SGLT2 Inhibitors May Predispose to Ketoacidosis

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Context: Sodium glucose cotransporter 2 (SGLT2) inhibitors are antidiabetic drugs that increase urinary excretion of glucose, thereby improving glycemic control and promoting weight loss. Since approval of the first-in-class drug in 2013, data have emerged suggesting that these drugs increase the risk of diabetic ketoacidosis. In May 2015, the Food and Drug Administration issued a warning that SGLT2 inhibitors may lead to ketoacidosis.

Evidence Acquisition: Using PubMed and Google, we conducted Boolean searches including terms related to ketone bodies or ketoacidosis with terms for SGLT2 inhibitors or phlorizin. Priority was assigned to publications that shed light on molecular mechanisms whereby SGLT2 inhibitors could affect ketone body metabolism.

Evidence Synthesis: SGLT2 inhibitors trigger multiple mechanisms that could predispose to diabetic ketoacidosis. When SGLT2 inhibitors are combined with insulin, it is often necessary to decrease the insulin dose to avoid hypoglycemia. The lower dose of insulin may be insufficient to suppress lipolysis and ketogenesis. Furthermore, SGLT2 is expressed in pancreatic α-cells, and SGLT2 inhibitors promote glucagon secretion. Finally, phlorizin, a nonselective inhibitor of SGLT family transporters decreases urinary excretion of ketone bodies. A decrease in the renal clearance of ketone bodies could also increase the plasma ketone body levels.

Conclusions: Based on the physiology of SGLT2 and the pharmacology of SGLT2 inhibitors, there are several biologically plausible mechanisms whereby this class of drugs has the potential to increase the risk of developing diabetic ketoacidosis. Future research should be directed toward identifying which patients are at greatest risk for this side effect and also to optimizing pharmacotherapy to minimize the risk to patients. **(*J Clin Endocrinol Metab* 100: 2849–2852, 2015)**

Sodium glucose cotransporter 2 (SGLT2) inhibitors decrease concentrations of plasma glucose by inhibiting proximal tubular reabsorption of glucose in the kidney. This relatively new class of drugs offers an attractive efficacy profile combining improved glycemic control with weight loss. Furthermore, studies with empagliflozin have suggested that SGLT2 inhibitors reverse glomerular hyperfiltration in insulin-treated patients with type 1 diabetes, which may potentially decrease the rate of progression of diabetic kidney disease (1). The favorable efficacy profile of these drugs need to be balanced against possible side-effects.

In this context, it is noteworthy that in May 2015 the Food and Drug Administration (FDA) warned that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis (2). The FDA's recent warning was preceded by reports in the medical literature suggesting that SGTL2 inhibitors increase the risk of ketoacidosis in patients with both type 1 (T1D) and type 2 diabetes (T2D). In an 8-week study in T1D patients, approximately 5% of patients

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Abbreviations: DKA, diabetic ketoacidosis; SGLT2, sodium glucose cotransporter 2; T1D, type 1 diabetes; T2D, type 2 diabetes.

treated with empagliflozin (2 of 42) were withdrawn from the study when they developed diabetic ketoacidosis (1, 3). Whereas the episodes of ketoacidosis occurred in the setting of well-recognized precipitating factors (ie, insulin pump failure or acute gastroenteritis), it is important to inquire whether the drug might also have contributed by rendering the patients more ketosis prone. SGLT2 inhibitors are currently being used off label in clinical practice to treat T1D patients, and this has been reported to cause diabetic ketoacidosis (4).

Real-world experience with SGLT2 inhibitors is further documented in a patient forum hosted by the Juvenile Diabetes Research Foundation's TypeOneNation social network (5). Two patients with longstanding T1D (23–27 y) described multiple episodes of ketoacidosis while receiving canagliflozin, even though neither had been hospitalized for diabetic ketoacidosis prior to initiation of SGLT2 inhibitor therapy. Importantly, both patients reported that their physicians were initially confused by the fact that the ketoacidosis was not accompanied by hyperglycemia. Although the syndrome of euglycemic ketoacidosis is well documented in other clinical contexts, it appears that SGLT2 inhibitors should be added to the list of factors that can predispose to euglycemic ketoacidosis. Although Henry et al (6) did not observe any episodes of diabetic ketoacidosis in a 2-week study of 70 T1D patients treated with dapagliflozin, a short 2-week study with only 29 individuals receiving a therapeutic dose (5–10 mg/d) of dapagliflozin does not entirely exclude the possibility of clinically significant risk. Case reports have also begun to appear describing episodes of diabetic ketoacidosis occurring in SGLT2 inhibitor-treated T2D patients. For example, 2 days after the initiation of canagliflozin in combination with metformin and glipizide, a T2D patient presented to the emergency department with euglycemic ketoacidosis in association with an anion gap of 19 mEq/L (7).

Furthermore, at least 20 cases of ketoacidosis in SGLT2 inhibitor treated patients were reported to the FDA Adverse Events Reporting System prior to June 6, 2014 (2), and additional cases have been reported since that cutoff date. Finally, at least one SGLT2 inhibitor (tofogliflozin) was reported to cause a dose-dependent increase in levels of both acetoacetate and β-hydroxybutyrate (8).

These case reports of diabetic ketoacidosis in SGLT2 inhibitor-treated patients raise the question of how this class of drugs might contribute either directly or indirectly to the pathogenesis of ketoacidosis. Perhaps the most straightforward ketosis-promoting mechanism is illustrated by studies of the investigational use of SGLT2 inhibitors to treat T1D patients. Because of the glucose-lowering property of SGLT2 inhibitors, the investigators decreased the dose of insulin administered to the patients to minimize the risk of hypoglycemia (1, 3). The resulting decrease in circulating insulin levels would be predicted to increase the rates of lipolysis in adipose tissue and ketogenesis in the liver, which would increase circulating ketone body levels (Figure 1). There are additional drug effects that may contribute to elevated ketone body levels. Studies in dogs demonstrated that phlorizin (a nonselective SGLT1/SGLT2 inhibitor) promoted renal tubular reabsorption of acetoacetate (9). This effect of phlorizin may be secondary to inhibition of SGLT1/SGLT2-mediated Na^+ reabsorption, which increases the concentration of Na^+ in the renal tubular fluid and thereby increases the electrochemical gradient driving carrier-mediated reabsorption of negatively charged ketone bodies. The combination of increased ketone body production plus decreased renal clearance would exert an additive effect to increase circulating ketone body levels. Thus, it is biologically plausible that administration of an SGLT2-inhbitor to an insulin-dependent T1D patient would increase circulating ketone body levels and predispose to the development of ketoacidosis.

Levels of β-hydroxybutyrate were not measured in this classic study of phlorizin in dogs (9). Nevertheless, sodium-monocarboxylate transporter-1 (SLC5A8) has been reported to mediate cotransport of Na^+ ions with monocarboxylate anions such as acetoacetate and β-hydroxybutyrate (10). Because SLC5A8 is expressed on the apical membrane of renal tubular epithelial cells, it is possible that the same transporters mediate proximal tubular reabsorption of both acetoacetate and β-hydroxybutyrate. Thus, SGLT2 inhibitors are expected to exert similar effects on renal clearance of both ketone bodies. In any case, it would be informative to conduct clinical studies to assess the effect of selective SGLT2 inhibitors on renal clearance of ketone bodies in humans. Historically, physicians have routinely relied on ketonuria rather than plasma levels of ketone bodies as a screen for the presence of ketosis. Accordingly, if SGLT2 inhibitors decrease urinary excretion of ketone bodies, this could potentially delay recognition and diagnosis of ketoacidosis in patients treated with SGLT2 inhibitors.

The scientific literature suggests additional mechanisms that could potentially mediate an effect of SGLT2 inhibitors to predispose to ketoacidosis in T2D patients in the absence of exogenous insulin therapy. When phlorizin was administered for 24 hours to fasted rats, the animals developed marked hyperketonemia comparable in magnitude with what was observed in streptozotocin-induced diabetes (11). In human studies, both dapagliflozin and empagliflozin have been reported to increase glucagon levels (12, 13), which would be predicted to promote hepatic

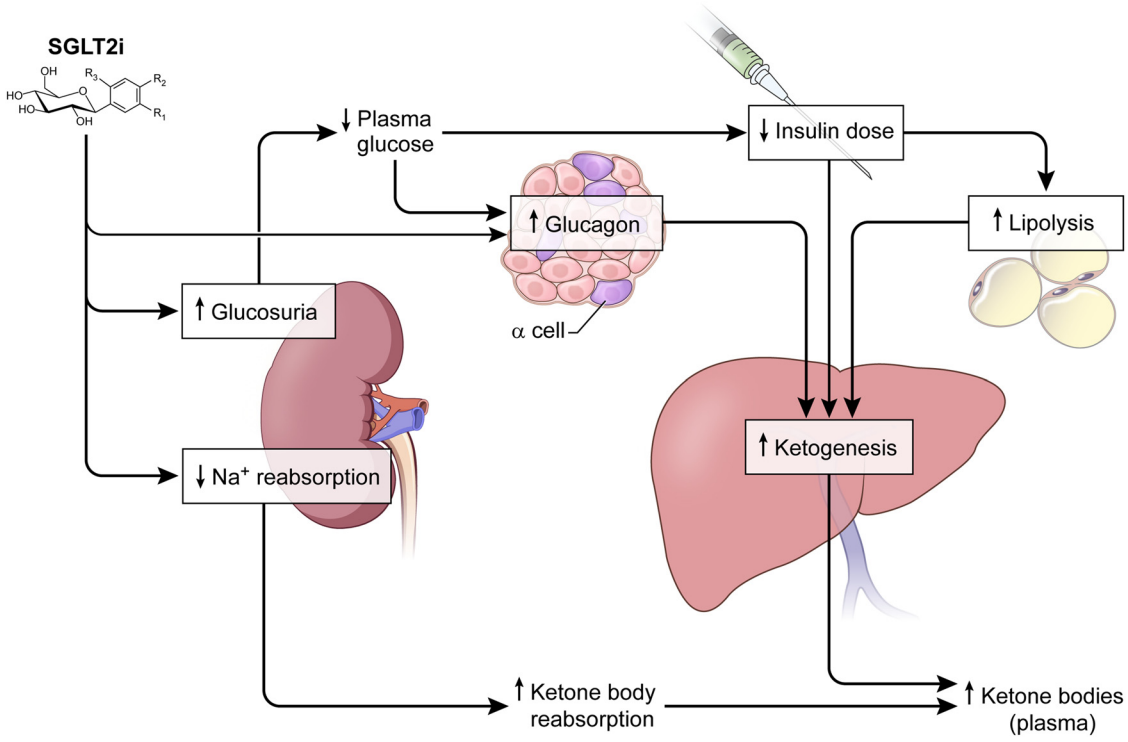

Figure 1. Potential mechanisms whereby adjunctive therapy with SGLT2 inhibitors may promote ketosis and increase the risk of ketoacidosis in T1D patients. SGLT2 inhibitors (SGLT2i) decrease glucose by an insulin-independent mechanism. To minimize the risk of hypoglycemia, T1D patients may need to decrease their insulin dose, which is predicted to increase the rate of adipose tissue lipolysis and hepatic ketogenesis. In addition, SGLT2 inhibitors have been demonstrated to increase plasma glucagon levels in T2D patients (12, 13), possibly to compensate for increased urinary excretion of glucose. In addition, it has recently been reported that SGLT2 inhibitors increase preproglucagon gene expression by acting directly upon pancreatic α-cells (14). Furthermore, phlorizin (a nonselective inhibitor of SGLT1 and SGLT2) has been demonstrated to increase renal tubular reabsorption of acetoacetate (9). If selective SGLT2 inhibitors mimic this action of phlorizin, it is possible that they could also decrease renal clearance of ketone bodies.

ketogenesis (14). A recent paper reported that SGLT2 is expressed on pancreatic α-cells (15) and that this transporter appears to function as part of the α-cells' glucose sensor mechanism. Furthermore, exposure of human islets to dapagliflozin increased glucagon secretion, presumably, by exerting a direct effect on α-cell function. The action of SGLT2 inhibitors to promote glucagon secretion would provide a strong drive to increase ketone body production. Furthermore, animal studies demonstrated that glucagon acts upon the liver to promote secretion of kisspeptin-1, which in turn suppresses glucose-stimulated insulin secretion (16). If such a mechanism were operative in humans, this could potentially further promote ketogenesis by decreasing endogenous insulin secretion in some patients.

In conclusion, although ketoacidosis is not a common adverse event in SGLT2 inhibitor-treated patients, the FDA has issued a formal warning that this class of drugs may indeed increase the risk of diabetic ketoacidosis (DKA). The existence of publications documenting multiple biologically plausible mechanisms for such an adverse effect reinforces the FDA's warning. Whereas available evidence may not achieve the scientific equivalent of proof beyond a reasonable doubt, we believe that the preponderance of evidence supports the causal role for SGLT2 inhibitors in the pathogenesis of DKA. Perkins et al (3) emphasized that coexisting risk factors (gastroenteritis or insulin pump failure) did not exclude the possibility that the drug may have contributed to the pathogenesis of diabetic ketoacidosis in 2 of 42 empagliflozin-treated T1D patients. For example, episodes of insulin pump failure do not invariably result in full-blown episodes of DKA. However, if SGLT2 inhibitors were to accelerate the rate of ketogenesis and/or decrease the clearance of ketone bodies, this could potentially render patients more vulnerable, even with relatively brief episodes of pump failure that might not have led to DKA in the absence of SGLT2 inhibitor therapy. Thus, in the setting of insulin-dependent diabetic patients, the introduction of concomitant therapy with SGLT2 inhibitor therapy may further complicate the challenges of navigating between the Scylla of hypoglycemia due to too much insulin and the Charybdis of ketoacidosis due to too little insulin.

Before embarking upon the voyage to treat T1D patients with SGLT2 inhibitors, it will be extremely impor-

tant to carefully evaluate the risk of drug-induced ketoacidosis. In retrospect, it is clear that the scientific literature on phlorizin contained sufficient information to identify DKA as a potential risk for selective SGLT2 inhibitor therapy. As discussed above, phlorizin induced hyperketonemia in rats (11) and decreased renal clearance of acetoacetate in dogs (9). In contrast, there is a relative paucity of published data prospectively evaluating the effect of selective SGLT2 inhibitors on ketone body metabolism in either animal models or humans.

Nevertheless, when ipragliflozin was administered to obese rats on a high-fat diet, this led to a significant increase in plasma levels of free fatty acids and a marked increase in the levels of β-hydroxybutyrate (17). Similarly, when administered to T2D patients (8), tofloglifozin caused a dose-dependent increase of total ketone body levels by 0.14 (±0.25) mEq/L from a baseline of 0.13 (±0.16) mEq/L [mean (±SD)] at the 40-mg dose of tofogliflozin. In light of the large SD, it is apparent that some individuals experienced a clinically relevant increase in ketone body levels, even if it did not eventuate in overt DKA. With the wisdom of hindsight, we wonder whether an opportunity was missed to document this potential adverse effect prior to the approval of SGLT2 inhibitor drugs.

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