose Co-transporter-2 Inhibitors in Type 1 Diabetes

In humans, Henry *et al.* in a phase 2b studies found, increased incidence of ketonuria in patients treated with dapaglifozin, although there was no reported cases of EuDKA, in this 2-week study with 70 T1DM patients. However, this study was primarily a proof-of-concept, dose-response-study, where patients were receiving dapagliflozin ranging from 1 to 10 mg and only 29 T1DM received a therapeutic dose of 5–10 mg.[12] Perkins *et al.* in an 8-week study, found 2 cases of EuDKA, treated with empagliflozin in 42 T1DM patient.[13] Very recently Sands

et al, reported 2 case of DKA observed with sotagliflozin (duel SGLT1 and SGLT2 inhibitor) in 33 T1DM patients.[14]

There are several other cases of EuDKA reported in T1DM. St-Hilaire *et al.* reported a case of EuDKA with canagliflozin in a 43-year-old T1DM, although it was found to be in the setting of concomitant canula attachment failure of an insulin pump.[15] In a real-world setting of the patient forum, hosted by Juvenile Diabetes Research Foundation, 2 cases of recurrent EuDKA reported with canagliflozin.[16]

In a recent international congress, few cases of EuDKA were also reported with SGLT-2i. In American College of Endocrinology (ACE) 2015 meeting, Kuhadiya *et al.* reported 1 case of EuDKA among 10 patients of T1DM, receiving triple therapy of insulin, liraglutide, and dapagliflozin.[17] Seven cases of EuDKA reported with canagliflozin in T1DM were also presented at American Diabetes Association meeting 2015, whose details are published in diabetes care journal.[18] Summary of these cases are described in Table 1.

While the exact reason for EuDKA in these series of 7 cases with T1DM of Peter *et al.*, are not exactly known, it is implicated to be due to associated insulin pump failure, infections, over-enthusiastic reduction in insulin doses, alcohol intake, acute illness, gastroenteritis, dehydration, and vomiting.[18] Two cases (13%) of DKA observed in sotagliflozin was also implicated to infusion set crimping or shallow cannula insertion.[14]

Euglycemic Diabetic Ketoacidosis with Sodium-Glucose Co-transporter-2 Inhibitors in Type 2 Diabetes

A few cases of EuDKA in T2DM have been recently presented and published. In US Endocrine meeting (ENDO) 2015, Burr *et al.* reported a case of DKA in 50-year-old women with HbA1c of 11%, who received only 6 doses of canagliflozin 300 mg in addition to the previous regime of glipizide and metformin. Interestingly, this patient additionally reported a 65 lb weight loss in last 6 months, due to recurrent episodes of gastroparesis when canagliflozin was added 2 days prior, due to poor glycemic control. Intriguingly, this patient developed glucosuria 11 days after stopping last dose of canagliflozin, thereby suggesting a delayed receptor inhibition.[19]

In recently concluded ACE 2015 meeting, Chaudhury reported a case of EuDKA with canagliflozin, in an 18-year-old female having diabetes since the age of 8 years with baseline HbA1c of 12.9%. Interestingly, this patient was described as type 2 diabetic at the age of 8 years who never received insulin, was antibody negative and receiving metformin monotherapy (2 g/day) recently, when canagliflozin was added 3 weeks earlier. Chaudhury reported another case of EuDKA with dapagliflozin, in 55-year-old male with HbA1c of 12.1%, with 6 years of diabetes duration, receiving metformin 2 gm and glipizide XR 5 mg daily, when dapagliflozin 5 mg was added a month earlier.[20]

An Indian case report found positive urinary ketones in a 29-year-old male with type 2 diabetes for past 2 years, who was taking metformin plus canagliflozin with HbA1c of 6.7% although currently undergoing religious fast. As this patient was asymptomatic, this has raised an alarm of "pseudo-ketoacidosis."[21]

Peters *et al.* reported 2 cases of EuDKA with canagliflozin in T2DM. One patient was a 58-year-old male with 2 years history of diabetes and with HbA1c of 9.8%, who had undergone sigmoid colectomy a week earlier and recuperating following surgery while taking canagliflozin 300 mg monotherapy. Another case of EuDKA was reported in a 65-year-old female with 6 years history of diabetes with HbA1c of 8.4%, who had undergone bilateral cervical foraminotomy 12 h earlier. This patient was earlier taking glibenclamide, sitagliptin, and insulin detemir (20 units). Interestingly, insulin was stopped when patient achieved HbA1c of 7.8%, when canagliflozin was up-titrated to 300 mg prior to surgery, although it was stopped on the day of surgery.[18] Table 2 summarizes these cases.

Table 1: Diabetic ketoacidosis (DKA) with SGLT2 inhibitors in type 1 diabetes

Author	Agent	*N*	DKA seen	Backgrounds reasons
Henry *et al*.	Dapagliflozin	70	0	-
Perkins *et al*.	Empagliflozin	42	2	Not available
Sands *et al*.	Sotagliflozin	33	2	Infusion set crimping, shallow cannula insertion
St Hillair *et al*.	Canagliflozin	-	1	Cannula-attachment failure
JDRF portal	Canagliflozin	-	2	Over-jealous reduction of insulin dosage
Kuhadiya *et al*.	Dapagliflozin	10	1	On liraglutide plus reduced insulin doses
Peters *et al*.	Canagliflozin	-	7	Reduction in insulin doses, upper respiratory tract infection, gastroenteritis, alcohol intake, vomiting, dehydration

SGLT2: Sodium-glucose co-transporter-2

A recent study reports overall 8 cases of DKA, from the empagliflozin, pooled data of phase 2/3 studies consisting of around 12,000 patients. While 5 events of DKA were observed in the placebo arm, 3 events reported with empagliflozin (2 cases with 10 mg, and 1 case with 25 mg dose) arm.[22] Moreover, a recently published pooled data from phase 2/3 studies of canagliflozin, found 12 case of DKA among 17,596 patients studied. Of the 12 cases, 4 cases were observed with canagliflozin 100 mg, 6 cases with canagliflozin 300 mg and 2 cases in comparator arm. Interestingly, in most of these cases, DKA were found in those who are on insulin and had some DKA-precipitating factors including T1DM and LADA.[23] Table 3 summarizes these data.

An unpublished personal communication from SGLT-2 inhibitors manufacturers observed few case reports of DKA during their phase 2/3 clinical development program. Data from 21 studies of phase 2/3 clinical development program of dapagliflozin recruiting 5,936 patients found 1 case of DKA and 2 cases of ketonuria, suggesting an event rate of 1 case per 6247.2-patient-year. Postmarketing surveillance global data on June 16, 2015, found, 13 cases of DKA reported with empagliflozin, thereby suggesting a reporting rate of 1 per-5000-patient-year. Taylor *et al.* also calculated this rare event of EuDKA ranging between 1 in 1000 to 1 in 10,000-patient-year.[10]

Euglycemic Diabetic Ketoacidosis with Sodium-Glucose Co-transporter-2 Inhibitors in Other Types of Diabetes

Hine *et al.* reported 2 cases of EuDKA, in 36-year-old female and a 34-year-old male from England, while initiating dapagliflozin. Interestingly, both cases were found to be pancreatic diabetes (type 3c diabetes). While the female patient was actually a known case of type 2 diabetes with associated polycystic ovary syndrome, she had undergone distal pancreatectomy for mucinous cystadenoma of pancreas earlier. The male patient had a history of pancreatitis and subsequent pancreatic atrophy.[24]

Hayami *et al.* reported a case of 32-year-old female on low-carbohydrate diet, a known case of Prader–Willi syndrome that developed severe ketoacidosis, 13 days after switching over to ipragliflozin (50 mg/day) monotherapy from the earlier regime of linagliptin plus glimepiride and metformin. Serum total ketone body found to be highly elevated (7473 μmol/L) even 15 h after initiation of insulin and out of these, 75% of ketone bodies was contributed by 3-hydroxybutyrate (5558 μmol/L) in this case. Acetoacetate contributed the rest 25% (1915 μmol/L) of ketones. Although antibodies to glutamic acid decarboxylase, islet antigen-2, and insulin were negative; serum C-petide was 0.4 ng/mL, and HbA1c was 9.3% at admission. Estimated carbohydrate intake was 66 g/day thereby suggesting that patient was chronically prone to ketosis on low carbohydrate diet.[25]

Although, the exact reason for EuDKA in these 5 presented/published cases with T2DM and 3 cases of others type of diabetes are not known; some or other precipitating factor could have been responsible for this acute event. Deranged metabolic state in postoperative phase of 2 cases of T2DM in Peter *et al.* case series, recurrent gastroparesis with acute weight loss (65 lb) in Burr *et al.* case; both these condition, can make these patient vulnerable to ketosis. One case of T2DM since the age of 8 years, on metformin monotherapy in Chowdhury series, could have been an undiagnosed late-onset type 1 diabetes (latent autoimmune diabetes of adults [LADA]), although auto-antibodies were initially found to be negative. Moreover, Prader–Willi syndrome of Hayami *et al.* was on very low carbohydrate diet of 66 g/day, which by themselves can precipitate ketosis. Table 4 summarizes these cases.

While these proposed reasons could have been the one of the precipitating factors for EuDKA, it would be pragmatic to find whether concomitant uses of SGLT-2i renders patient vulnerable to become ketosis-prone.

Table 3: Diabetic ketoacidosis (DKA) with SGLT2 inhibitors in phase 2/3 studies

Drugs	DKA observed	Total no. of patient exposed
Empagliflozin	8	12, 000
Canagliflozin	12	17, 596
Dapagliflozin	2	5, 936

DKA: Diabetic ketoacidosis, SGLT2: Sodium-glucose co-transporter-2

Table 2: Diabetic ketoacidosis (DKA) with SGLT2 inhibitors in type 2 diabetes

Author	Source	DKA seen	Drug	Patient profile	Background reasons
Burr *et al.*	Endo 2015	1	Canagliflozin	50 year female, HbA1c- 11%	65 lb weight loss in 6 month, recurrent gastroparesis
Chowdhury F	ACE 2015	1	Canagliflozin	18 year female, HbA1c- 13%,	Diabetes from the age of 8 year, on metformin monotherapy
		1	Dapagliflozin	55 year male, HbA1c- 12%	No reason available
Peters *et al.*	ADA 2015	1	Canagliflozin	58 year male, HbA1c- 10%	Undergone sigmoid colectomy a week ago
		1	Canagliflozin	65 year female, HbA1c- 8.4%	Undergone cervical foraminotomy 12 hour ago, stopped insulin

ACE: American college of endocrinology, ADA: American diabetes association, DKA: Diabetic ketoacidosis, SGLT2: Sodium-glucose co-transporter-2

Sodium-Glucose Co-transporter-2 Inhibitors and Proposed Mechanism of Ketosis

DKA is a well-recognized complication in untreated type 1 diabetes and has often been encountered in T2DM, especially in those who are severely insulinopenic. Although its prevalence varied from 5% to 25%, depending upon the survey used, a recent estimate suggests that DKA in youth with type 1 diabetes still remains a major problem, and almost one-third of them presenting with DKA. DKA is less common in youth with type 2 diabetes and found to be decreasing by around 10%/year, thereby suggesting an improved detection or earlier diagnosis.[26,27]

As mentioned earlier, DKA event associated with SGLT-2i is extremely rare, somewhere ranging between 1 in 1000 to 1 in 10,000 patient/year. Nevertheless, these case reports raise the question as to how this class of drugs might be contributing in the initiation of ketoacidosis. It could be either directly or indirectly.

Historically, phlorizin was the first nonselective SGLT receptor inhibitor which was found to increase renal tubular absorption of acetoacetate in experimental dog studies. It was proposed that the increase load of sodium in renal tubules, due to the complete inhibition of sodium reabsorption by a combined SGLT-2 and SGLT-1 inhibitors, can create an increase in positive electrochemical gradient which in turn can led to enhanced carrier mediated reabsorption of negatively charged ketones. Interestingly, serum ketones were not measured in this experimental study to substantiate this finding.[28] However, in another experimental study, there was a marked increase in ketone body in serum comparable to streptozocin-induced diabetes, when phlorizin was administered for 24 h in fasted rat.[29] Sodium-monocarboxylate transporter-1 (SLC5A8) which is expressed on the apical membrane of renal tubular epithelial cells, has been reported to mediate cotransport of sodium with monocarboxylate ion. It is possible that this transporter could be responsible for the reabsorption of monocarboxylate ion (acetoacetate and beta-hydroxybutyrate) from proximal renal tubules.[30] In any case, if pholrizin or possibly other SGLT-2 inhibitors truly increases the ketones reabsorption from the tubules than it would also reveal very less ketone in urine and may potentially delay the appearance of urine ketone, which can eventually delay the recognition of ketoacidosis if it ensues. Additionally, Yokono *et al.* also found enhanced lipolysis, increase free fatty acid oxidation and increase in ketone bodies (β-hydroxybutyrate) with ipragliflozin (10 mg/kg once daily) in a high-fat diet-induced obese rat.[31]

Human studies also suggested, a dose-dependent hyperketonemia, including a significant increase in total serum ketone, acetoacetic acid, and β-hydroxybutyrate in T2DM patient taking tofogliflozin. This hyperketonemia was accompanied by associated ketonuria, although it was surprisingly absent on the highest doses of tofogliflozin [Table 5].[32] This may also suggest that the highest dose of tofogliflozin could be responsible for ketones reabsorption form renal tubules making urine ketones negative. However, given the large standard deviation (SD) in these data, it is apparent that some patients do have clinically relevant increase in ketone body levels, even if it did not eventuate in to an overt DKA. These findings have been further replicated in recent studies.

A double-blind placebo-controlled crossover study, also found marked increase in (maximum 3030 μmol/L) beta-hydroxybutyrate in T2DM, taking luseogliflozin on low carbohydrate diet.[33] Moreover, Nakayama *et al.* recently studied (n = 19) the changes in the diurnal profile of serum ketone bodies after 7 days of ipragliflozin

Table 4: Diabetic ketoacidosis (DKA) with SGLT2 inhibitors in other types of diabetes

Author	Drug	DKA seen	Patient	Type of DM	Background reasons
Hine *et al.*	Dapagliflozin	1	36 year female	Pancreatic diabetes	Distal pancreatectomy for mucinous cystadenoma of pancreas
	Dapagliflozin	1	34 year male	Pancreatic diabetes	Chronic pancreatitis and pancreatic atrophy
Hayami *et al.*	Ipragliflozin	1	32 year female	Prader-Willi syndrome	Low carbohydrate diet of 66 gm/day

DKA: Diabetic ketoacidosis, SGLT2: Sodium-glucose co-transporter-2

Table 5: Tofogliflozin and ketones production

Biochemical parameters	Placebo	Tofogliflozin 10 mg	Tofogliflozin 20 mg	Tofogliflozin 40 mg
Hyperketonemia	1.8%	3.4%	12.1%	13.8%
Ketonuria	0.0%	1.7%	5.1%	0.0%
Δ Total serum ketone (μmol/L)	+29.7	+45.6	+59.5	+141.2
Δ Acetoacetic acid (μmol/L)	+7.1	+10.7	+14.8	+31.0
Δ β-hydroxybutyrate ((μmol/L)	+22.6	+34.7	+44.7	+110.0

administration. Results suggested that the plasma level of 3-hydroxybutyrate was increased with ipragliflozin, with most obvious elevation observed during prebreakfast and predinner time. A correlation analysis found, patients age and body weight loss were negatively ($P < 0.001$) and positively ($P < 0.02$) associated with a peak level of 3-hydroxybutyrate on day 7, respectively. This study thereby suggests that it is prudent to monitor ketone body level in younger subjects and in patients with rapid weight loss while using SGLT-2i [Table 6].[34]

Furthermore, literature suggests several other mechanisms which could be operating and has the potential to generate ketoacidosis. While insulinopenia promotes lipolysis and ketogenesis, hyperglucagonemia stimulates hepatic ketogenesis. Animal studies have also demonstrated that the increase in glucagon promotes hepatic kisspeptin-1 secretion, which in turn suppresses glucose-stimulated insulin secretion.[35]

Intriguingly, SGLT-2 inhibitors have been found to be associated with the increase in glucagon and reduction of insulin. Merovci *et al.* showed fasting glucagon/insulin ratio increased from 12 ± 2 to 27 ± 7 at day 14 in the dapagliflozin group, while it remained unchanged in the placebo group (8 ± 2 to 8 ± 2). This finding overall suggests, approximately 23% increase in glucagon/insulin ratio in dapagliflozin group.[36] Ferrannini *et al.* found, significantly decreased prehepatic insulin/glucagon molar concentration ratio in emapgliflozin arm compared to baseline, which was observed both in fasting and postmeal phase. Overall, there was roughly 25% decrease in insulin/glucagon ratio in empagliflozin arm. Interestingly, these differences were seen with even a single 25-mg dose of empagliflozin, which persisted after chronic administrations for 28 days ($P < 0.0001$).[37] Table 7 depicts the changes in glucagon and insulin ratio following SGLT-2 inhibitors use.

Glucagon is a known strong stimulator of hepatic glucose production. The increase in plasma glucagon concentrations observed with dapagliflozin and empagliflozin, also provides a reliable explanation for the 17–30% increase in endogenous glucose production (EGP) observed with these agents [Table 8].[36-38] Paquot *et al.*, have earlier demonstrated that the 20–32% increase in fasting plasma glucagon concentration is sufficient enough to increase basal hepatic glucose production.[39] Although in a study by Mudaliar *et al.*, no clinically significant increase in mean EGP from baseline was observed after 12 weeks with dapagliflozin. This perhaps suggest that either the amount of glucosuria was not sufficient to trigger a compensatory increase in EGP or in part this was compensated by improvement in hepatic insulin sensitivity. It should be noted that in this randomized double-blind placebo-controlled parallel-group 12-week ($n = 44$) study, dapagliflozin 5 mg/day shown a significantly improvement in insulin sensitivity (Δ 19.97%; 95% confidence interval [CI], 5.75 to 36.10; $P = 0.0059$), as assessed by measuring the glucose disappearance rate (G_{DR}) during the last 40 min of a 5-h hyperinsulinemic, euglycemic clamp. Nevertheless, a clear trend of rise in glucagon was also observed. The mean ± SD change in fasting serum glucagon from baseline was 1.2 ± 22.6 pg/mL (95% CI, -9.4 to +11.8) and 9.4 ± 20.9 pg/mL (95% CI, 0.1 to 18.6) in the placebo and dapagliflozin groups, respectively. Additionally, a greater change in fatty acid oxidation and shift from carbohydrate oxidation were observed with dapagliflozin treatment.[40] These collective finding clearly hints toward a meaningful rise in glucagon with SGLT-2 inhibitors.

While the decrease in insulin response can be explained by the lower glucose levels following SGLT-2i use, the mechanism of the rise of glucagon still remains unclear. Lower insulin levels can augment glucagon production through a well-known paracrine feedback loop between beta and alpha cells. Compensatory counter-rise in response to the glucosuria could be another mechanism.[41] Recently, a newer mechanism has been proposed which suggest inhibition of SGLT-2 activity might directly induce glucagon secretion through alpha cells.[42] This induction of hyperglucagonemia and relative insulinopenia, in the background of true insulinopenia of T2DM, could be another mechanism behind ketoacidosis. Figure 1 depicts the proposed mechanism of ketone bodies formation with SGLT-2i.

Taken together, it is biologically plausible that the SGLT-2i may potentiate the generation of ketoacidosis in spite of achieving euglycemia through various mechanisms. Increase in glucagon with concomitant decrease in insulin, increased reabsorption of ketone with concomitant delayed clearance of ketone, shift in substrate utilization to fatty

Table 6: Serum ketone and SGLT2 inhibitors

Author	Source	Drug	Serum ketones
Kaku *et al.*	Cardiovascular Diabetology 2014	Tofogliflozin	↑ Ketones
Nishimura *et al.*	ADA 2015, Poster 948	Luseogliflozin	↑ Ketones
Nakayama *et al.*	ADA 2015, Poster 1236	Ipragliflozin	↑ Ketones (pre-breakfast and pre-dinner)

SGLT2: Sodium-glucose co-transporter-2

Table 7: Effects of SGLT2 inhibitors (SGLT2i) on insulin (I), glucagon (G), and G/I or I/G ratio

Authors, year	Drug	No. (duration)	Baseline serum insulin	Post SGLT2i serum insulin	Baseline serum glucagon	Post SGLT2i serum glucagon	Baseline G/I[a] or I/G[b] ratio	Post SGLT2i G/I[aa] or I/G[bb] ratio
Merovci *et al.*, 2014	DAPA 10 mg	12 (a. day 3) (b. day 14)	7±1 μU/ml	a. 4±1 μU/ml* b. 5±1 μU/ml*	64±4 pg/ml	a. 85±7 pg/ml* b. 77±6 pg/ml*	12±2[a]	a. 28±7[aa]* b. 27±7[aa]*
Ferraninni *et al.*, 2014	EMPA[@] 25 mg	66 (a. day 1) (b. day 28)	93 [65] nmol/l/h	a. 80 [59] nmol/l/h[#] b. 76 [59] nmol/l/h[#]	1.07±0.3 nmol/l/h	a. 1.33±0.42 nmol/l/h[#] b. 1.15±0.36 nmol/l/h[#]	29 [19][b] (mol/mol)	a. 22 [17][bb#] b. 24 [19][bb#] mol/mol

*P<0.05, #P<0.0001, [@]All AUC data – area under the curve, [aa]23% increase in glucagon/insulin (G/I) ratio, [bb]25% decrease in insulin/glucagon (I/G) ratio, [interquartile ratio], DAPA: Dapagliflozin, EMPA: Empagliflozin

Table 8: Effect of SGLT2 inhibitors (SGLT2i) on endogenous glucose production (EGP)

Authors, year	Drug	No. of patient (duration)	EGP baseline	EGP after SGLT2i	Remarks
Merovci *et al.*, 2014	DAPA 10 mg	12 (a. day 3) (b. day 14)	2.1±0.1 mg/kg/min	a. 2.53±0.16 mg/kg/min b. 2.55±0.20 mg/kg/min	17% increase in EGP (P<0.05)
Ferraninni *et al.*, 2014	EMPA 25 mg	66 (a. day 1) (b. day 28)	a. 13.8 [5.2] μmol/kg/min b. 13.8 [5.2] μmol/kg/min	a. 17.6 [4.8] μmol/kg/min b. 17.5 [4.1] μmol/kg/min	30% increase in EGP (P<0.0001)
Smulders *et al.*, 2013	IPRA 100 mg	12 (day 6)	12.7±1.6 μmol/kg/min	Δ vs placebo: +0.91±1.4 μmol/kg/min, P<0.05	-

EGP: Endogenous glucose production, DAPA: Dapagliflozin, EMPA: Empagliflozin, IPRA: Ipragliflozin

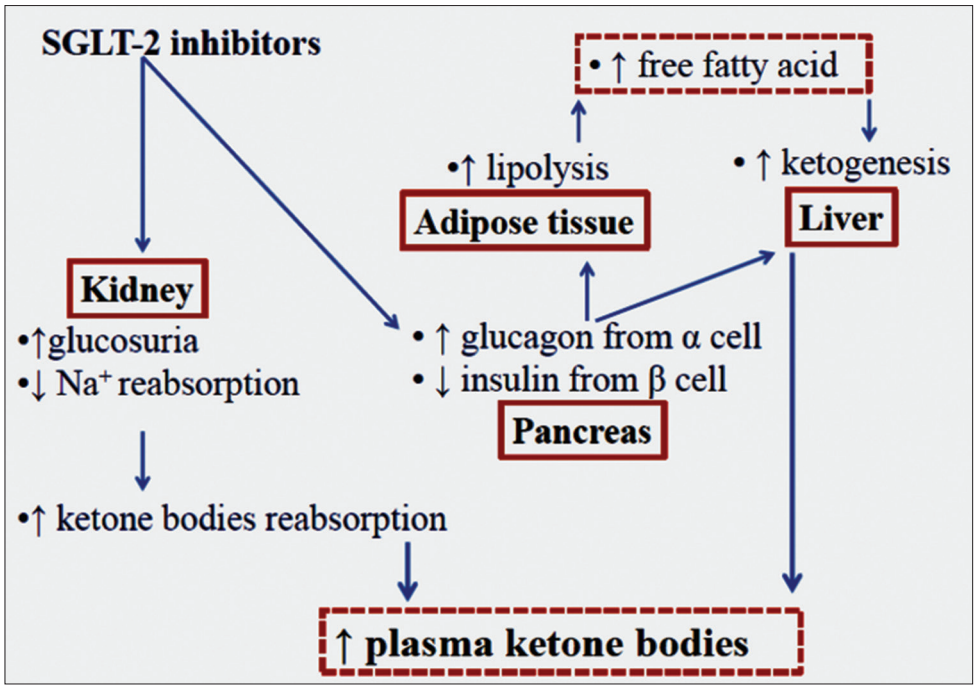

Figure 1: Mechanism of ketoacidosis with SGLT-2 inhibitors

acid with concomitant increase in ketone body production, and weight loss with concomitant sarcopenia; all could be playing a complementary role in the genesis of ketonemia. Associated dehydration, fluid loss (gastroenteritis) or poor fluid intake (vomiting) and infections, in a poor metabolic milieu, might also trigger the process of this event, making the patient ketosis-prone.

In light of these emerging issues, logically a drug which reduces EGP through liver, like metformin, or a drug which reduces glucagon and concomitantly increases insulin, like SUs or ideally an incretin-based therapy, could be an attracting add-on option to counter and correct this imbalance.[36,42] Only further studies in this regard can enlighten in future.

Conclusion

There is no absolute evidence or proof beyond a reasonable doubt that SGLT-2 inhibitors can precipitate ketoacidosis in spite of achieving euglycemia. While the preponderance of unwanted derangement following its acute or chronic use may mechanistically appears to mediate this unwarranted side effect; from the available data, it appears that ketoacidosis could have been compounded by concomitant precipitating risk factors.

Off-label use of SGLT-2 inhibitors in type 1 diabetes needs to be discouraged. The clinician must not venture for the experiment of using this drug to reduce insulin burden in type 1 diabetes, except in clinical trial settings with strict vigilance. In addition, its use in pancreatic or secondary diabetes, syndromic diabetes, maturity-onset diabetes in young, and LADA should be avoided, until further data is available.

Development of EuDKA in type 2 diabetes appears to be a very rare event. However, given the available modest efficacy data in favor of SGLT-2 inhibitors, this class is supposedly going to be used widely. Hence, their widespread use needs the pragmatic wisdom of foresight. Pharmacovigilance toward this unwanted side effect would be a key to leverage its benefit of additional weight loss and blood pressure reduction.

Meanwhile, patients with type 2 diabetes should preferably and proactively be educated regarding sufficient hydration, genital hygiene, and adequate carbohydrate intake, while using SGLT-2 inhibitors. Persistent nausea and vomiting in any sick patients, while on SGLT-2 inhibitors should promptly alert clinicians to search for ketosis, even when this incidence of EuDKA appears pretty low. However, serial urinary ketone measurement while on SGLT-2 inhibitors is not recommended at this point of time except in doubtful situation.

In authors' opinion, SGLT-2 inhibitors should preferably be avoided in patient who are hospitalized, sick and cannot eat properly, having recurrent gastro-paresis, peri-operative, with catabolic features, or extreme weight loss, as well as patient on very low carbohydrate diet. In other words, a close supervision is required, in a setting of decompensated and deranged metabolic control, when insulin should be preferably used rather than SGLT-2 inhibitors.

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Conflicts of interest

There are no conflicts of interest.

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