RESPONSE TO 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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Using the power of stable isotope techniques, our study explored the physiological effects of the SGLT2 inhibitor dapagliflozin on glucose flux, lipolysis, and ketone body concentration in people with acute absolute insulin withdrawal (1). The power of our study from the clinical perspective was the crossover design with each individual undergoing an identical insulin withdrawal protocol with the only difference being the presence or absence of an SGLT2 inhibitor.

Bolli et al. (2) argue that we would have seen a greater effect on nonesterified fatty acids (NEFAs) and ketones at baseline (prior to withdrawal of insulin) if the insulin dose had been adjusted in the SGLT2 arm during the 7 days preceding the study. As this was a double-blind study, this wasn't feasible. It is possible that adjusting the insulin dose would have resulted in a greater effect on NEFAs and ketones at baseline, but this is hypothetical.

We agree that the extreme insulin deficiency in our study design is unlikely to occur in clinical practice, but it was designed to illustrate effect of SGLT2 inhibitors on ketone body physiology and worked well. Bolli et al. (2) argue that because this model generates maximal effects, it is difficult to observe enhanced lipolysis by SGLT2 that might occur with only a moderate decrease in insulin. This is speculative, and we would welcome experimental evidence to substantiate it.

A 10–20% reduction in insulin, as suggested, may or may not have shown anything significant. Bolli et al. refer to a study by Miles et al. in 1980 (3), where patients with type 1 diabetes were withdrawn from insulin after a 2-h insulin infusion, exactly as in our current study. We demonstrated a gradual rise in ketones as shown in the study by Miles et al., although the rise in ketones was considerably smaller. In the study by Miles et al., all patients ($n = 7$) were within 95–110% of their ideal body weight but no BMI is given. In our study, BMI ranged from 19.8 to 34.5 and the ketone response was greater the lower their BMI (see Supplementary Fig. 1). The lower ketone response in our study may have been simply a consequence of our subjects having much higher BMI than those studied by Miles et al.

We believe our protocol has produced some informative physiological data and thank Bolli et al. for their comments and agree that a range of future different protocols may shed further light on this interesting field.

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