



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

Gayatri Sarkar,¹ May Alattar,¹
Rebecca J. Brown,¹ Michael J. Quon,²
David M. Harlan,³ and Kristina I. Rother¹

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 DESIGN AND METHODS

Fourteen patients with type 1 diabetes participated in a crossover study of 6 months' duration on exenatide (10 μ g four times a day) 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 A_{1c}. Exenatide increased insulin sensitivity beyond the effects expected as a result of weight reduction.

CONCLUSIONS

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

Diabetes Care 2014;37:666–670 | DOI: 10.2337/dc13-1473

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 Food and Drug Administration approved, and other members of this class of drugs have been shown to improve fasting and postprandial blood glucose and hemoglobin A_{1c} (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 of 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).

¹Diabetes, Endocrinology, and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

²Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine, Baltimore, MD

³Diabetes Division, Internal Medicine Department, University of Massachusetts School of Medicine and UMass Memorial Health Care, Worcester, MA

Corresponding author: Kristina I. Rother, kristina.rother@nih.gov.

Received 20 June 2013 and accepted 30 October 2013.

A slide set summarizing this article is available online.

© 2014 by the American Diabetes Association. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

RESEARCH DESIGN AND METHODS

The current ancillary study to a clinical trial was conducted to ascertain whether exenatide could improve β -cell function in patients with long-standing type 1 diabetes (2). This study (clinical trial reg. no. NCT00064714, clinicaltrials.gov) was performed at the National Institutes of Health in Bethesda, Maryland, after obtaining institutional review board approval. Written informed consent was obtained from all

subjects. Twenty subjects (nine male) 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) (Fig. 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 μ g twice a day and gradually increased to 10 μ g four times a day. Prandial insulin doses were reduced by 50% at the initiation of exenatide therapy and then gradually increased, with blood glucose goals of 80–140 mg/dL (home blood glucose monitoring was performed approximately seven times a day and recorded on an electronic worksheet).

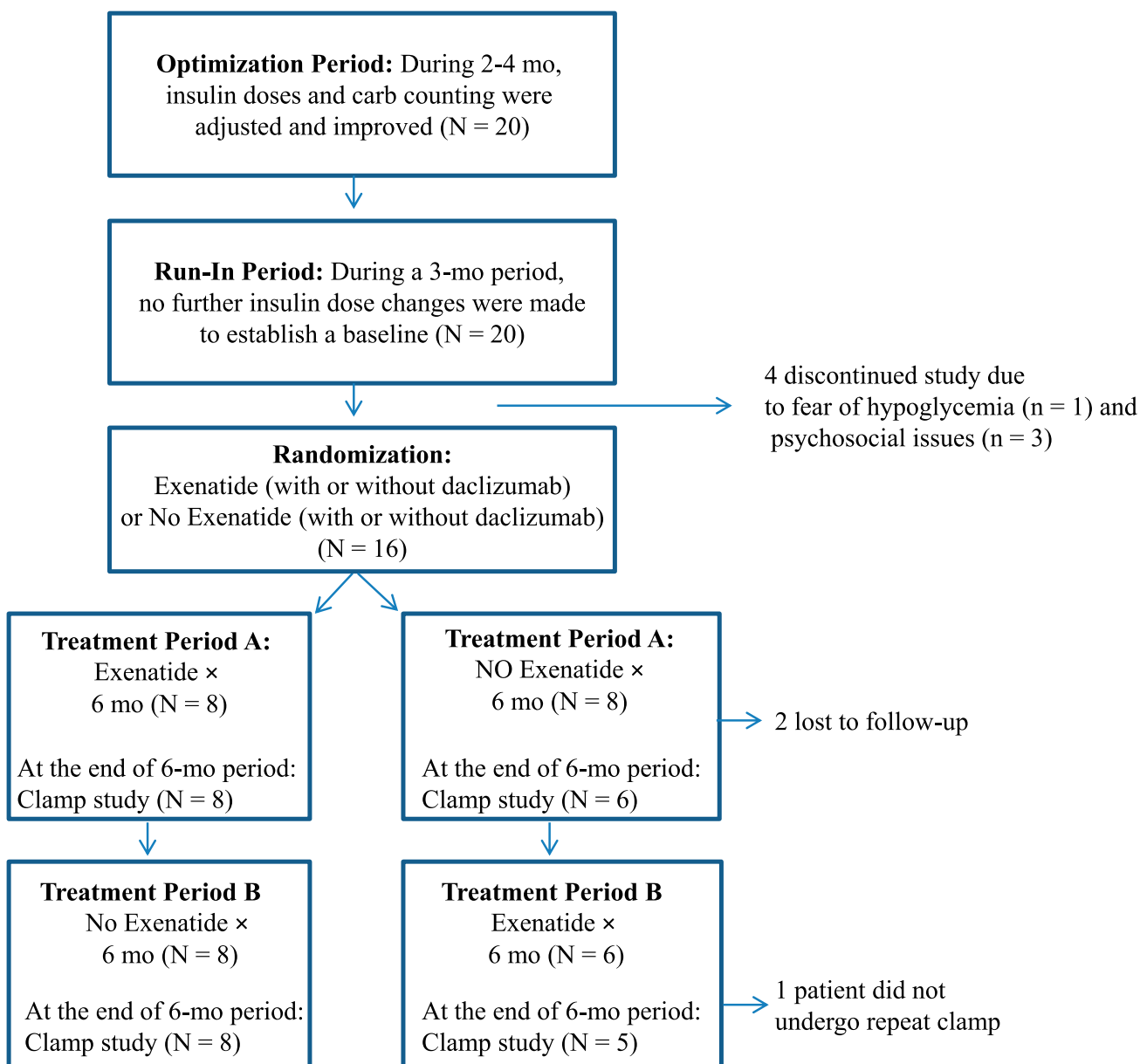


Figure 1—Study design and timeline for testing. Twenty patients with long-standing type 1 diabetes were enrolled, 14 completed both treatment periods, and 13 completed two hyperinsulinemic-euglycemic clamp studies at the end of periods A and B. Analyses focused on exenatide treatment. The interaction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

Thirteen of the 14 subjects who completed the trial participated in two 3-h hyperinsulinemic-euglycemic clamp studies, which were conducted at the end of the 6-month treatment periods on and off exenatide (Fig. 1). These 13 subjects comprised the subgroup included in the present analyses. Subjects 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 before 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 $120 \mu\text{U}/\text{m}^2/\text{min}$ with a Razel calibrated syringe pump. After starting the insulin infusion, glucose analyses were performed every 5 min at the bedside with a blood glucose analyzer (YSI 2300 Stat; YSI, Yellow Springs, OH). Dextrose infusion (20%) was adjusted to maintain blood glucose at ~ 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 $\text{mg}/\text{m}^2/\text{min}$ per $\mu\text{U}/\text{mL}$.

Statistical analyses were conducted with SAS Enterprise Guide version 5.1. Because 50% of subjects also received daclizumab, two-way ANOVAs were run to assess daclizumab treatment and its possible interaction with exenatide. Because 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 vs. 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 and off exenatide periods. Mixed models were used to assess change in SI

on and off exenatide, adjusting for change in body weight. Data are reported as mean \pm SD. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the 13 subjects at enrollment are shown in Table 1. The mean age was 37.3 ± 10.7 years, and mean diabetes duration was 20.5 ± 11.8 years. Mean BMI was 26.1 ± 3.5 kg/m^2 , and mean A1C was $7.0 \pm 0.8\%$. At the conclusion of the run-in period, weight was 77.7 ± 11.0 kg, A1C was $6.4 \pm 0.7\%$, 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, $P = 0.0003$) (Fig. 2A). Furthermore, A1C remained unchanged ($6.7 \pm 0.6\%$ off vs. $6.6 \pm 0.5\%$ on exenatide, $P = 0.39$). Patients required significantly less insulin (from 0.54 ± 0.13 units/kg/day off exenatide to 0.47 ± 0.1 units/kg/day on exenatide, $P = 0.007$); this was a result of 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 off exenatide

to 0.29 ± 0.10 units/kg/day on exenatide, $P = 0.57$) (Fig. 2B).

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 mg/dL on exenatide, $P = 0.0002$) (Fig. 2C). SI increased from 5.21 ± 1.64 $\text{mg}/\text{m}^2/\text{min}$ per $\mu\text{U}/\text{mL}$ off exenatide to 7.15 ± 2.05 $\text{mg}/\text{m}^2/\text{min}$ per $\mu\text{U}/\text{mL}$ on exenatide ($P = 0.0039$) (Fig. 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

With exenatide therapy, we observed significantly lower postprandial glycemia despite a reduction in preprandial insulin doses. Postprandial glucose has emerged as a strong predictor of cardiovascular risk compared with fasting glucose (6). This effect mostly resulted from a 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 the present patients, which might be explained by the inability of exenatide

Table 1—Demographics of study subjects at enrollment

Subject number	Sex	Age (years)	Disease duration (years)	BMI (kg/m^2)	A1C (%)
1	F	47	10.2	24.3	7.6
2	F	43	22.0	27.1	6.2
3	F	29	6.3	21.0	8.4
5	F	26	16.8	30.9	6.5
6	M	54	38.4	23.8	7.1
7	F	31	22.5	21.7	7.4
8	M	35	25.6	22.6	7.5
9	F	31	16.8	31.2	7.1
10	M	48	5.9	24.7	5.9
11	M	31	24.0	24.6	7.9
12	M	44	36.1	29.8	5.6
13	M	48	37.1	27.1	7.0
14	F	18	4.9	30.0	7.0
Mean	6M/7F	37.3	20.5	26.1	7.0

These data and additional details on the subjects have been previously published (2). Subject numbers correspond to those presented in the prior publication (subject 4 underwent only one clamp study; thus, insulin sensitivity on and off exenatide could not be evaluated).

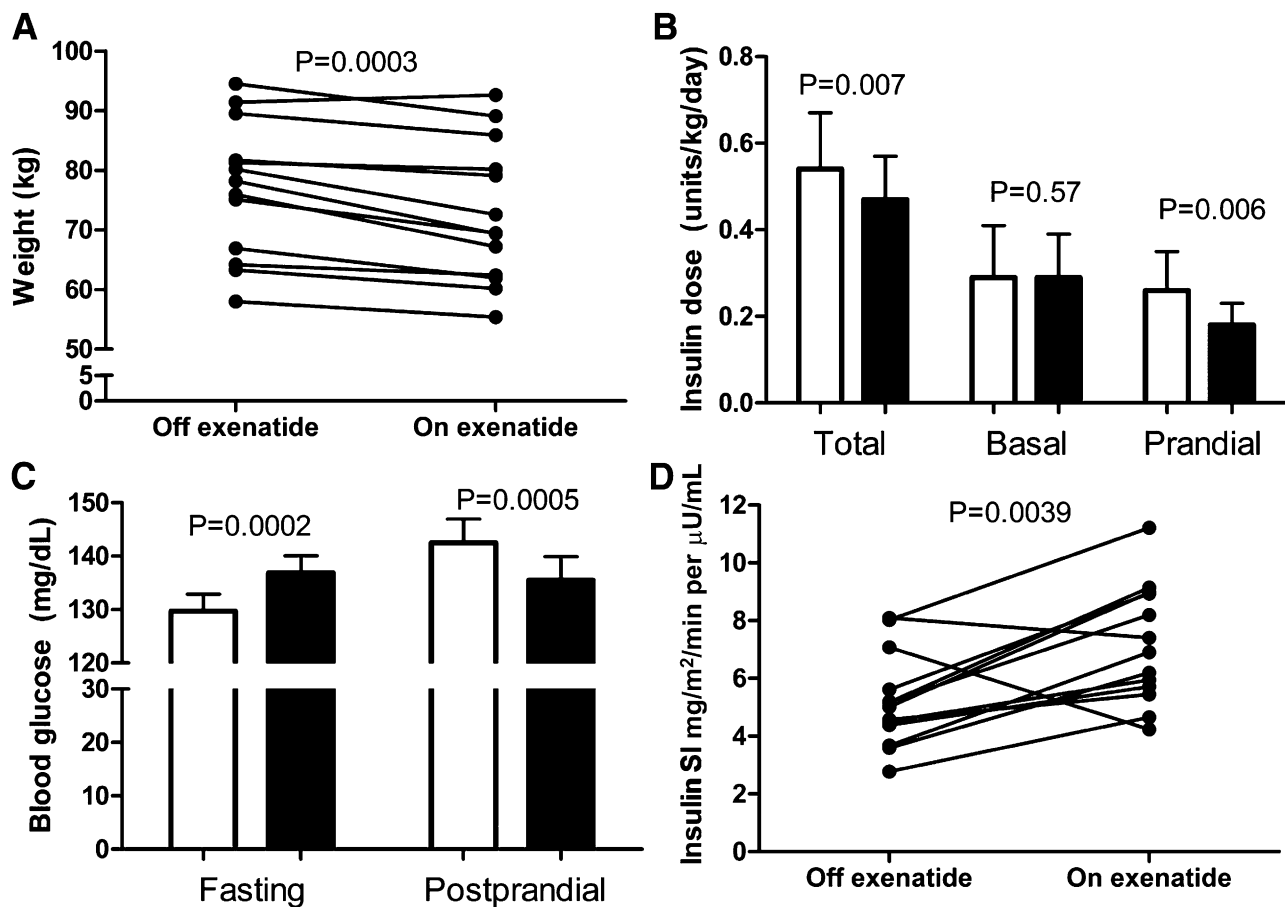


Figure 2—Changes in weight (A), insulin dosing (B), fasting and postprandial blood glucose (C), and insulin sensitivity (SI) (D) for each subject off exenatide (open bars) and on exenatide (solid bars). Data are mean \pm SD.

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), which contrasts the findings of Dupré et al. (3). Possible explanations for the discrepancy among 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 the subjects had an initial SI at or below the cutoff for insulin resistance (5 mg/m²/min per μU/mL), and 85% had a marked improvement beyond what was expected as a result of 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

phosphatidylinositol 3-kinase, leading to increased insulin-stimulated glucose uptake in muscle and fat concordant with results in L6 myoblasts and 3T3 adipocytes (13).

The present study is limited by its small sample size, higher doses of exenatide than typically administered in clinical practice, and subjects' excellent glycemia at baseline. We also did not differentiate between hepatic and peripheral insulin sensitivity by using stable isotopes in the 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 with 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.

Funding. This research was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institutes of Health Clinical Center.

Duality of Interest. A Co-operative Research and Development Agreement was established between the National Institute of Diabetes and Digestive and Kidney Diseases and Amylin Pharmaceuticals, which provided funding for a research nurse, T-cell assays, and hormone assays performed by Esoterix. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.S., M.A., and R.J.B. contributed to the data analysis and writing of the manuscript. 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. K.I.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the

integrity of the data and the accuracy of the results.

Prior Presentation. Portions of this study were presented orally at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, PA, 8–12 June 2012.

References

- Raman VS, Mason KJ, Rodriguez LM, et al. The role of adjunctive exenatide therapy in pediatric type 1 diabetes. *Diabetes Care* 2010;33:1294–1296
- Rother KI, Spain LM, Wesley RA, et al. Effects of exenatide alone and in combination with daclizumab on beta-cell function in long-standing type 1 diabetes. *Diabetes Care* 2009;32:2251–2257
- Dupré J, Behme MT, McDonald TJ. Exendin-4 normalized postcibal glycemic excursions in type 1 diabetes. *J Clin Endocrinol Metab* 2004;89:3469–3473
- Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab* 2008;294:E15–E26
- Brown RJ, Wijewickrama RC, Harlan DM, Rother KI. Uncoupling intensive insulin therapy from weight gain and hypoglycemia in type 1 diabetes. *Diabetes Technol Ther* 2011;13:457–460
- Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes* 2005;54:1–7
- Edwards CM, Stanley SA, Davis R, et al. Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* 2001;281:E155–E161
- Kolterman OG, Buse JB, Fineman MS, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 2003;88:3082–3089
- Gromada J, Franklin I, Wollheim CB. Alpha-cells of the endocrine pancreas: 35 years of research but the enigma remains. *Endocr Rev* 2007;28:84–116
- Robertson RP. The welcome resurgence of the α -cell: a pro glucagon commentary. *Diabetes* 2010;59:2735–2736
- Bergman BC, Howard D, Schauer IE, et al. Features of hepatic and skeletal muscle insulin resistance unique to type 1 diabetes. *J Clin Endocrinol Metab* 2012;97:1663–1672
- Gedulin BR, Nikoulina SE, Smith PA, et al. Exenatide (exendin-4) improves insulin sensitivity and beta-cell mass in insulin-resistant obese fa/fa Zucker rats independent of glycemia and body weight. *Endocrinology* 2005;146:2069–2076
- Idris I, Patiag D, Gray S, Donnelly R. Exendin-4 increases insulin sensitivity via a PI-3-kinase-dependent mechanism: contrasting effects of GLP-1. *Biochem Pharmacol* 2002;63:993–996
- Schauer IE, Snell-Bergeon JK, Bergman BC, et al. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: the CACTI study. *Diabetes* 2011;60:306–314