Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors

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THE CASE AT HAND

Recently, the U.S. Food and Drug Administration (FDA) issued a Drug Safety Communication that warns of an increased risk of diabetic ketoacidosis (DKA) with uncharacteristically mild to moderate glucose elevations (euglycemic DKA [euDKA]) associated with the use of all the approved sodium–glucose cotransporter 2 (SGLT2) inhibitors (1). This Communication was based on 20 clinical cases requiring hospitalization captured between March 2013 and June 2014 in the FDA Adverse Event Reporting System database. The scarce clinical data provided suggested that most of the DKA cases were reported in patients with type 2 diabetes (T2D), for whom this class of agents is indicated; most likely, however, they were insulin-treated patients, some with type 1 diabetes (T1D). The FDA also identified potential triggering factors such as intercurrent illness, reduced food and fluid intake, reduced insulin doses, and history of alcohol intake. The following month, at the request of the European Commission, the European Medicines Agency (EMA) announced on 12 June 2015 that the Pharmacovigilance Risk Assessment Committee has started a review of all of the three approved SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) to evaluate the risk of DKA in T2D (2). The EMA announcement claimed

that as of May 2015 a total of 101 cases of DKA have been reported worldwide in EudraVigilance in T2D patients treated with SGLT2 inhibitors, with an estimated exposure over 0.5 million patient-years. No clinical details were provided except for the mention that "all cases were serious and some required hospitalisation. Although [DKA] is usually accompanied by high blood sugar levels, in a number of these reports blood sugar levels were only moderately increased" (2).

With this background, it is very timely that in this issue of *Diabetes Care* there are two articles on this subject. Erondu et al. (3) report cases of DKA in T2D from a large clinical development program and Peters et al. (4) discuss cases from clinical practice observations of T1D and T2D patients.

It is not unusual that serious safety issues related to a new drug go undetected during the relatively short clinical development programs for regulatory drug approval. This is particularly true when the safety issue is unexpected, occurring as an off-target effect, or only emerges once the drug is used widely. If serious enough, the issue may require a label warning and a mitigation plan or even consideration of drug withdrawal. DKA is an overt serious clinical condition that may be missed only if presenting with mild to moderate hyperglycemia, as it may be the case with use of SGLT2

inhibitors, which could delay diagnosis and treatment and even accelerate the progressive metabolic deterioration. Interestingly, the large clinical development programs of the three marketed SGLT2 inhibitors, comprising >40,000 T2D patients, bore no clear signal of DKA. Erondu et al. (3), representing Janssen, the manufacturer of canagliflozin, report a relatively low frequency of DKA (15 cases, 12 on canagliflozin and 3 still blinded in the CANagliflozin cardioVascular Assessment Study [CANVAS]) detected in a retrospective analysis of 17,596 participants in the development program up to May 2015. The estimated incidence rates—0.5, 0.8, and 0.2 per 1,000 patient-years with canagliflozin 100 mg, canagliflozin 300 mg, and comparator, respectively—if underwhelming, are double with the SGLT2 inhibitor. Upon our inquiry, the other two manufacturers of approved SGLT2 inhibitors, AstraZeneca and Boehringer Ingelheim, provided preliminary (unpublished) figures that are even lower than the Janssen data. In more than 18,000 patients exposed to dapagliflozin in the randomized controlled T2D study program, including DECLARE (Dapagliflozin Effect on Cardiovascular Events), the frequency of reported events suggestive of DKA (blinded and unblinded events) is less than 0.1%. Similarly in DECLARE, aiming for 17,150 patients randomized to dapagliflozin or placebo, the total number

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of reported blinded events of potential DKAs is less than 0.1% (E. Johnsson, AstraZeneca, personal communication). In a retrospective analysis of randomized phase 2 and 3 empagliflozin trials ($>$13,000 T2D participants), there were eight events consistent with DKA with no imbalance observed between patients treated with empagliflozin 10 mg (two events), empagliflozin 25 mg (one event), and placebo (five events). In the cardiovascular outcome trial EMPA-REG Outcome with approximately 7,000 patients, the frequency of reported blinded events of DKA is less than 0.1% (U. Broedl, Boehringer Ingelheim, personal communication).

Of note, the canagliflozin data reported by Erondu et al. (3) appeared to have a greater incidence of DKA, but 6 out of the 12 cases had evidence of latent autoimmune diabetes in adults or T1D or tested positive for GAD65 antibodies, and, perhaps, some of the other cases may have been T2D misdiagnoses. And even if the diagnosis was correct, most of the patients were on insulin treatment and were part of CANVAS, suggesting a more advanced T2D stage with significant β-cell failure.

The FDA did acknowledge that some of the cases occurred in T1D, where increasing off-label use of SGLT2 inhibitors has been observed, most likely due to the favorable insulin-independent glucose-lowering and weight-loss effects. Indeed, preliminary proof-of-concept pilot studies in T1D have reported improvements in short-term glucose control with less glucose variability, weight loss, and lower insulin doses (5–7). Social media have disseminated initial favorable experiences and could have contributed to the raised expectations, leading to many T1D patients discussing with their physicians the addition of an SGLT2 inhibitor in an attempt to ameliorate their diabetes control. Indeed, despite new insulin analogs and technological improvements in insulin delivery devices and glucose monitoring systems, T1D remains an intrusive and challenging disease, fraught with wide glucose swings and hypoglycemic episodes that frustrate patients, families, and health care providers. There is no better example than the Diabetes Control and Complications Trial (DCCT). Despite 6 years of monthly visits with outstanding diabetes treatment teams with limitless resources to achieve an HbA_{1c} of 7%, the T1D patients in the intensive intervention group

escalated back to an HbA_{1c} of 8% in the posttrial years (8). In a recent report from the T1D Exchange clinic registry (which provides the best cross-sectional U.S. data), the average HbA_{1c} was ~8%, and only 30% achieved a goal HbA_{1c} of $<$7%, severe hypoglycemia occurred in 9–20% of patients per year depending on age and diabetes duration, overweight/obesity was present in 68% of patients, and, interestingly, DKA still occurred at 10% per year in patients aged 13–26 years and at 4–5% per year in the older patients (9). Therefore, it is not surprising that given the burden of T1D and its challenging unmet needs, the pharmacological properties of SGLT2 inhibitors prompted clinical development programs seeking regulatory approval and attracted off-label use in T1D. The data presented in this issue of *Diabetes Care* in T2D (3) and, in particular, the cases associated with T1D as presented by Peters et al. (4) do provide a good opportunity to discuss how these agents modulate the pathophysiology leading to DKA. Thus, it is in this context that we need to analyze the potential problem of euDKA associated with SGLT2 inhibitors to provide a more realistic and practical perspective.

THE PATHOPHYSIOLOGY

Ketosis results from restriction of carbohydrate usage with increased reliance on fat oxidation for energy production. The pathogenesis of DKA is well established (10). Briefly, absolute insulin deficiency leads to reduced glucose utilization and enhanced lipolysis; increased delivery of free fatty acids (FFAs) to the liver coupled with raised glucagon levels promotes FFA oxidation and production of ketone bodies. In both T1D and T2D, DKA presents with marked hyperglycemia ($>$250 mg/dL, typically 350–800 mg/dL), profuse glycosuria (2–4 mg $\cdot$ min^{-1} $\cdot$ kg^{-1}), and hyperketonemia (plasma β-hydroxybutyrate 4.2–11.0 mmol/L) (11,12). The hyperglycemia of DKA is associated with extreme insulin resistance, manifesting itself as markedly ($>$70%) reduced tissue glucose disposal and increased endogenous glucose production (EGP) (12).

euDKA was originally defined as DKA with plasma glucose levels $<$300 mg/dL occurring in young T1D patients, two-thirds of whom were female (13). The primary cause was reduced availability

of carbohydrate, possibly in conjunction with reduced insulin dose. The euDKA reported in T2D patients with SGLT2 inhibitor treatment has a different origin. Full-dose SGLT2 inhibition induces a rapid increase in urinary glucose excretion, ranging 50–100 g/day equally in men and women and lasting slightly longer than 24 h (14). In a typical 60-year-old, overweight T2D patient (BMI 28 kg/m^2) consuming 50% of daily calories as carbohydrate (15), this glucose loss amounts to 17–34% of estimated carbohydrate intake in men and 22–44% in women. Of note, in a comparative study of Japanese and European T2D patients treated with an SGLT2 inhibitor, urinary glucose excretion was, if anything, larger in the former (averaging 110 g/day) than in the latter (60 g/day) groups (16); thus, in the Japanese group (BMI 25 kg/m^2), the glucose loss through the urine represented 47% of estimated daily carbohydrate intake in men and 57% in women. In general, depending on body size, glomerular filtration rate, and degree of hyperglycemia, SGLT2-induced glucose loss can make up a substantial fraction of daily carbohydrate availability.

Abstracting from a study in well-controlled drug-naïve or metformin-treated T2D patients on chronic therapy with an SGLT2 inhibitor (17), plasma glucose levels decreased by 20–25 mg/dL both in the overnight fasted state and following a mixed meal. As glucose is the chief stimulus for insulin release under all circumstances, plasma insulin levels also fell (by ~10 pmol/L fasting and ~60 pmol/L postmeal). In contrast, plasma glucagon concentrations increased significantly, partly because of a diminished paracrine inhibition by insulin (18) and possibly also because of decreased SGLT2-mediated glucose transport into α-cells (19). As a consequence, the calculated prehepatic insulin-to-glucagon molar concentration ratio dropped from 9 to 7 mol/mol in the fasting state and from 29 to 24 mol/mol during the meal. This hormonal shift, which releases inhibition of gluconeogenesis in the liver (20), augmented EGP both in the fasting state and during the meal (17). Insulin sensitivity, however, was improved, as also shown with the use of the euglycemic insulin clamp, as a result of attenuated glucotoxicity (21).

The difference in the pathophysiology of DKA versus SGLT2 inhibitor–induced euDKA is schematized in Fig. 1. In euDKA,
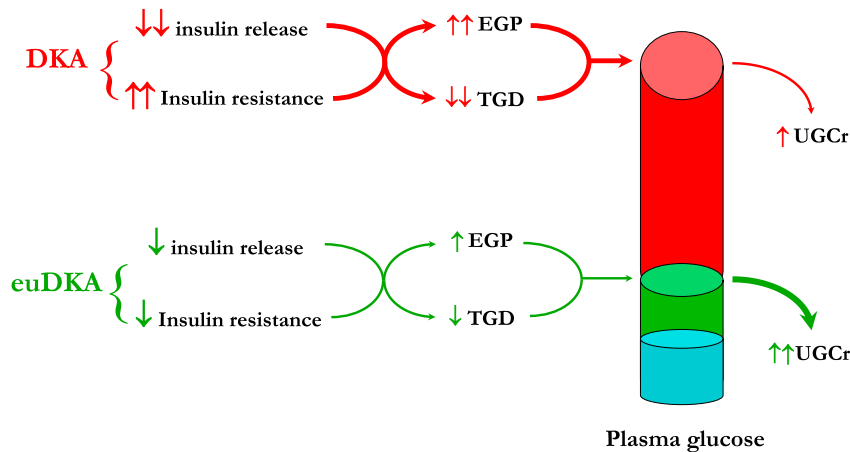
Making DKA

Figure 1—Essential pathophysiology of DKA and euDKA consequent of the use of SGLT2 inhibitors. TGD, tissue glucose disposal; UGCr, urinary glucose clearance rate.

insulin deficiency and insulin resistance are milder (and insulin resistance may actually be improved); therefore, glucose overproduction and underutilization are quantitatively lesser than in DKA. More importantly, renal glucose clearance (i.e., the ratio of glycosuria to prevailing glycemia) is twice as large with euDKA than with DKA. In fact, from previous studies of patients admitted with DKA it can be calculated that renal glucose clearance averaged $0.3 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (12), whereas in T2D patients it rose from a near-negligible value in the baseline study to $0.6 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ with SGLT2 treatment (17). Thus, it is the entity of glycosuria viz. the height of hyperglycemia that marks the difference between the two metabolic states. This difference can actually be amplified as DKA frequently occurs in patients with impaired renal function (and hence less glycosuria) (11), while SGLT2 inhibitors may be used in patients with glomerular hyperfiltration (and more abundant glycosuria) (5).

Ketoacidosis follows with the same sequence of events in euDKA as in DKA. Thus, in SGLT2-treated T2D patients (17), the lower insulin-to-glucagon ratio stimulated lipolysis (circulating FFAs were ~40% higher during the meal) and enhanced lipid oxidation (by 20% on average) at the expense of carbohydrate oxidation (which fell by 60%). In the face of lower substrate (glucose) concentrations, nonoxidative glucose disposal (i.e., glycogen synthesis and lactate release) also fell by 15%. The augmented FFA delivery to the liver resulted in mild stimulation of ketogenesis, whereby both fasting and mean postmeal β-hydroxybutyrate levels rose ~twofold higher than in the baseline study (though not exceeding 1 mmol/L); conversely, plasma lactate levels decreased ~20%, a readout of reduced carbohydrate utilization (E. Ferrannini et al., unpublished data). Had insulin deficiency been more profound—as can happen in T1D patients—or had carbohydrate availability been drastically restricted, this mild ketosis would have evolved toward ketoacidosis, with decreased blood pH and bicarbonate and increased anion gap (12). It must be noted that in the only study that looked at insulin administration (22)—dating back to 1951—it was found that insulin decreased the transport maximum for glucose in patients with diabetes, implying that starting or escalating exogenous insulin treatment would induce glycosuria in its own right. While these studies have not been repeated and the mechanism of this insulin effect has not been investigated, it is nevertheless intriguing that insulin may intensify SGLT2-induced glycosuria.

All in all, euDKA is pathophysiologically similar to DKA except for the circumstance—SGLT2-induced glycosuria—that "artificially" lowers plasma glucose levels and predisposes to increased ketogenesis.

THE CLINICAL LESSON

The evidence reviewed above suggests that the risk of bona fide euDKA (and not simple ketosis) in T2D related to the use of SGLT2 inhibitors will probably turn out to be very low, with an "acceptable" frequency. Still, physicians and patients need to be made aware that such risk may be increased in long-standing T2D patients with marked β-cell insufficiency or in latent autoimmune diabetes in adults with rapid evolution toward T1D and during prolonged starvation, after surgery, or during intercurrent illness. In T1D, however, the euDKA risk appears to be more concrete for reasons entirely within the pathophysiology: 1) in T1D patients hyperglycemia typically is higher than in T2D patients, 2) in early T1D glomerular filtration rate may be increased, 3) insulin may enhance the effect of SGLT2 inhibition on glycosuria, and 4) changes in insulin dose are not infrequent and may be inappropriate for the amount and kind of carbohydrate intake.

We submit that this potential complication related to SGLT2 inhibition is predictable, detectable, and preventable (or mitigable) so that the balance of benefits and risks favors the use of SGLT2 inhibitors in the T1D population, which is in desperate need of adjunct therapies. It is predictable because the persistent glycosuria induced by SGLT2 inhibition sets off a sequence of metabolic changes that are obligatory quantitative consequences of a large glucose subtraction from the body glucose pool. In particular, enhanced ketogenesis is seen already even in nondiabetic subjects receiving SGLT2 inhibitors and is inscribed on already modestly raised plasma β-hydroxybutyrate levels in patients with diabetes (E. Ferrannini et al., unpublished observations). This background ketonemia is asymptomatic and clinically irrelevant in most T2D patients but is certainly more of a concern in T1D patients who are already prone to develop ketosis under circumstances of reduced insulin doses, stress, and intercurrent illnesses and following a hypoglycemic episode and during prolonged fasting or starvation.

Thus, one can envision a sequence of clinical events that could evolve into a full-blown episode of DKA (Fig. 2). First,
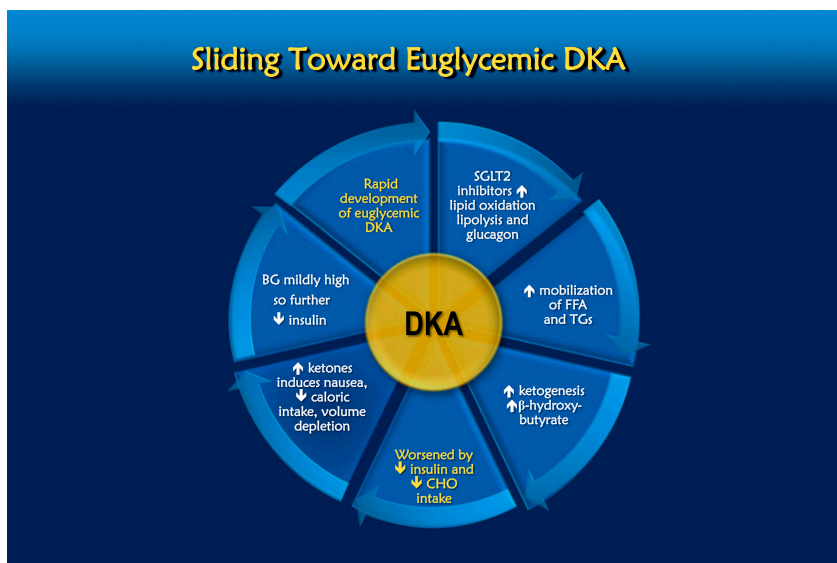
Figure 2—Demonstration of the cascade of clinical events and metabolic changes that contribute sequentially to progressive clinical deterioration and development of full-blown episodes of euDKA. BG, blood glucose; CHO, carbohydrate; TGs, triglycerides.

inappropriate reductions of insulin doses or any factor that may increase insulin demand, such as stress, a sick day, or even alcohol intake, may induce hyperketonemia. Under these circumstances, initially patients may just not feel well or experience some malaise and perhaps mild nausea with no vomiting. Their first impulse is to check their blood glucose; because of the persistent glycosuria, glycemia will be only mildly elevated so that they would tend to reduce or withhold insulin and avoid eating. These maneuvers will accelerate ketone production and metabolic decompensation toward DKA. The metabolic picture will be further compounded by the volume depletion caused by the persistent glycosuria and vomiting.

The cases reported by Peters et al. (4) exemplify some of the factors that triggered DKA: most commonly they were insulin reductions, low caloric and fluid intake, intercurrent illness, and alcohol use. Time was wasted because of delayed diagnosis due to deceptively "acceptable" blood glucose levels. Peters et al. (4) do provide a further understanding of the clinical clues that can contribute to the early detection and help raise awareness of the potential for SGLT2 inhibition to cause euDKA in T1D. We believe that euDKA is in fact easily *detectable* because reliable tools are currently available to monitor ketonuria and ketonemia and should be recommended to be used at any time an SGLT2 inhibitor–treated patient feels unwell regardless of the ambient glucose levels. This should be part of any educational element for those treated with an SGLT2 inhibitor. If *detectable*, then euDKA is *preventable* because detection of significant ketonuria and/or ketonemia any time symptoms such as nausea and/or vomiting—or even just malaise—appear, especially after alcohol intake or a recent cut in insulin dose, can prompt advice to maintain vigorous fluid intake and to consume carbohydrates to allow at least full-dose insulin therapy until the ketosis resolves. Patients should temporarily stop the SGLT2 inhibitor, contact their medical provider, and take supplemental boluses of rapid insulin along with liquids and carbohydrates. Even if patients are unable to adjust the insulin dose, euDKA can be *mitigable* by drinking and eating as tolerated without fear of hyperglycemia and seeking prompt medical attention for parenteral fluid replacement and insulin therapy.

In any event, T1D patients who choose to take this medication off-label should sign an ad hoc informed consent that makes them fully aware of the potential for euDKA, the precipitating factors, the warning symptoms and signs, and the preventative measures to adopt.

CONCLUSIONS

The ongoing long-term, randomized, placebo-controlled studies will provide the necessary information on the safety and efficacy of SGLT2 inhibitors in T1D (as well as insulin-treated T2D). Regulatory scrutiny of these compounds will balance their beneficial impact on overall glycemic control, glycemic variability, and weight management against the risk of hypoglycemia and overall safety, including risk of euDKA. A reduction in insulin dose should not be regarded as a positive outcome in itself and should be achieved by slow, gentle decrements simultaneously to avoid hypoglycemia and sliding toward euDKA. Hopefully, these clinical development programs will quickly expand so as to offer to patients and physicians a potential adjunct against the day-to-day management challenges of such a demanding disease.

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