RESPONSE TO COMMENT ON SARKAR ET AL.

# Exenatide Treatment for 6 Months Improves Insulin Sensitivity in Adults With Type 1 Diabetes. Diabetes Care 2014;37:666–670

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Chaudhuri et al. (1) raised the question of why exenatide increased insulin sensitivity in our patients with long-standing type 1 diabetes without simultaneously improving $HbA_{1c}$ (2). The authors expressed concern about the possibility that GLP-1 analogs might be dismissed as ineffective, which would counter their own positive experience with liraglutide in type 1 diabetes.

They speculated that we had attempted to safely introduce exenatide without increasing the frequency of hypoglycemia and thus had cautiously decreased insulin doses. This is correct; we initially lowered prandial insulin doses by 50% and thereafter increased insulin doses as needed (3). Thus, we were not surprised to observe an unchanged $HbA_{1c}$. In our trial, the active intervention periods had been preceded by an "optimization period" in which better glycemia was achieved by adjusting insulin doses, reviewing carbohydrate counting, and having frequent patient contact. We found that "fine-tuning" of glycemia could often be achieved by lowering basal or long-acting insulin doses and simultaneously increasing prandial doses (4). Thus, total daily insulin doses remained unchanged and $HbA_{1c}$ improved (0.7% in 4–6 months) without more frequent hypoglycemia or weight gain.

However, Chaudhuri et al. incorrectly stated the primary aim of our original study. Rather than assessing exenatide's effect on insulin sensitivity, we had set out to investigate whether prolonged near-normal glycemia, coupled with immunosuppression and GLP-1 receptor agonist therapy, might promote improvement of β-cell functional mass (3). Within this study, we had performed hyperinsulinemic-euglycemic insulin clamps and observed the recently reported reduction in insulin resistance (2). Similar to the experience of Chaudhuri et al., we found weight loss (4.2 kg in 6 months, $P = 0.003$) and a trend toward lower blood pressure (systolic $-4.5 \pm 11.4$, diastolic $-1.6 \pm 7.2$ mmHg; differences not statistically significant). Yet, we found no evidence of clinically relevant improvement of β-cell function/mass with exenatide treatment in these patients with long-standing type 1 diabetes (mean duration 21 years).

An important lesson learnt from this study was that we observed detectable, though very low, C-peptide concentrations in most individuals screened for study participation (i.e., even before receiving exenatide). When exposed to physiological or pharmacological stimuli, the remaining β-cells responded with increased insulin secretion; however, tightened blood glucose control, as introduced in the optimization period, suppressed the residual β-cell function often to undetectable levels. This observation may serve as an important teaching point for the design of future studies (5).

Our study was among the earliest to use GLP-1 receptor agonists in type 1 diabetes. In the meantime, several clinical trials have been initiated to explore different aspects of incretin therapy in type 1 diabetes (presently there are 16 active, recruiting, registered trials with exenatide and liraglutide in type 1 diabetes [ClinicalTrials.gov, June 2014]). While we agree that it is important to figure out which cellular pathways are responsible for successful incretin therapy, we do not feel that most clinical trials are effective tools to do so. Thus, we will abstain from further speculation about exenatide's mechanisms.

In summary, we fully support the notion that incretin therapy may play an important role as adjunct therapy in the treatment of type 1 diabetes.

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