**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 ibrulglin, tofoglin, and luseogliflozin are also approved in Japan. Of these six glifozins, the most selective SGLT-2i, to the SGLT-2 receptor over SGLT-1 receptor, in decreasing order are tofoglin (1:3000), empaglin (1:2500), luseogliflozin (1:1770), dapaglin (1:1200), ibrulglin (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...
inducing significant hypoglycemia, during their phase 3 clinical trials.\cite{5,4}
Moreover, these once daily oral drugs can also be safely combined with other anti-diabetic drugs (metformin, sulfonylureas [SUs], pioglitazone, and dipeptidylpeptidase-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.\cite{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.\cite{7}

**SODIUM-GLOUCECO-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.\cite{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.\cite{9}
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.\cite{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.\cite{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.\cite{10} Kalra et al. have also briefly communicated on this issue very recently, and proposed a pragmatic approach for the clinician.\cite{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-GLOUCECO-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 dapagliflozin, 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.\cite{12} Perkins et al. in an 8-week study, found 2 cases of EuDKA, treated with empagliflozin in 42 T1DM patient.\cite{13} Very recently Sands...
et al, reported 2 case of DKA observed with sotagliflozin (dual SGLT1 and SGLT2 inhibitor) in 33 T1DM patients.

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. In a real-world setting of the patient forum, hosted by Juvenile Diabetes Research Foundation, 2 cases of recurrent EuDKA reported with canagliflozin.

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. 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. 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. Two cases (13%) of DKA observed in sotagliflozin was also implicated to infusion set crimping or shallow cannula insertion.

**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.

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.

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.”

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.

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 Hilaire et al.| Canagliflozin | -  | 1        | Cannula-attachment failure              |
| JDRF portal     | Canagliflozin | -  | 2        | Over-enthusiastic 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.[23] 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, 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.[19]

**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 ketoadisisis, 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. Acetoadacetate 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 |
| Peters et al. | ADA 2015 | 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 |
| Peters et al. | ADA 2015 | 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.\(^{[29]}\)

Human studies also suggested, a dose-dependent hyperketonemia, including a significant increase in total serum ketone, acetoacetate acid, and \(\beta\)-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].\(^{[31]}\) 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 \(\mu\)mol/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](image)

| 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 |
| Hine et al. | 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](image)

| 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%                |
| \(\Delta\) Total serum ketone (\(\mu\)mol/L) | +29.7    | +45.6               | +59.5               | +141.2              |
| \(\Delta\) Acetoacetate acid (\(\mu\)mol/L) | +7.1     | +10.7               | +14.8               | +31.0               |
| \(\Delta\) \(\beta\)-hydroxybutyrate (\(\mu\)mol/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].

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.[30]

Intriguingly, SGLT-2 inhibitors have been found to be associated with the increase in glucagon and reduction of insulin. Meroci 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.[31] Ferrannini et al. found, significantly decreased prehepatic insulin/glucagon molar concentration ratio in empagliflozin 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 \( P < 0.0001 \).[32] 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 \( \Delta 19.97\% ; 95\% \) confidence interval [CI], 5.75 to 36.10; \( P = 0.0059 \), as assessed by measuring the glucose disappearance rate \( (G_{\text{DGR}}) \) 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. of patient (duration) | Baseline serum insulin | Post SGLT2i serum insulin | Baseline serum glucagon | Post SGLT2i serum glucagon | Baseline G/I or I/G ratio | Post SGLT2i G/I or I/G ratio |
|--------------|------|--------------------------|------------------------|--------------------------|------------------------|----------------------------|--------------------------|-----------------------------|
| Merovci et al., 2014 | DAPA 10 mg | 12 (a. day 3) | 7±1 μU/ml | a. 4±1 μU/ml* | 64±4 pg/ml | a. 85±7 pg/ml* | 12±2* | a. 28±7** |
| | | (b. day 14) | b. 5±1 μU/ml* | | | b. 77±6 pg/ml* | | b. 27±7** |
| Ferraninni et al., 2014 | EMPA 25 mg | 66 (a. day 1) | 93 [65] nmol/l/h | a. 80 [59] nmol/l/h* | 1.07±0.3 nmol/l/h | a. 1.33±0.42 nmol/l/h* | 29 [19]* | a. 22 [17]** |
| | | (b. day 28) | b. 76 [59] nmol/l/h* | | | b. 1.15±0.36 nmol/l/h* | | b. 24 [19]** |

*P<0.05, **P<0.0001, *All AUC data – area under the curve, **23% increase in glucagon/insulin (G/I) ratio, ***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) | 2.1±0.1 mg/kg/min | a. 2.53±0.16 mg/kg/min | 17% increase in EGP (P<0.05) |
| | | (b. day 14) | | b. 2.55±0.20 mg/kg/min | |
| Ferraninni et al., 2014 | EMPA 25 mg | 66 (a. day 1) | 13.8 [5.2] μmol/kg/min | a. 17.6 [4.8] μmol/kg/min | 30% increase in EGP (P<0.0001) |
| | | (b. day 28) | b. 13.8 [5.2] μmol/kg/min | b. 17.5 [4.1] μmol/kg/min | |
| 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

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 SU’s 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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: Rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495-502.
2. Washburn WN, Poucher SM. Differentiating sodium-glucose co-transporter-2 inhibitors in development for the treatment of type 2 diabetes mellitus. Expert Opin Investig Drugs 2013;22:463-86.
3. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiaris E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2013;159:262-74.
4. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papaetheodorou K, et al. Efficacy and safety of empagliflozin for type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2014;16:984-93.
5. 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:e001007.
6. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: A meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16:457-66.
7. Singh AK. Deciding oral drugs after metformin in type 2 diabetes: An evidence-based approach. Indian J Endocrinol Metab 2014;18:617-23.
8. FDA Drug Safety Communication: FDA Warns that SGLT2 Inhibitors for Diabetes May Result in a Serious Condition of Too Much Acid in the Blood. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm. [Last accessed on 2015 Jul 03].
9. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/SGLT2_inhibitors/human_referral_prac_000052.jsp&mid=WC0b01ac05805c516f. [Last accessed on 2015 Jul 03].
10. Taylor SI, Blau JE, Rother CI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100:2849-52.
11. Kalra S, Sahay R, Gupta Y. Sodium glucose transporter 2 (SGLT2) inhibition and ketogenesis. Indian J Endocrinol Metab 2015;19:524-8.
12. Henry RR, Rosenstock J, Edelman S, Mudaliar S, Chalmandaris AG, Kasischyanula S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: A randomized, double-blind, placebo-controlled pilot study. Diabetes Care 2015;38:412-9.
13. Perkins BA, Cherney DZ, Partridge H, Soleymanolou N, Tschirhart H, Zinnman B, et al. 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 2014;37:1480-3.
14. Sands AT, Zambrowicz BP, Rosenstock J, Lapuerta P, Bode BW, Garg SK, et al. Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes. Diabetes Care. 2015;38(7):1181-8.
15. St Hilaire R, Costello H. Prescriber beware: Report of adverse effect of sodium-glucose cotransporter 2 inhibitor use in a patient with contraindication. Am J Emerg Med 2014. pii: S0735-6703(14)00163-7.
16. Available from: http://www.typeonevolution.org/groups/adults/forum/topic/invokana-fort1d/. [Last downloaded on 2015 Jul 03].
17. Kuhadiya N, Mehta A, Ghanim H, Hejna J, Makdissi A, Chaudhuri A, et al. American Association of Clinical Endocrinology Meeting 2015, Nashville, TN: Late-Breaking Abstract 1213. Available from: http://www.am2015.aace.com/sites/all/files/Late-Breaking.pdf. [Last accessed on 2015 Jul 03].
Singh: SGLT-2 inhibitors and ketosis

18. Peters AE, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015. pii: Dc150843. [Epub ahead of print]

19. Burr K, Nguyen AT, Rasouli N. Endocrine Society Meeting, San Diego, California. SAT 586-604-Diabetes Case Reports II Clinical. 2015. Available from: https://www.endo.confex.com/endo2015endo/webprogram/Paper21461.html. [Last accessed on 2015 Jul 03].

20. Chaudhury F. Diabetic ketoacidosis following SGLT2 inhibitor therapy in T2DM. American Association of Clinical Endocrinology Meeting 2015, Nashville, TN. Abstract 203. Available from: http://www.am2015.aace.com/sites/all/files/2015-Final-Abstract.pdf. [Last accessed on 2015 Jul 03].

21. Kelwade J, Sethi BK, Nagesh SV, Vaseem A. A case of "pseudo-ketoacidosis". Indian J Endocrinol Metab 2014;18:743.

22. Kohler S, Salsali A, Hantel S, Kim G, Woerle HJ, Broedl UC. Safety and tolerability of empagliflozin in patients with type 2 diabetes. Poster Presentation. American Diabetic Association, Boston; 2014. p. 1173.

23. Erondo N, Desai M, Ways K, Meininger G. Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program. Diabetes Care 2015; Jul 22. pii: dc151251. [Epub ahead of print]

24. Hine J, Paterson H, Abrol E, Russell-Jones D, Herring R. SGLT inhibition and euglycaemic diabetic ketoacidosis. Lancet Diabetes Endocrinol 2015;3:503-4.

25. Hayami T, Kato Y, Kamiya H, Kondo M, Naito E, Sugiyura Y, et al. A case of ketoacidosis by a SGLT2 inhibitor in a diabetic patient with low carbohydrate diet. J Diabetes Invest 2015; DOI: 10.1111/ jdi.12330. [Epub ahead of print]

26. Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, Peters AL, et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: Results from the T1D Exchange clinic registry. J Clin Endocrinol Metab 2013;98:3411-9.

27. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: The SEARCH for diabetes in youth study. Pediatrics 2014;133:e938-45.

28. Cohen JJ, Benglund F, Lotspeich WD. Renal tubular reabsorption of acetoacetate, inorganic sulfate and inorganic phosphate in the dog as affected by glucose and phlorizin. Am J Physiol 1956;184:91-6.

29. Ruderman NB, Ross PS, Berger M, Goodman MN. Regulation of glucose and ketone-body metabolism in brain of anesthetized rats. Biochem J 1974;138:1-10.

30. Martin PM, Gopal E, Ananth S, Zhaung L, Itagaki S, Prasad BM, et al. Identity of SMCT1 (SLC5A8) as a neuron-specific Na coupled transporter for active uptake of L-lactate and ketone bodies in the brain. J Neurochem 2006;98:279-88.

31. Yokono M, Takasu T, Hayashizaki Y, Mitsuoka K, Kihara R, Muramatsu Y, et al. SGLT2 selective inhibitor ipragliflozin reduces body fat mass by increasing fatty acid oxidation in high-fat diet-induced obese rats. Eur J Pharmacol 2014;727:66-74.

32. Kaku K, Watada H, Iwamoto Y, Utsunomiya K, Terauchi Y, Tobe K, et al. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: A combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovasc Diabetol 2014;13:65.

33. Nishimura R, Osono T, Jinnouchi H, Kanada S, Omija H, Sakal S, et al. Low carbohydrate did not affect the behaviour of luseogliflozin, a selective SGLT2 inhibitor on glycemic control over 24 hours measured by continuous glucose monitoring in Japanese patients with type 2 diabetes. Poster Presentation. American Diabetes Association Meeting, Boston; 2015, p. 948.

34. Nakayama H, Yoshinobu S, Kawano S, Tsuruta M, Nohara M, Soga R, et al. Factors associated with the effect of ipragliflozin on the diurnal profiles of plasma glucose and 3-hydroxybutyrate in patients with type 2 diabetes. Poster Presentation. American Diabetes Association Meeting, Boston; 2015. p. 1236.

35. Song WJ, Mondal P, Wollé A, Alonso LC, Stamateris R, Ong BW, et al. Glucagon regulates hepatic kisspeptin to impair insulin secretion. Cell Metab 2014;19:667-81.

36. Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509-14.

37. Ferramini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499-508.

38. Smulders RA, Leeflang S, Schless F. The effect of ipragliflozin on the total glucose turnover after OGTT in healthy subjects and patients with type 2 diabetes mellitus. Diabetologia 2013;56:S399-400.

39. Paquot N, Schneider P, Jéquier E, Gaillard R, LeFebvre PJ, Scheen A, et al. Effects of ingested fructose and infused glucagon on endogenous glucose production in obese NIDDM patients, obese non-diabetic subjects, and healthy subjects. Diabetologia 1996;39:580-6.

40. Mudaliar S, Henry RR, Boden G, Smith S, Chalamandaris AG, Duchesne D, et al. Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. Diabetes Technol Ther 2014;16:137-44.

41. Kalra S, Gupta Y, Patil S. Sodium-glucose cotransporter-2 inhibition and the insulin: Glucagon ratio: Unexplored dimensions. Indian J Diabetes Technol Ther 2014;16:137-44.

42. Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thévenet J, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21:512-7.