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The Effect of Adding Exenatide to a Thiazolidinedione in Suboptimally Controlled Type 2 Diabetes

A Randomized Trial

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Background: Exenatide therapy is effective in combination with metformin or sulfonylureas for treating type 2 diabetes. Thiazolidinediones (TZDs) also are commonly used, but the efficacy of exenatide with a TZD has not been reported.

Objective: To compare the effects of exenatide versus placebo on glycemic control.

Design: Placebo run-in, randomized, double-blind, placebo-controlled trial conducted from May 2004 to August 2005.

Setting: 49 sites in Canada, Spain, and the United States.

Patients: 233 (exenatide group, $n = 121$; placebo group, $n = 112$) patients with type 2 diabetes that was suboptimally controlled with TZD treatment (with or without metformin). Mean (±SE) baseline glycated hemoglobin A_{1c} level was 7.9% ± 0.1%.

Interventions: Subcutaneous abdominal injections of 10 μg of exenatide or placebo twice daily, added to a TZD (with or without metformin) for 16 weeks.

Measurements: The primary outcome was change from baseline in hemoglobin A_{1c} level. Other outcomes were fasting serum glucose level, body weight, self-monitored blood glucose level, and any adverse events.

Results: Exenatide treatment reduced hemoglobin A_{1c} level (mean difference, −0.98% [95% CI, −1.21% to −0.74%]), serum fasting glucose level (mean difference, −1.69 mmol/L [−30.5 mg/dL] [CI, −2.22 to −1.17 mmol/L {−40.0 to −21.1 mg/dL}]), and body weight (mean difference, −1.51 kg [CI, −2.15 to −0.88 kg]). Sixteen percent of patients in the exenatide group and 2% of patients in the placebo group discontinued treatment because of adverse events. In the exenatide group, 40% ($n = 48$) of patients experienced nausea (mostly mild [$n = 21$] or moderate [$n = 19$]), 13% experienced vomiting, and 11% experienced hypoglycemia. In the placebo group, 15% of patients experienced nausea, 1% experienced vomiting, and 7% experienced hypoglycemia.

Limitations: Combinations with TZDs and sulfonylureas were not tested. Trial duration was relatively short. Only 71% and 86% of patients in the exenatide and placebo groups, respectively, completed the study.

Conclusions: Exenatide therapy improved glycemic control, reduced body weight, and caused gastrointestinal symptoms more than placebo in patients with type 2 diabetes that was suboptimally controlled with TZD therapy.

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Exenatide is the first in a new class of medications called incretin mimetics that share several glucoregulatory effects with the incretin hormone glucagon-like peptide-1 and have been shown to bind the glucagon-like peptide-1 receptor in vitro (1–4). Consequently, exenatide exerts glucoregulatory effects by enhancing glucose-dependent insulin secretion (5–7), inhibiting inappropriately elevated glucagon secretion (8, 9), slowing gastric emptying (8–10), and reducing food intake (10). Exenatide therapy has also been shown to result in moderate weight reduction (11). In addition, 82 weeks of exenatide therapy in an open-label extension trial resulted in weight loss associated with favorable effects on several cardiovascular risk factors, including triglyceride level, high-density lipoprotein cholesterol level, and diastolic blood pressure (12).

Insulin-sensitizing thiazolidinediones (TZDs) are widely used for treating type 2 diabetes. These peroxisome proliferator–activated receptor-γ activators improve insulin action in muscle and adipose tissue (13–16) with some reduction in hepatic glucose production (17). They also seem to exert favorable effects on cardiovascular risk factors, including blood pressure, high-density lipoprotein cholesterol level, and triglyceride level, and on the proinflammatory and prothrombotic vascular environment in patients with type 2 diabetes (13–15). However, TZD therapy is associated with an increased risk for fluid retention and worsening of heart failure and often results in weight gain (18, 19).

Exenatide therapy in combination with the commonly used glucose-lowering agents—metformin or a sulfonylurea—improves glucose control in patients with type 2 diabetes (20–22). Both exenatide and TZDs regulate glucose levels through several mechanisms. These unique and potentially complementary mechanisms target the primary pathophysiologic defects that lead to hyperglycemia of type

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Context

The effects of adding exenatide to thiazolidinediones (TZDs) for treating type 2 diabetes are not clear.

Contribution

The investigators of this double-blind trial randomly assigned 233 adults with type 2 diabetes that was suboptimally controlled with TZD (with or without metformin) to twice-daily injections of exenatide or placebo. At 16 weeks, exenatide reduced hemoglobin A_{1c} levels (mean difference, −0.98%), fasting glucose levels (mean difference, −1.69 mmol/L [−30.5 mg/dL]), and body weight (mean difference, −1.51 kg) more than placebo. More patients in the exenatide group than in the placebo group had nausea (40% vs. 15%) and vomiting (13% vs. 1%).

Implications

Adding exenatide to TZD modestly improves glycemic control and reduces body weight but causes nausea and vomiting in some patients.

—The Editors

2 diabetes, namely progressive β-cell dysfunction and insulin resistance. In this context, our study compares the glycemic and body weight effects of exenatide versus placebo in patients with type 2 diabetes with suboptimal glycemic control who are receiving a background therapy of TZD or TZD plus metformin.

METHODS

Design Overview

All patients participated in a 2-week, single-blind, placebo lead-in period, during which placebo was administered as twice-daily subcutaneous injections into the abdomen. After the placebo lead-in period, patients self-administered exenatide or placebo by subcutaneous injection into the abdomen within 15 minutes before the morning and evening meals. Exenatide-treated patients received fixed 5-μg doses twice daily for 4 weeks, followed by 10-μg doses twice daily for 12 weeks. The dosages of TZD and metformin were constant throughout the study. Lifestyle interventions were not included in the study protocol. The institutional review board approved a common clinical protocol for each site that was in accordance with the principles described in the Declaration of Helsinki (23). All participants gave informed written consent before participation. The trial was conducted from May 2004 to August 2005.

Setting and Participants

Forty-nine research clinics, hospitals, and primary care facilities in Canada, Spain, and the United States participated. Site investigators recruited patients through local investigators' practices and advertising. Patients were 21 to 75 years of age and were treated with a stable dosage of a TZD (rosiglitazone, ≥4 mg/d, or pioglitazone, ≥30 mg/d) for at least 4 months before screening. Patients received TZD therapy alone or in combination with a stable dosage of metformin (no minimum dosage required) for 30 days. Other inclusion criteria were a hemoglobin A_{1c} value between 7.1% and 10.0% at screening, body mass index greater than 25 kg/m^2 but less than 45 kg/m^2, and a history of stable body weight (≤10% variation) for at least 3 months before screening.

Randomization and Interventions

Within 3 weeks after screening, patients who met the inclusion criteria were randomly assigned (with equal probability) to receive exenatide or placebo according to a central randomization table. The sponsor (Eli Lilly and Company, Indianapolis, Indiana) generated the central randomization table, and an automated, interactive voice-response system administered the assignments. Randomization was concealed and stratified by investigative site and current treatment (TZD alone or TZD plus metformin). Prefilled disposable injection pens or cartridges containing indistinguishable exenatide and placebo solutions (packaged centrally by Eli Lilly and Company) were used.

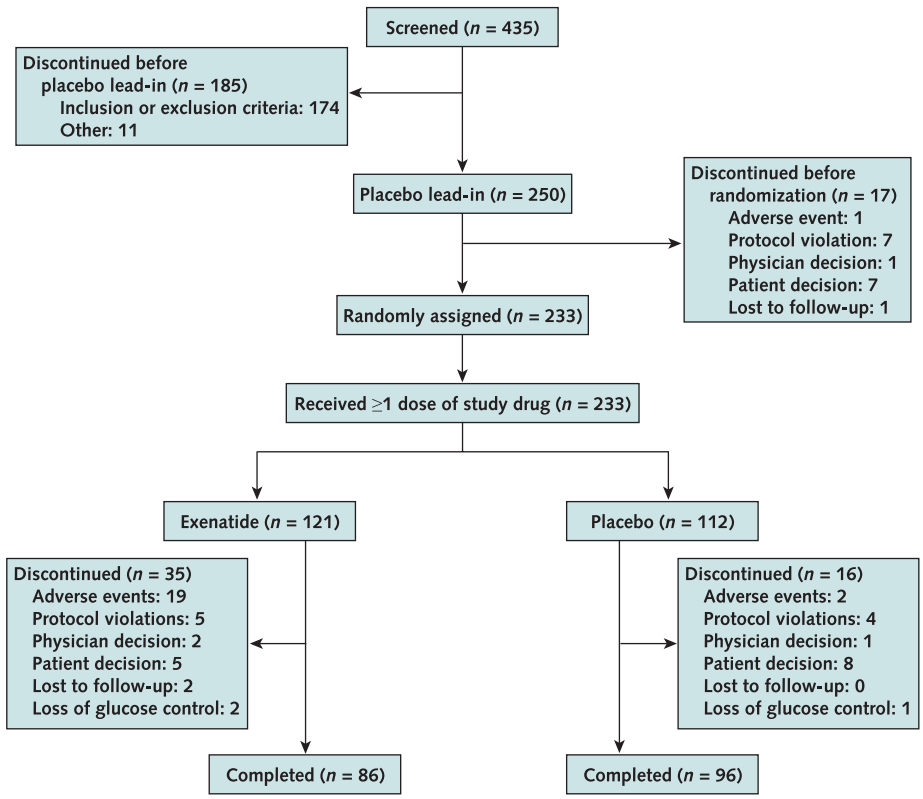
Outcomes and Measurements

We measured hemoglobin A_{1c} at screening, randomization (baseline or week 0), and week 16 (or, if possible, at the time of early discontinuation). We assessed fasting serum glucose concentrations at weeks 0 and 16 (or at early discontinuation) and measured body weight each month. We collected profiles of 7-point, self-monitored blood glucose levels (measured before the morning, midday, and evening meals; 2 hours after the start of each meal; and at bedtime) at weeks 0, 4, 8, 12, and 16. We determined homeostasis model assessment (HOMA) of β-cell function and insulin sensitivity, estimates of the contributions of β-cell dysfunction and insulin resistance to hyperglycemia (24), at weeks 0 and 16 (or at early discontinuation). We measured plasma antiexenatide antibody levels at week 0 and the final visit.

Adverse Events and Follow-up

We assessed blood chemistries for safety monitoring at screening and week 16 (or at early discontinuation). At monthly visits, we examined patients for pedal edema and asked them to report any adverse events. We classified adverse events according to the Medical Dictionary for Regulatory Activities. Study centers provided patients with study diaries, glucose monitors, and instructions for their use. Patients were encouraged to check their glucose levels when signs or symptoms of hypoglycemia (including sweating, shaking, palpitations, or confusion) occurred. In the diaries, patients recorded illnesses, concomitant medications, any changes to their antidiabetic oral medications (TZDs or metformin), hypoglycemic episodes, glucose monitor readings, associated hypoglycemic symptoms, and treatments for the hypoglycemic events. The diaries contained modules dedicated to hypoglycemic events and were

Figure 1. **Study flow diagram.**



reviewed by investigative staff at each study visit. We defined hypoglycemia as an incident when a patient obtained a glucose monitor reading less than 3.4 mmol/L (<60 mg/dL) or experienced symptoms of hypoglycemia. We defined severe hypoglycemia as an incident when a patient required the assistance of another person and either obtained a glucose monitor reading less than 2.8 mmol/L (<50 mg/dL) or promptly recovered after carbohydrate intervention. We assessed the severity of each adverse event (mild, moderate, or severe).

We assessed concomitant therapy and cointerventions at each visit, and we recorded any deviations from the prescribed dosage regimens. We did not collect specific data about treatment adherence. No patient crossovers occurred during the trial.

Statistical Analysis

The primary efficacy variable was the change in hemoglobin A_{1c} level from baseline. We determined that a sample size of 103 patients per group was needed to provide 90% power to detect a difference of 0.5% between groups in change in hemoglobin A_{1c} level. We determined this on the basis of an estimated 25% dropout rate after randomization and with a 2-sided *t*-test at a significance level of 0.05, assuming a common SD of 1.1%.

We defined 2 cohorts for the analyses of the efficacy measures: an intention-to-treat sample of patients who were randomly assigned to study medication and a per protocol sample of randomly assigned patients who had no violations of the inclusion or exclusion criteria, met no discontinuation criteria, and either completed the trial or discontinued at the last visit and had at least 16 weeks of exposure to study medication.

The primary efficacy analysis of change in hemoglobin A_{1c} level used a likelihood-based mixed-effects model analysis. The model included change in hemoglobin A_{1c} level as the dependent variable; treatment, week of visit, treatment-by-week interaction, baseline hemoglobin A_{1c} level, TZD stratum, and pooled investigator (sites with <5 randomly assigned patients with ≥1 postbaseline measure were pooled with another site or sites within the same country) as fixed effects; and patient and error as random effects. We included only patients with a baseline measure and at least 1 postbaseline value in the mixed-effects model analysis. We included all postbaseline measurements of change in hemoglobin A_{1c} level in the analysis, including unscheduled measurements or measurements from patients who discontinued early. We did not impute missing data in the analysis. The mixed-effects model analysis assumed that the

missing data were missing at random (25). We examined week 16 for inferential purposes only, because week 16 was the scheduled week for hemoglobin A_{1c} measurement. We used compound symmetry to model the covariance structure within patients. We found that the variables of treatment-by-TZD stratum and treatment-by-pooled investigator were not statistically significant, and therefore we excluded these in the final model. Using the PROC MIXED analysis in SAS software (SAS Institute Inc., Cary, North Carolina), we obtained least-squares estimates of the group differences and SEs from the model to compute the 2-sided 95% CIs (based on *t* distribution) that were used to test for superiority.

We used similar mixed-effects models to analyze other continuous measures (for example, body weight, fasting serum glucose level, HOMA of β-cell function and insulin sensitivity, and self-monitored blood glucose level). For body weight and self-monitored blood glucose values, we used data from all weeks for inferential purposes because we obtained those measurements at each week. Results from mixed-effects model analyses are expressed as adjusted (least-squares) means. We conducted tests of treatment effects at a 2-sided significance level of 0.05 and determined all 95% CIs on the basis of the difference between exenatide and placebo. We used the intention-to-treat sample in all analyses with the exception of the analyses comparing the percentage of patients achieving hemoglobin A_{1c} levels of 7.0% or less or 6.5% or less.

Role of the Funding Sources

This study was designed by medical personnel at Eli Lilly and Company, including Drs. Brodows and Trautmann, and medical personnel at Amylin Pharmaceuticals Inc. The study was conducted by Eli Lilly and Company. Drs. Zinman, Hoogwerf, and Durán García were principal investigators at their respective study sites. Data analyses were performed by Ms. Milton, a statistician employed by Eli Lilly and Company, and the full set of raw data is available at Eli Lilly and Company. A research physician at Eli Lilly and Company monitored adverse events throughout the study. All authors interpreted the data and were involved in the drafting or critical review of the manuscript. Each author provided approval of the final manuscript content.

Table 1. **Baseline Characteristics***

Variable	Exenatide Group (*n* = 121)	Placebo Group (*n* = 112)
Sex, *n (%)*		
Male	65 (53.7)	64 (57.1)
Female	56 (46.3)	48 (42.9)
Race, *n (%)*		
White	103 (85.1)	92 (82.1)
Other	18 (14.9)	20 (17.9)
TZD stratum, *n (%)*		
TZD alone	28 (23.1)	22 (19.6)
TZD plus metformin	93 (76.9)	90 (80.4)
Mean age (SD), *y*	55.6 (10.8)	56.6 (10.2)
Mean body weight (SD), *kg*	97.5 (18.8)	96.9 (19.0)
Mean BMI (SD), *kg/m²*	34.0 (5.1)	34.0 (5.0)
Mean fasting plasma glucose level (SD)		
mmol/L	9.1 (2.6)	8.8 (1.9)
mg/dL	164.0 (46.8)	158.6 (34.2)
Mean hemoglobin A_{1c} level (SD), %	7.9 (0.9)	7.9 (0.8)
Mean duration of diabetes (SD), *y*	7.3 (4.9)	8.2 (5.8)
Mean metformin dose (SD), *mg*	1804 (459)	1810 (420)
Country, *n (%)*		
Canada (5 sites)	28 (23.1)	22 (19.6)
Spain (7 sites)	30 (24.8)	30 (26.8)
United States (37 sites)	63 (52.1)	60 (53.6)

* BMI = body mass index; TZD = thiazolidinedione.

Results

Patients

Of the 435 patients screened, 250 participated in the placebo lead-in period (**Figure 1**). Seventeen patients discontinued during this time, resulting in 233 patients who were randomly assigned and analyzed in the intention-to-treat sample. All 233 patients received at least 1 dose of study drug. Of those, 175 (75%) were included in the per protocol sample: 86 patients assigned to exenatide and 89 patients assigned to placebo.

Of the intention-to-treat patients, 183 (79%) were receiving background therapy of a TZD plus metformin and 50 (21%) were receiving TZD alone. At baseline, the exenatide and placebo groups were similar in age, body weight, duration of disease, and glycemic control (**Table 1**). Most patients were white (>82%) and male (55%). Mean hemoglobin A_{1c} level was less than 8.0%. Eighty-six (71%) patients receiving exenatide and 96 (86%) patients receiving placebo completed the study. The percentages of patients who reported the use of concomitant medications in each group were similar throughout the study.

Hemoglobin A_{1c}, Fasting Serum Glucose, and Self-Monitored Blood Glucose Levels

Table 2 shows the estimated mean changes in efficacy measures from baseline to week 16 in both groups. Hemoglobin A_{1c} levels decreased by a mean (±SE) of 0.89% ± 0.09% in the exenatide group ($P < 0.001$; intention-to-treat sample) but increased by a mean (±SE) of 0.09% ± 0.10% in the placebo group. The mean between-group difference in hemoglobin A_{1c} levels (exenatide minus placebo) at week 16 was −0.98% (95% CI, −1.21% to −0.74%; $P < 0.001$). Among per protocol patients, 62% of patients in the exenatide group and 16% of patients in the placebo group achieved hemoglobin A_{1c} levels of 7% or less ($P < 0.001$), and 30% and 8% of patients, respectively, achieved hemoglobin A_{1c} levels of 6.5% or less ($P < 0.001$). Mean fasting serum glucose level decreased more in the exenatide (intention-to-treat sample) group (mean [±SE] change, −1.59 ± 0.22 mmol/L [−28.6 ± 3.96 mg/dL]) than in the placebo group (mean [±SE] change, 0.10 ± 0.21 mmol/L [1.80 ± 3.78 mg/dL]). The mean between-group difference in fasting serum glucose level at week 16 was −1.69 mmol/L (−30.4 mg/dL)

Table 2. **Estimates of Mean Changes in Efficacy Measures from Baseline to Week 16***

Efficacy Measure	Exenatide Group (n = 121)	Placebo Group (n = 112)	Difference (95% CI)†
Hemoglobin A_{1c} level			
Baseline level, %‡	7.89	7.91	
Change from baseline to week 16, %§	–0.89	0.09	–0.98 (–1.21 to –0.74)
Fasting plasma glucose level			
Baseline level, *mmol/L*‡	9.13	8.84	
Change from baseline to week 16, *mmol/L*§	–1.59	0.10	–1.69 (–2.22 to –1.17)
Mean daily self-monitored blood glucose level‖			
Baseline level, *mmol/L*‡	9.46	9.18	
Change from baseline to week 16, *mmol/L*§	–1.85	–0.14	–1.71 (–2.09 to –1.33)
Daily mean postprandial self-monitored blood glucose level¶			
Baseline level, *mmol/L*‡	1.74	1.99	
Change from baseline to week 16, *mmol/L*§	–1.58	–0.31	–1.27 (–1.64 to –0.91)
Body weight			
Baseline, *kg*‡	97.53	96.75	
Change from baseline to week 16, *kg*§	–1.75	–0.24	–1.51 (–2.15 to –0.88)
HOMA of β-cell function**			
Baseline, %‡	37.85	35.91	
Ratio of week 16 to baseline§	1.19	0.94	1.27 (1.08 to 1.51)
HOMA of insulin sensitivity**			
Baseline, %‡	71.55	78.58	
Ratio of week 16 to baseline§	1.23	1.10	1.11 (0.94 to 1.31)

* The numbers of patients in the exenatide group in each analysis were 117 for hemoglobin A_{1c}, 114 for fasting plasma glucose, 95 for self-monitored blood glucose, 106 for postprandial self-monitored blood glucose, 121 for body weight, 109 for HOMA of β-cell function, and 110 for HOMA of insulin sensitivity. Corresponding numbers of patients in the placebo group were 105, 105, 93, 108, 110, 101, and 102, respectively. To convert glucose values from mmol/L to mg/dL, divide value by 0.0555. HOMA = homeostasis model assessment.
† Difference is calculated as follows: exenatide − placebo.
‡ Baseline means are presented for descriptive purposes.
§ Least-squares means are obtained from a likelihood-based mixed-effects model that includes baseline as a covariate.
‖ Average of all nonmissing values throughout the day.
¶ Average of all nonmissing excursion values associated with each meal.
** Changes in HOMA of β-cell function and HOMA of insulin sensitivity were performed on log-transformed data where the analysis variable was a change [log(final) − log(baseline)] and where back-transformations were expressed as ratios.

(CI, −2.22 to −1.17 mmol/L [−40.0 to −21.1 mg/dL]; $P < 0.001$).

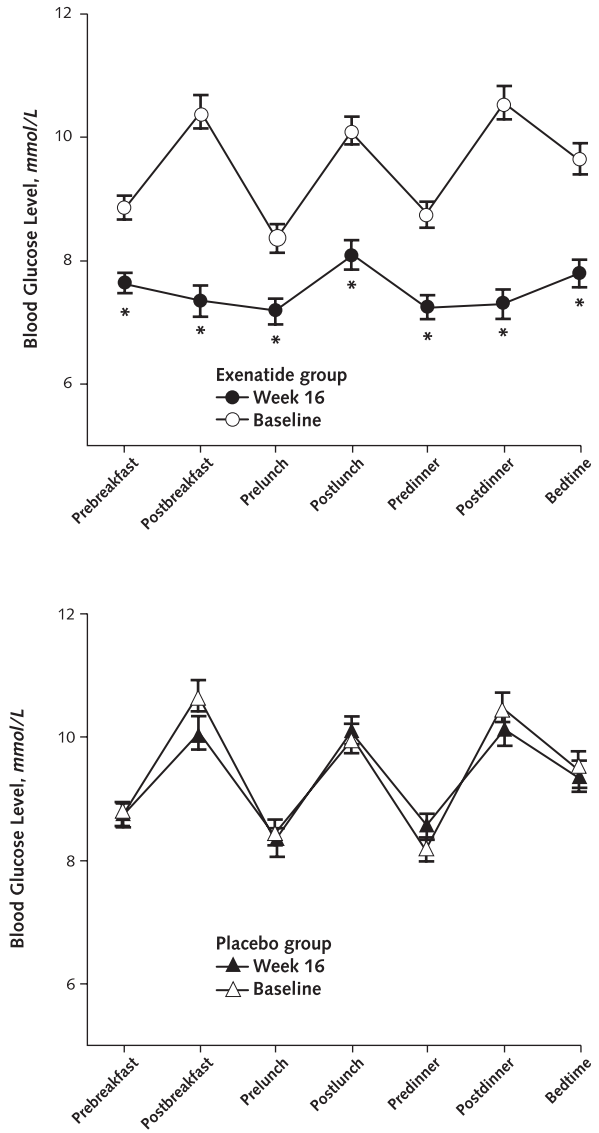
The existing oral antihyperglycemic treatment at baseline (TZD alone versus TZD plus metformin) did not influence observed changes in hemoglobin A_{1c} levels ($P = 0.87$ for interaction). Patients treated with exenatide and TZD alone ($n = 27$) had mean hemoglobin A_{1c} levels that decreased from 7.93% (SD, 0.87%) to 7.15% (SD, 1.05%), and patients treated with exenatide and TZD plus metformin ($n = 90$) had mean levels that decreased from 7.88% (SD, 0.92%) to 7.10% (SD, 0.92%). Patients who received placebo and TZD alone ($n = 19$) had mean hemoglobin A_{1c} levels that increased from 7.83% (SD, 0.89%) to 7.90% (SD, 0.93%), and patients who received placebo and TZD plus metformin ($n = 86$) had mean levels that increased from 7.93% (SD, 0.79%) to 8.02% (SD, 1.13%).

Self-monitored blood glucose profiles for patients in the exenatide group were lower at each measurement throughout the day at week 16 compared with baseline measurements ($P < 0.001$) (**Figure 2**); however, measurements for patients in the placebo group were similar to baseline measurements. Each 16-week measurement was lower for the exenatide group compared with the placebo group ($P < 0.001$). In addition, exenatide treatment blunted postprandial glucose excursions. Compared with placebo, exenatide treatment was associated with reductions in glucose excursions after the morning (mean [±SE] change in glucose level, −1.73 ± 0.27 mmol/L [−31.17 ± 4.86 mg/dL]; $P < 0.001$) and evening (−1.68 ± 0.30 mmol/L [−30.27 ± 5.41 mg/dL]; $P < 0.001$) meals.

HOMA of β-Cell Function and Insulin Sensitivity, Body Weight, and Lipid Levels

Homeostasis model assessment of β-cell function at week 16 had increased by 19% from a mean (±SE) baseline value of 37.85 ± 2.46 (**Table 2**) for the exenatide group but had decreased by 6% from a mean (±SE) baseline value of 35.91 ± 2.50 for the placebo group ($P = 0.005$). Homeostasis model assessment of insulin sensitivity increased for both treatment groups at week 16: 23% increase in the exenatide group (from a mean [±SE] base-

Figure 2. **Effects of exenatide and placebo on glycemic control in patients with type 2 diabetes treated with a thiazolidinedione with or without metformin.**



Effects of exenatide (*top*) and placebo (*bottom*) on 7-point, self-monitored blood glucose profiles at baseline (*open symbols*) and week 16 (*closed symbols*) are shown. All results (reported as means [±SE]) were obtained from the mixed-effects model analyses of the intention-to-treat sample. Numbers of exenatide patients at each point were 115 at prebreakfast, 111 at postbreakfast, 113 at prelunch, 111 at postlunch, 114 at predinner, 109 at postdinner, and 99 at bedtime. Corresponding numbers of patients in the placebo group were 110, 109, 108, 108, 109, 109, and 94, respectively. To convert glucose values from mmol/L to mg/dL, divide by 0.0555. *$P < 0.001$.

line value of 71.55 ± 4.22) and 10% increase in the placebo group (from a mean [±SE] baseline value of 78.58 ± 5.56). Treatment groups did not significantly differ in HOMA of insulin sensitivity ($P = 0.20$).

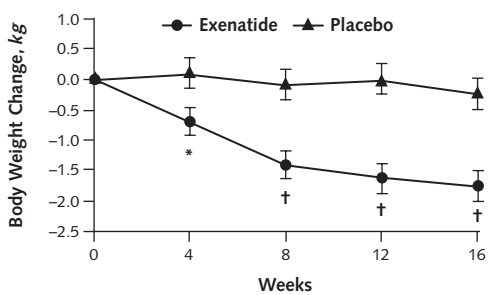
Exenatide treatment reduced mean (±SE) body weight from 97.53 kg ± 1.73 kg to 95.38 kg ± 0.25 kg. Body weight did not change in the placebo group (mean [±SE] body weight, 96.75 kg ± 1.81 kg and 96.89 kg ± 0.26 kg at baseline and week 16, respectively). At week 16, the mean difference in body weight reduction between groups was −1.51 kg (CI, −2.15 to −0.88 kg; $P < 0.001$). Exenatide-treated patients had reductions in body weight at all postbaseline visits, and differences between groups were statistically significant (**Figure 3**). Patients in the exenatide group had reductions in body weight regardless of their experience with nausea (mean [±SE] change in body weight, −1.95 kg ± 0.43 kg for patients who had nausea vs. −1.25 kg ± 0.35 kg for patients without nausea).

No clinically significant changes occurred in any fasting serum lipid level for either group (data not shown). No clinically significant changes in blood pressure were observed in either group over the 16 weeks of study.

Adverse Events

Table 3 lists the most commonly reported adverse events. The most frequent adverse event was nausea, which was the reason for withdrawal of 9% and 1% of patients in the exenatide and placebo groups, respectively. The between-group difference (exenatide minus placebo) in percentage of patients reporting nausea was 24.5 percentage points (CI, 12.7 to 36.3 percentage points). Nausea was mostly mild (21 [44%] exenatide recipients) or moderate (19 [40%] exenatide recipients) and intermittent. Thirty-four (71%) of patients in the exenatide group who reported nausea had episodes at more than 1 visit. Most reports of nausea occurred after a dose increase of exenatide from 5 to 10 μg twice daily (weeks 4 to 8); reports of nausea declined from a maximum of 41 reports (week 8) to 19 reports (week 16). The between-group difference in percentage of patients reporting vomiting was 12.3 percentage points (CI, 5.2 to 19.5 percentage points).

Figure 3. **Effects of exenatide and placebo on body weight at each visit in patients with type 2 diabetes treated with a thiazolidinedione with or without metformin.**



All results were obtained from the mixed-effects model of 121 patients who received exenatide (*circles*) and 110 patients who received placebo (*triangles*) in the intention-to-treat analysis. Mean (±SE) body weight changes at week 16 were −1.75 kg ± 0.25 kg for exenatide recipients and −0.24 kg ± 0.26 kg for placebo recipients. *$P < 0.01$. †$P < 0.001$.

Table 3. **Adverse Events and Symptoms That Occurred in 5% or More Patients Who Received at Least 1 Dose of Study Drug***

Adverse Event	Exenatide Group (n = 121), n (%)	Placebo Group (n = 112), n (%)	Difference (95% CI)†
Patients reporting ≥1 adverse event	92 (76.0)	73 (65.2)	10.9 (−1.7 to 23.4)
Patients reporting a serious adverse event	2 (1.7)	0 (0)	1.7 (−1.5 to 4.8)
Nausea	48 (39.7)	17 (15.2)	24.5 (12.7 to 36.3)
Nasopharyngitis	16 (13.2)	9 (8.0)	5.2 (−3.5 to 13.9)
Vomiting	16 (13.2)	1 (0.9)	12.3 (5.2 to 19.5)
Hypoglycemia	13 (10.7)	8 (7.1)	3.6 (−4.6 to 11.8)
Dyspepsia	9 (7.4)	1 (0.9)	6.5 (0.7 to 12.4)
Edema	7 (5.8)	9 (8.0)	−2.3 (−9.6 to 5.1)
Headache	7 (5.8)	5 (4.5)	1.3 (−5.2 to 7.8)
Diarrhea	7 (5.8)	3 (2.7)	3.1 (−2.9 to 9.1)
Influenza	6 (5.0)	5 (4.5)	0.5 (−5.8 to 6.8)

* Values refer to numbers and percentages of patients who reported particular symptoms that occurred ≥1 times during the trial.
† Difference (reported in percentage points) is calculated as exenatide minus placebo.

Vomiting was mostly mild (5 [31%] exenatide recipients) or moderate (10 [63%] exenatide recipients).

The incidence of treatment-emergent edema was similar in both groups (**Table 3**). The overall incidence of hypoglycemia also was low and similar between groups (between-group difference, 3.6 percentage points [CI, −4.6 to 11.8 percentage points]) (**Table 3**). No severe hypoglycemia was reported.

Nineteen (16%) patients in the exenatide group discontinued because of adverse events: 11 because of nausea, 6 because of vomiting, 1 because of chest pain, and 1 because of an injection site reaction. As with incidences of nausea, most discontinuations because of adverse events occurred after a dose increase of exenatide from 5 to 10 μg (10 at week 8); discontinuations declined to 2 at week 12 and an additional 2 at week 16. Two patients in the placebo group discontinued because of adverse events: 1 because of nausea and 1 because of somnolence. Baseline characteristics within groups for patients who discontinued the study were similar to those of patients who completed the study.

Two patients in the exenatide group reported a serious adverse event: 1 reported chest pain and 1 reported allergic alveolitis. Neither incident resulted in discontinuation from the study. The investigator did not consider the case of chest pain, which resolved within 2 days, to be related to the study drug, but did consider the case of allergic alveolitis to be possibly related. Although the patient who experienced allergic alveolitis did not discontinue the study because of the event, the patient eventually discontinued because of treatment-emergent nausea.

Of the 115 patients in the exenatide group who were assessed for treatment-emergent antiexenatide antibodies, 46 (40%) had positive titers at end point. Of these antibody-positive patients, 36 [78%] developed lower antibody titers (1:5 to 1:125). Hemoglobin A_{1c} responses between antibody-negative (mean response, −0.84% [SD, 1.03%]) and antibody-positive (mean response, −0.72% [SD, 0.68%]) patients were similar at end point. We observed no clinically meaningful differences in adverse events between antibody-positive and antibody-negative patients.

DISCUSSION

Our study demonstrates that exenatide in combination with a TZD improves glycemic control in patients with type 2 diabetes that is suboptimally controlled with a TZD, either alone or in combination with metformin. Exenatide therapy, in combination with TZD therapy, improved hemoglobin A_{1c} levels, fasting blood glucose levels, and postprandial glucose excursions and reduced body weight over 16 weeks. Exenatide treatment also improved clinical measures of β-cell function. The most commonly reported adverse event associated with exenatide treatment was mild to moderate nausea that diminished with time and continued use of exenatide. Nonetheless, some individuals did not tolerate these side effects well (9% and 5% of patients discontinued the study because of nausea and vomiting, respectively). No clinically significant episodes of hypoglycemia were reported.

More patients in the exenatide group (n = 35 [29%]) discontinued the study, primarily owing to adverse events, than patients in the placebo group (n = 16 [14%]). To address the differential dropout rates, our primary analysis used a mixed-effects model approach, which assumes that missing data are missing at random (25). In addition, we performed a sensitivity analysis to explore the assumption that missing data were not missing at random by using a pattern-mixture model method (26). For this analysis, we grouped patients into 3 patterns: 2 dropout patterns (early [week 4] and middle [weeks 8 and 12]) and completers (week 16). The model variables of interest were the treatment differences for each group and the proportion of patients in each pattern. Conclusions from the pattern-mixture model analysis were consistent with those found by using the mixed-effects model approach.

The progressive nature of type 2 diabetes has led to combination therapy with conventional glucose-lowering

agents to help patients achieve glucose control (15, 27–29); however, many patients have not achieved optimal glycemic levels despite these efforts (30). Weight gain and hypoglycemia that result from the use of some currently available agents are among the side effects that limit the use or effectiveness of therapy and complicate the management of type 2 diabetes (31, 32). Since their approval, the use of TZDs has increased rapidly over the last decade, particularly in the United States (33), and their use in combination with other glucose-lowering agents has also increased (34).

Incretin mimetics target several metabolic processes that result in glucose-lowering effects (1–4). Exenatide, approved for combination therapy with the commonly available oral agent metformin, a sulfonylurea, or metformin plus a sulfonylurea, also recently has been approved for combination therapy with a TZD for treating type 2 diabetes. The glucose-dependent action of exenatide in promoting insulin secretion makes exenatide less likely than conventional secretagogues to induce hypoglycemic events (20–22), and weight reduction associated with exenatide may have clinical significance for the management of type 2 diabetes (32).

In this context, we designed our study to evaluate exenatide in combination with TZD therapy. The combination may have particular appeal for the treatment for type 2 diabetes, offering the possibility of disease modification with little risk for hypoglycemia and perhaps minimal weight gain, a common concern with TZD use. Although patients in our study experienced weight loss, the study was not designed to determine whether simultaneous initiation of exenatide and TZD therapies would prevent weight gain associated with the use of TZDs. In our trial, weight reduction occurred without the use of additional lifestyle interventions as part of the study protocol.

Given increased attention to achieving and maintaining clinical practice guideline targets for patients with type 2 diabetes (27–29), our findings contribute to data supporting the use of exenatide in combination with TZDs in patients who do not achieve glycemic targets. Reduction in hemoglobin A_{1c} levels resulted from improvements in fasting serum glucose levels and postprandial blood glucose excursions (35). The robust effect on postprandial glucose control is particularly relevant given the suggestion that postprandial glucose excursions may play an increasingly important role in reaching guideline recommendations in individuals with hemoglobin A_{1c} levels close to 7% (36) and the fact that postprandial glucose excursions may be an independent risk factor for cardiovascular events (37). Our findings (decreasing of hemoglobin A_{1c} levels, postprandial glucose level control, body weight effects, and tolerability) are similar to those reported in published trials (20–22) and provide evidence that exenatide may be suitably combined with the 3 major classes of oral antidiabetic agents: metformin, sulfonylureas, and TZDs.

Our study limitations include a relatively short interval of active treatment. Within this short follow-up, we could not assess whether a sustained effect on β-cell function, weight loss, or improved glucose control would have been achieved. In addition, the completion rates for the exenatide and placebo groups were not similar, because more patients who received exenatide withdrew from the study owing to adverse events. The trial did not distinguish between the efficacies of the TZDs (pioglitazone or rosiglitazone) and did not rigorously evaluate the role of metformin in these therapeutic combinations. Although sulfonylurea is another common glucose-lowering agent, we did not evaluate the effect of exenatide in patients concurrently treated with a TZD plus sulfonylurea. This may result in different outcomes with respect to weight effects and hypoglycemic risk.

In summary, exenatide therapy improved glycemic control in patients with type 2 diabetes that was suboptimally controlled with ongoing TZD therapy either alone or in combination with metformin. Over a relatively short duration of active treatment, exenatide therapy resulted in reductions in hemoglobin A_{1c} levels and weight loss and did not statistically significantly increase the incidence of hypoglycemia or edema. Exenatide therapy also caused mild to moderate nausea and some cases of vomiting. These data support considering adding exenatide to TZD therapy for patients with suboptimally controlled type 2 diabetes. Longer-term study of combination therapy of exenatide and TZDs may provide insight into the potential disease-modifying effects and effect on vascular complications of diabetes.

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References

1. **Drucker DJ.** Enhancing incretin action for the treatment of type 2 diabetes. Diabetes Care. 2003;26:2929-40. [PMID: 14514604]
2. **Nielsen LL, Baron AD.** Pharmacology of exenatide (synthetic exendin-4) for the treatment of type 2 diabetes. Curr Opin Investig Drugs. 2003;4:401-5. [PMID: 12808878]
3. **Nielsen LL, Young AA, Parkes DG.** Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. Regul Pept. 2004;117:77-88. [PMID: 14700743]
4. **Schnabel C, White J, Campbell K.** Incretin mimetics and DPP-IV inhibitors in the treatment of type 2 diabetes mellitus. U S Pharmacist. 2004;35-49.
5. **Egan JM, Clocquet AR, Elahi D.** The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. J Clin Endocrinol Metab. 2002;87:1282-90. [PMID: 11889200]
6. **Parkes DG, Pittner R, Jodka C, Smith P, Young A.** Insulinotropic actions of exendin-4 and glucagon-like peptide-1 in vivo and in vitro. Metabolism. 2001; 50:583-9. [PMID: 11319721]
7. **Degn KB, Brock B, Juhl CB, Djurhuus CB, Grubert J, Kim D, et al.** Effect of intravenous infusion of exenatide (synthetic exendin-4) on glucose-dependent insulin secretion and counterregulation during hypoglycemia. Diabetes. 2004;53: 2397-403. [PMID: 15331551]
8. **Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, et al.** Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. J Clin Endocrinol Metab. 2003; 88:3082-9. [PMID: 12843147]
9. **Kolterman OG, Kim DD, Shen L, Ruggles JA, Nielsen LL, Fineman MS, et al.** Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. Am J Health Syst Pharm. 2005;62:173-81. [PMID: 15700891]
10. **Edwards CM, Stanley SA, Davis R, Brynes AE, Frost GS, Seal LJ, et al.** Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. Am J Physiol Endocrinol Metab. 2001;281:E155-61. [PMID: 11404233]
11. **Poon T, Nelson P, Shen L, Mihm M, Taylor K, Fineman M, et al.** Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. Diabetes Technol Ther. 2005;7:467-77. [PMID: 15929678]
12. **Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, et al.** Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab. 2006;8:436-47. [PMID: 16776751]
13. **Kendall DM.** Thiazolidinediones: the case for early use. Diabetes Care. 2006; 29:154-7. [PMID: 16373917]
14. **Kudzma DJ.** Effects of thiazolidinediones for early treatment of type 2 diabetes mellitus. Am J Manag Care. 2002;8:S472-82. [PMID: 12408410]
15. **Meriden T.** Progress with thiazolidinediones in the management of type 2 diabetes mellitus. Clin Ther. 2004;26:177-90. [PMID: 15038941]
16. **Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, et al.** Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med. 1998;338:867-72. [PMID: 9516221]
17. **Seufert J, Lübben G, Dietrich K, Bates PC.** A comparison of the effects of thiazolidinediones and metformin on metabolic control in patients with type 2 diabetes mellitus. Clin Ther. 2004;26:805-18. [PMID: 15262452]
18. **Bloomgarden ZT.** Thiazolidinediones. Diabetes Care. 2005;28:488-93. [PMID: 15677823]
19. **Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, et al.** Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2004;27:256-63. [PMID: 14693998]
20. **Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD, et al.** Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004;27:2628-35. [PMID: 15504997]
21. **DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD.** Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28:1092-100. [PMID: 15855572]
22. **Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al.** Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005;28:1083-91. [PMID: 15855571]
23. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA. 1997; 277:925-6. [PMID: 9062334]
24. **Wallace TM, Levy JC, Matthews DR.** Use and abuse of HOMA modeling. Diabetes Care. 2004;27:1487-95. [PMID: 15161807]
25. **Little RJ, Rubin DB.** Statistical Analysis with Missing Data. 2nd ed. New York: J Wiley; 2002.
26. **Verbeke G, Molenberghs G.** Linear Mixed Models for Longitudinal Data. New York: Springer-Verlag; 2000.
27. **Dailey GE 3rd, Noor MA, Park JS, Bruce S, Fiedorek FT.** Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med. 2004;116: 223-9. [PMID: 14969649]
28. **Fonseca V, Rosenstock J, Patwardhan R, Salzman A.** Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA. 2000;283:1695-702. [PMID: 10755495]
29. **Morton AP, McIntyre HD.** Effectiveness and side effects of thiazolidinediones for type 2 diabetes [Letter]. Med J Aust. 2005;182:492-3. [PMID: 15865597]
30. **Koro CE, Bowlin SJ, Bourgeois N, Fedder DO.** Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care. 2004;27:17-20. [PMID: 14693960]
31. **DeFronzo RA.** Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med. 1999;131:281-303. [PMID: 10454950]
32. **Purnell JQ, Weyer C.** Weight effect of current and experimental drugs for diabetes mellitus: from promotion to alleviation of obesity. Treat Endocrinol. 2003;2:33-47. [PMID: 15871553]
33. **Wysowski DK, Armstrong G, Governale L.** Rapid increase in the use of oral antidiabetic drugs in the United States, 1990-2001. Diabetes Care. 2003;26: 1852-5. [PMID: 12766122]
34. **Cohen FJ, Neslusan CA, Conklin JE, Song X.** Recent antihyperglycemic prescribing trends for US privately insured patients with type 2 diabetes. Diabetes Care. 2003;26:1847-51. [PMID: 12766121]
35. **Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG, et al.** Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005;143:559-69. [PMID: 16230722]
36. **Monnier L, Lapinski H, Colette C.** Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care. 2003;26:881-5. [PMID: 12610053]
37. **Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, et al.** Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab. 2006;91: 813-9. [PMID: 16352690]

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