COMMENT ON HERRING ET AL.

Metabolic Effects of an SGLT2 Inhibitor (Dapagliflozin) During a Period of Acute Insulin Withdrawal and Development of Ketoacidosis in People With Type 1 Diabetes. Diabetes Care 2020;43:2128–2136

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The recent article by Herring et al. (1) is an interesting attempt to establish the mechanisms of diabetic ketoacidosis (DKA) associated with use of SGLT inhibitors (SGLT-i) in type 1 diabetes (T1D). The unmet needs of T1D treated with either multiple daily insulin injections (MDII) or continuous subcutaneous insulin infusion (CSII) have stimulated interest in using "adjunct therapy" (2). SGLT-i are popular in T2D and appear attractive also in T1D (2). However, because of the greater risk of DKA, the use of SGLT-i in T1D is, at present, controversial.

Herring et al. (1) treated a small group of people with T1D on CSII for 7 days with SGLT2-i or placebo, then switched them from s.c. to i.v. insulin for at least 2 h, after which they acutely withdrew insulin and studied glucose and lipid metabolism over a period of 10 h fasting. As expected, acute insulin deficiency resulted in lower increase in plasma glucose (PG) with SGLT2-i despite higher endogenous glucose production versus placebo. However, there was little or no difference in lipolysis (rate of appearance of glycerol) and serum free fatty acid (FFA) concentration with SGLT2-i. In addition, β-hydroxybutyrate (BOH) production and its blood concentration were similar in the initial 3 h of insulin withdrawal with SGLT2-i versus placebo, and only later was there a statistically significant, but quantitatively small, increase of BOH. These negative results would not speak in favor of the hypothesis that SGLT2-i, by reducing the insulin dose to prevent hypoglycemia in the presence of lower PG due to urinary (and fecal) excretion, desuppresses lipolysis and leads to DKA in the setting of prehepatic lower insulin and higher glucagon concentrations.

However, the model of investigation of Herring et al. (1) studies experimentally glucose and lipid metabolism after acute withdrawal of i.v. insulin infusion. This extreme insulin deficiency is different from the insulin deficiency that might occur in the everyday life of people with T1D, for example, during pump failure (CSII), or subsequently due to a missed administration of long-acting insulin with MDII. On both of these not uncommon occasions, insulin deficiency would develop gradually and slowly over several hours, not within a few minutes (1). Acute withdrawal of i.v. insulin (1) generates immediately the maximal effects of abrupt absence of insulin effects on lipid metabolism (3), and it would be difficult to observe under these conditions additional effects of enhanced lipolysis by SGLT-i due to only a moderate decrease in insulin dose.

In this regard, the results of Herring et al. (1) before disconnecting CSII at 0600 h, i.e., while people with T1D were still on insulin, are interesting. SGLT2-i resulted in greater lipolysis and higher serum FFA and glucagon concentrations as well as greater BOH production and blood concentration and a lower insulin-to-glucagon ratio. These findings are underestimated by the study design, which predicated unchanged insulin dose with SGLT-i versus placebo (although some patients reduced the insulin dose and others reported more hypoglycemia events) (1). Had Herring et al. (1) reduced the insulin dose with SGLT2-i versus placebo according to PG during the 7-day treatment, as in clinical trials and practice, and had they maintained the basal rate of CSII, reducing it 10–20% for the 10 h fasting rather than acutely withdrawing insulin, likely the effects of SGLT2-i on lipolysis and ketogenesis would have been more relevant.

The results of Herring et al. (1) at baseline help in understanding the cascade of events that may ultimately result in "the perfect storm" of SGLT-i–induced DKA. Although additional mechanisms cannot be excluded, reduction of insulin dose (prandial and basal) is necessary to avoid hypoglycemia due to the 24-h PG-lowering effect by SGLT-i. It is likely that the reduction of basal more than prandial insulin is critical for desuppression of lipolysis, as indirectly suggested by studies where prandial insulin is left out during 24-h fasting but basal is injected (4). Since the reduction of insulin dose with SGLT-i is not associated with an increase in insulin

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sensitivity, as it otherwise occurs with physical exercise, lipolysis is then desuppressed, as anticipated by the steep dose-response curve of insulin-regulated lipolysis (5). Increased availability of substrates (FFA), in the setting of a lower insulin-to-glucagon portal ratio, shifts the liver toward enhanced ketogenesis. Circumstances of acute decreases in insulin sensitivity may then abruptly precipitate DKA, which is especially insidious for the absence of typical hyperglycemia.

It is difficult to imagine how the insulin dose would not have to be reduced in T1D and how people might avoid "the perfect storm" of nonhyperglycemic DKA when adding SGLT-i to MDII/CSII.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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