Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Pre-Diabetes

Julio Rosenstock, MD1
Leslie J. Klaff, MD, PhD2
Sherwyn Schwartz, MD3
Justin Northrup, MPT4
John H. Holcombe, MD4
Kenneth Wilhelm, MD5
Michael Trautmann, MD4

OBJECTIVE — To assess the effects of exenatide on body weight and glucose tolerance in nondiabetic obese subjects with normal or impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).

RESEARCH DESIGN AND METHODS — Obese subjects (n = 152; age 46 ± 12 years, female 82%, weight 108.6 ± 23.0 kg, BMI 39.6 ± 7.0 kg/m², IGT or IFG 25%) were randomized to receive exenatide (n = 73) or placebo (n = 79), along with lifestyle intervention, for 24 weeks.

RESULTS — Exenatide-treated subjects lost 5.1 ± 0.5 kg from baseline versus 1.6 ± 0.5 kg with placebo (exenatide − placebo, P < 0.001). Placebo-subtracted difference in percent weight reduction was −3.3 ± 0.5% (P < 0.001). Both groups reduced their daily calorie intake (exenatide, −449 cal; placebo, −387 cal). IGT or IFG normalized at end point in 77 and 56% of exenatide and placebo subjects, respectively.

CONCLUSIONS — Exenatide plus lifestyle modification decreased caloric intake and resulted in weight loss in nondiabetic obesity with improved glucose tolerance in subjects with IGT and IFG.

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Several well-designed trials have demonstrated that weight reduction can reduce diabetes risk (1–4). However, with only lifestyle modification, even modest weight loss is difficult to achieve over time (5,6); therefore, optimal pharmacologic strategies for treating obesity are being developed. This study explored exenatide in combination with lifestyle modification as treatment for weight loss in nondiabetic obese subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or impaired fasting glucose (IFG).

From the 1Dallas Diabetes and Endocrine Center at Medical City, Dallas, Texas; the 2Rainier Clinical Research Center, Renton, Washington; 3Diabetes & Glandular Disease Research Associates, San Antonio, Texas; 4Eli Lilly and Company, Indianapolis, Indiana; 5Amylin Pharmaceuticals, San Diego, California.

Corresponding author: Julio Rosenstock, juliorosenstock@dallasiabetes.com.

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greater percentage of exenatide-treated subjects experienced ≥5% body weight reduction at 24 weeks compared with placebo (32 vs. 17%, respectively; P = 0.039). Exenatide-treated subjects who did (n = 18) or did not (n = 55) experience nausea had mean body weight reductions at 24 weeks (nausea: −3.8 ± 1.2 kg; no nausea: −4.1 ± 0.8 kg).

Most subjects with IGT or IFG normalized glucose tolerance at end point (exenatide 77%, placebo 56%). Five participants (three exenatide, two placebo) developed type 2 diabetes during the study, three of which (two exenatide, one placebo) had IGT or IFG at baseline. Both groups significantly (P < 0.05) reduced their daily calorie intake (exenatide −449 ± 64 calories; placebo −387 ± 63 calories). Significant baseline–to–end point changes were not observed for A1C, fasting glucose, oral glucose tolerance test, and physical activity. Similar changes in lipid concentrations and blood pressure were observed in both treatment groups.

No deaths, serious adverse events, or hypoglycemia were observed during the study. Nausea was experienced by 25 and 4% and diarrhea by 14 and 3% of exenatide- and placebo-treated subjects, respectively. The majority of adverse events were mild or moderate in severity.

**CONCLUSIONS**— GLP-1 receptor agonists are among the few treatments for type 2 diabetes in which substantial weight loss was recognized as an added value. This study of exenatide, combined with a pragmatic lifestyle intervention, was designed to evaluate the potential for weight loss in obese (mean baseline BMI 39.6 kg/m²) nondiabetic subjects in clear need of therapeutic intervention, as recommended by current guidelines (7,8). Exenatide treatment plus lifestyle modification was associated with significantly greater mean percent reduction in body weight (treatment difference, −3.3%) than lifestyle modification alone. The placebo-subtracted change in weight (−3.5 kg) was similar to the change observed with liraglutide at the 2.4-mg dose (9). It is unknown if higher doses of exenatide might achieve greater weight reductions than those observed in the present study.

Although we did not evaluate possible mechanisms to explain the substantial weight loss observed, GLP-1 receptor agonism may activate central pathways mediating satiety- and nausea-regulating mechanisms (10,11). The finding that weight loss in exenatide-treated subjects with type 2 diabetes is sustained in the absence of continued nausea (12) supports a satiety-related mechanism (10,13).

Normalization of glucose tolerance and reduction of caloric intake favored subjects treated with exenatide. The current findings warrant further studies to explore the potential role of GLP-1 receptor agonists for the treatment of obese subjects with IGT or IFG. Exenatide, in addition to lifestyle modification, has potential as a treatment for obesity in subjects at high risk for developing type 2 diabetes. Because of the high recidivism observed with weight loss interventions, sustained weight loss demonstrated in long-term studies is a key issue for future anti-obesity research.

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