RESPONSE TO COMMENT ON ROSENSTOCK AND FERRANNINI

Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. Diabetes Care 2015;38:1638–1642

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We were surprised that Dr. Cushard felt uneasy (1) with our commentary (2) stating that euglycemic diabetic ketoacidosis (euDKA) induced by sodium–glucose cotransporter 2 inhibitors (SGLT2i) was not just "predictable" but also "detectable" and "preventable." However, in regard to the case he reports, it is clear that more efforts should have been spent to persuade the patient to start the much needed insulin to address the severe hyperglycemia and ketonuria instead of doing unnecessary testing such as serum insulin, C-peptide, and, for whatever clinical purpose, HOMA-B and insulin resistance calculation. Thus, as outlined in our commentary, this event could have been easily prevented. Clearly this patient with poorly controlled diabetes despite treatment with sitagliptin, metformin, and glipizide needed insulin instead of switching to dapagliflozin and stopping the sulfonylurea, as presumably the SGLT2i only counteracted the expected deterioration of glucose control with the discontinuation of glipizide.

Before SGLT2i treatment was initiated, Dr. Cushard's patient had severe hyperglycemia and ketonuria (a fasting glucose of 236 mg/dL easily rises to the range of 400–500 mg/dL after a meal), and interestingly, no HbA_{1c} information was provided and the reader was not told the patient's age, BMI, presence of complications, previous insulin use, lifestyle, compliance, previous history of DKA hospital admissions, etc. Short of this information, we (and we would expect the readers) can only assume that the patient was prescribed a SGLT2i and sent home. Therefore, we do not know what explanation or education was provided to the patient or whether there was a plan to monitor with ketone strips (Ketostix). Whether vomiting developed as a cause or consequence of the ketosis and whether any of the precipitating factors emerged during the period leading up to DKA is omitted from the cursory narrative of the case, thereby making it a tool for polemic rather than a professional scientific inquiry. Had our article (2) been carefully read, Cushard would have appreciated that this episode of DKA could have been prevented if he had advised the patient to communicate with him to intervene when she started to feel unwell and "symptomatic later that morning" (1). Presumably, she must have had significant vomiting, which he eludes to report, allowing for rapidly developing DKA by later that evening. Thus, if one had carefully read our article, one would have learned the following.

First, euDKA was initially described by Munro et al. (3) long before SGLT2i were developed, with a fairly complete review of its circumstances and precipitating factors. Second, our article collated information from reported cases (4,5) and, having pressed manufacturers, referred to the accumulated experience in their clinical development programs, leading to the conclusion that the chances of euDKA were very low in type 2 diabetes (T2D), as recently demonstrated in the large BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial (6) and in the meta-analysis of all SGLT2i randomized controlled trials by Tang et al. (7) (nonsignificant event rates of DKA 0.1% in the group of SGLT2i users vs. 0.06% in the control groups). Third, the article recalled the pathophysiology of DKA, both the typical and the euglycemic variety, making the point that the latter is not an off-target effect of SGLT2i but a potential sequela of the target effect, glycosuria. Fourth, the sequence of events that can precipitate euDKA was recapitulated in a sketch (Fig. 2 in ref. 2) in order to engage the interest of even the hasty reader. Finally, after reiterating that SGLT2i are not currently indicated for type 1 diabetes (T1D)—the condition most prone to DKA—our commentary's title reflected the fact that euDKA is "predictable," especially in a patient like Cushard's, and therefore "detectable" and "preventable." Thus, we refer Cushard to the end of the text where he would have read

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> ...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. (2)

The words "safety concern" appear in the title.

In general, clinical researchers may analyze available evidence using knowledge and reason and regulators may issue early warnings in the interest of the public, but in the end, good clinical judgment should always prevail!

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