Exenatide Treatment for 6 Months Improves Insulin Sensitivity in Adults with Type 1 Diabetes Mellitus

Running title: Exenatide therapy in type 1 diabetes

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Abstract

Objective: Exenatide treatment improves glycemia in adults with type 2 diabetes and has been shown to reduce postprandial hyperglycemia in adolescents with type 1 diabetes. We studied the effects of exenatide on glucose homeostasis in adults with long-standing type 1 diabetes.

Research Designs and Methods: 14 patients with type 1 diabetes participated in a cross-over study of 6 months duration on exenatide (10 mcg four times daily) and 6 months off exenatide. We assessed changes in fasting and postprandial blood glucose and changes in insulin sensitivity before and after each study period.

Results: High dose exenatide therapy reduced postprandial blood glucose but was associated with higher fasting glucose concentrations without net changes in hemoglobin A1C. Exenatide increased insulin sensitivity beyond the effects expected due to weight reduction.

Conclusions: Exenatide is a promising adjunctive agent to insulin therapy due to its beneficial effects on postprandial blood glucose and insulin sensitivity in patients with type 1 diabetes.
Introduction

Glucagon-like-peptide-1 (GLP-1) agonists including exenatide are promising agents for the treatment of type 2 diabetes. Exenatide, the first GLP-1 agonist to be FDA approved, and other members of this class of drugs have been shown to improve fasting and postprandial blood glucose, hemoglobin A1C, and to promote weight loss, resulting in increased insulin sensitivity (1-3). Few reports have focused on GLP-1 agonist treatment in patients with type 1 diabetes. Herein, we report the effects of 6 months therapy with exenatide in patients with long-standing type 1 diabetes focusing on outcomes related to glucose homeostasis including fasting and postprandial blood glucose and insulin sensitivity, as determined by the reference glucose clamp method (4).

Study design and methods

The current study is an ancillary study to a clinical trial conducted to ascertain whether exenatide could improve beta-cell function in patients with long standing type 1 diabetes (2). This study (Clinical Trial identifier NCT00064714) was performed at the National Institutes of Health (NIH), Bethesda, Maryland after obtaining IRB approval. Written informed consent was obtained from all patients. Twenty subjects (9 males) with long-standing type 1 diabetes (mean duration 21.3 ± 10.7 years) were enrolled and their insulin treatment was optimized as previously reported (2; 5) (Figure 1). After a 3-month run-in period, during which no further insulin dose changes were made, patients were randomized to continue insulin or insulin plus exenatide (with or without daclizumab) for 6 months, after which, treatment assignment for exenatide was reversed. Exenatide was administered subcutaneously at a starting dose of 2.5 mcg twice daily, and gradually increased to 10 mcg four times daily. Prandial insulin doses were reduced by 50% at the initiation of exenatide therapy and were gradually increased with blood glucose goals of 80-140 mg/dL (home blood glucose monitoring was performed ~ 7 times daily and recorded in an electronic work sheet).

Thirteen of our 14 subjects who completed the trial participated in two 3 hour hyperinsulinemic euglycemic clamp studies, which were conducted at the end of the 6-month treatment periods on and off exenatide (Figure 1). These 13 subjects constitute the subgroup included in the present analyses. Patients fasted overnight, and a basal insulin drip (Humulin, Eli Lilly, Indianapolis, IN) was adjusted to maintain euglycemia overnight. Glucose concentrations were maintained at 100±10 mg/dL and no insulin dose changes were made for 4 h prior to the clamp study. A cannula was placed into the dorsum of the hand which was warmed with a heating blanket to 41°C to arterialize the blood. Insulin was infused at a constant rate of 120 µU/m²/min with a razel calibrated syringe pump. After starting the insulin infusion, glucose analyses were performed every 5 minutes at the bedside using a YSI blood glucose analyzer (YSI 2300-Stat; YSI, Yellow Springs, OH). Dextrose infusion (20%) was adjusted to maintain blood glucose at approximately 90 mg/dL. The amount of glucose infused during the last 60–120 min of the clamp at steady-state reflected the glucose disposal rate, which was normalized for body surface
area and steady-state clamp plasma insulin concentration to calculate an insulin sensitivity index (SI) expressed in mg/m²/min per µU/ml.

Statistical analysis were conducted using SAS Enterprise Guide version 5.1. Because 50% of patients had also received daclizumab, two-way analyses of variance (ANOVAs) were run to assess daclizumab treatment and its possible interaction with exenatide. Since the interaction was nonsignificant ($P = 0.87$), the daclizumab and no-daclizumab groups were combined in the analyses of exenatide. Mixed models (PROC MIXED) were used to determine changes in weight, fasting and postprandial glucose, A1C, and insulin requirements on versus off exenatide, assessing the effect of treatment order (exenatide first versus second) as a covariate. There was no significant effect of treatment order for any outcome; thus, paired t-tests were used to assess differences between on versus off exenatide periods. Mixed models were used to assess change in SI on versus off exenatide, adjusting for change in body weight. Data are reported as mean ± SD. A $P$ value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the 13 subjects at enrollment are in Table 1. The mean age was 37.3±10.7 years and mean diabetes duration was 20.5±11.8 years. Mean body mass index (BMI) was 26.1±3.5 kg/m² and mean A1C was 7.0±0.8 %. At the conclusion of the run-in period, weight was 77.7±11.0 kg, A1C was 6.4±0.7 %, and insulin requirements were 0.55±0.12 units/kg/day (0.31±0.08 units/kg/day meal associated and 0.24±0.09 units/kg/day basal). Exenatide use was associated with an average weight loss of 4.2 kg over 6 months (from 76.9±11.3 kg off exenatide to 72.7±11.8 kg on exenatide, $P=0.0003$) (Figure 2 A). Furthermore, A1C remained unchanged (6.7±0.6 % off versus 6.6±0.5 % on exenatide, $P=0.39$). Patients required significantly less insulin (from 0.54±0.13 unit/kg/day off exenatide to 0.47±0.1 unit/kg/day on exenatide, $P=0.007$); this was due to a reduction in meal-associated insulin (from 0.26±0.09 units/kg/day off exenatide to 0.18±0.05 units/kg/day on exenatide, $P=0.006$) with no change in basal insulin requirements (from 0.29±0.12 units/kg/day on exenatide to 0.29±0.10 units/kg/day on exenatide, $P=0.57$) (Figure 2 B).

As expected, exenatide therapy resulted in lower postprandial glucose concentrations (142.5±4.4 mg/dL off exenatide vs. 135.5±4.4 mg/dL on exenatide, $P=0.0005$), but was associated with higher fasting plasma glucose (129.7±3.2 mg/dl off exenatide vs.136.9±3.2 on exenatide mg/dL, $P=0.0002$) (Figure 2C). SI increased from 5.21±1.64 mg/m²/min per µU/ml off exenatide to 7.15±2.05 on exenatide ($P=0.0039$) (Figure 2D). This 40% increase in insulin sensitivity remained significant after adjustment for body weight ($P=0.0076$) and was independent of the sequence of treatment periods.

Conclusions
On exenatide therapy, we observed significantly lower postprandial glycemia despite reduction in preprandial insulin doses. Postprandial glucose has emerged as a strong predictor of cardiovascular risk compared to fasting glucose (6). This effect was mostly due to slowing of gastric emptying (2). Unlike in subjects with type 2 diabetes and healthy volunteers (7; 8), we did not observe lower fasting glucose concentrations in our patients. This might be explained by the inability of exenatide to effectively inhibit glucagon secretion with resultant unopposed hepatic glucose production (9; 10). We and others have shown a lack of glucagon suppression with exenatide (1; 2), in contrast to the findings of Dupre et al. (3). Possible explanations for the discrepancy between these studies are variable disease duration and duration of exenatide treatment.

Insulin resistance in type 1 diabetes has recently received more attention (11). Of note, 70% of our patients had an initial SI at or below the cut-off for insulin resistance (5 mg/m²/min per µU/ml) and 85% had a marked improvement beyond what was expected due to weight reduction alone. This action of exenatide leading to improvement of whole body insulin-mediated glucose utilization has previously been shown in animal models (11-14) but the exact mechanisms in humans remain unclear. Possible pathways include activation of PI-3-kinase leading to increased insulin-stimulated glucose uptake in muscle and fat concordant with results in L6 myoblasts and 3T3 adipocytes (13).

Our study is limited by its small sample size, higher doses of exenatide than typically administered in clinical practice and our patients’ excellent glycemia at baseline. We also did not differentiate between hepatic and peripheral insulin sensitivity by using stable isotopes in our clamp studies. Nevertheless, the observed effects of exenatide have potential clinical applicability. This pilot study suggests the need for further investigation to determine whether the improved insulin resistance we observed can be achieved using conventional doses of GLP-1 agonists. In summary, exenatide holds promise as an adjunctive agent to insulin therapy in patients with type 1 diabetes, mainly for its beneficial effects on postprandial blood glucose and insulin sensitivity.

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

G.S., M.A., and R.J.B. contributed to writing the manuscript and they conducted data analysis. M.J.Q. supervised the euglycemic clamp studies, analyzed data and edited the manuscript. D.M.H. and K.I.R. designed the experiments, conducted the clinical studies, analyzed the data and edited the manuscript.

Part of this work was presented as an oral presentation at the 2012 American Diabetes Association Annual Meeting, Philadelphia, 8-12 June 2012.

References:


### Table 1: Demographics of study participants at enrollment

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1These data and additional details on these subjects have been previously published in Diabetes Care 2009; 32:2251-7 (2). Subject numbers correspond to those presented in the prior publication (patient 4 underwent only one clamp study and thus, insulin sensitivity on and off exenatide could not be evaluated).
Figure Legends:

Figure 1

Study design and timeline for testing. Twenty patients with long-standing type 1 diabetes were enrolled, 14 completed both treatment periods and 13 completed 2 euglycemic hyperinsulinemic clamp studies at the end of period A and B. Analyses focused on exenatide treatment. The interaction between exenatide and daclizumab was nonsignificant ($P = 0.87$), thus, the daclizumab and no-daclizumab groups were combined in the analyses of exenatide.

Figure 2

Changes in weight (A), insulin dosing (B), fasting and postprandial blood glucose (C), and changes in insulin sensitivity (SI, mg/m$^2$/min per μU/ml) (D) for each single subject off exenatide (white bars) and on exenatide (black bars) Data are presented as mean ± SD.