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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We read with interest the article by Sarkar et al. (1) that reported that when exenatide in high doses is administered to patients with type 1 diabetes it has an insulin-sensitizing action. In spite of this effect, there was no improvement in HbA_{1c} levels; however, there was a reduction in insulin dose. As the aim of the study was to investigate the effect of exenatide on insulin sensitivity and the baseline HbA_{1c} in this group of patients was 7%, it is possible that the investigators were cautious in preventing any possible hypoglycemia and so the dose of insulin was reduced rather than titrated to obtain the best possible glycemic control.

As these observations may lead to the impression that exenatide and possibly other GLP-1 receptor agonists may not improve glycemia in patients with type 1 diabetes, we would like to state that in two previously published studies using liraglutide in patients with type 1 diabetes, our group has shown that this GLP-1 receptor agonist reduces HbA_{1c} by approximately 0.5% over a period of 6 months (2,3). In the first study, patients with a baseline HbA_{1c} of 6.6% had their HbA_{1c} reduced to 6.15%, without an increase in hypoglycemia and with a marked reduction in glycemic excursions as recorded by continuous glucose monitoring (2). In addition, the patients had a significant weight loss of 4 kg. In the second study, which included only obese patients with type 1 diabetes, we observed a reduction in HbA_{1c} by 0.5%, a marked weight loss, and a fall in systolic blood pressure (3). Again, there was no increase in hypoglycemia. The fall in blood pressure is of interest as it has implications for cardiovascular outcomes and it has been observed consistently in trials with GLP-1 receptor agonists since we first described it in patients with type 2 diabetes taking insulin and treated with exenatide in 2007 (4). We, therefore, wonder if there was a fall in blood pressure in the series of patients included in the current study.

As far as the mechanism underlying insulin sensitization is concerned, Sarkar et al. suggest an activation of the phosphatidylinositol 3-kinase pathway. Our previous observations demonstrate that exenatide exerts a potent anti-inflammatory effect, an important component of which is the suppression of interleukin-1β and Jun NH_2-terminal kinase-1 expression. Both modulate the expression of SOCS3, which interferes with insulin receptor substrate-1 phosphorylation and thus with insulin signal transduction (5). Another possible mechanism that needs to be tested is the suppression of PTP1B, which limits and reverses the autophosphorylation of the insulin receptor and thus limits insulin signaling.

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

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