RESPONSE TO COMMENT ON KRAMER ET AL.

Glucagon Response to Oral Glucose Challenge in Type 1 Diabetes: Lack of Impact of Euglycemia. Diabetes Care 2014;37:1076–1082

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We thank Takahashi et al. for their comments (1) on our study (2) and for the opportunity to clarify our study design. In our study, we evaluated the impact of euglycemia versus hyperglycemia on the glucagon response to an oral glucose tolerance test (OGTT) in 10 participants with type 1 diabetes and showed that these patients have a paradoxical increase in glucagon in response to oral glucose that is not reversed when euglycemia is achieved prior to the test. As discussed in our article, although the mechanism through which hyperglucagonemia occurs in diabetes is complex, insulin has been suggested to regulate glucagon secretion (3). For this reason, the insulin infusion during the test under both euglycemic and hyperglycemic conditions was maintained constant. In other words, once the target plasma glucose (PG) range of each test day was reached (i.e., PG level between 4–6 mmol/L on the euglycemic day or PG level between 9–11 mmol/L on the hyperglycemic day), the insulin infusion was set to the participant's usual basal insulin rate, such that there were no differences in insulin doses during the test between the glycemic settings. In addition, the mean basal insulin rate of the participants is shown in Table 1 (basal insulin dosage 0.7 $\pm$ 0.3 UI/h).

Takahashi et al. also note that the occurrence of hypoglycemia is another potential confounder that might impact glucagon secretion. In this context, we should clarify that we included only participants who did not have any hypoglycemic episodes during the night before the test and during the test itself. Finally, although previous reports in animal models have suggested an extrapancreatic source of glucagon secretion (4), studies in humans have yielded contradictory results (5,6). For example, Dammann et al. (5) evaluated eight totally pancreatectomized patients and found no evidence of glucagon secretion, suggesting that the impact of functioning α-cell tissue in extrapancreatic sites is less relevant to total glucagon secretion in humans than that of pancreatic glucagon. Thus, considering all of these data together, we believe that our study was properly designed to mitigate the known potential confounders that impact glucagon secretion and that our results provide important additional information on the physiology of glucagon secretion in patients with type 1 diabetes. Nonetheless further studies are warranted for the complete understanding of the physiology of glucagon regulation.

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

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