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A Systematic Review of Exenatide in Glycemic Control

Alvaro Ramos

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Abstract

**Background:** Type II diabetes is characterized by hyperglycemia, insulin resistance or having impairment with insulin secretion. Patients are traditionally treated with oral medication and lifestyle modification before adding insulin to their treatment. Exenatide is an adjunct subcutaneous therapy to improve glycemic control and weight loss.

**Method:** The focus of this study was to review clinical trials of exenatide on diabetes mellitus type II. A thorough review of clinical trials from 2000 to 2010, pertaining to exenatide versus standard oral hypoglycemic were selected and analyzed. One double-blind, two triple-blind, and randomized control trials were identified by systematic literature search using PubMed, Cochrane, Medline and CINHAL search engines. The comprehensive literature search resulted in a total of 36 articles that were analyzed thoroughly, but only three articles were chosen.

**Results:** The 30 week study from DeFronzo et al. (2005) demonstrate HbA(1c) changes from baseline +/- SE for each group were -0.78 +/- 0.10% (10 microg), -0.40 +/- 0.11% (5 microg), and +0.08 +/- 0.10% (placebo; intent to treat; adjusted P < 0.002). The Buse et al. study show HbA(1c) changes from baseline were -0.86 +/- 0.11, -0.46 +/- 0.12, and 0.12 +/- 0.09% (+/-SE) in the 10-microg, 5-microg, and placebo arms, respectively (adjusted P < 0.001). Zinman et al. 16 week study demonstrate a mean HbA1c decrease of 0.89% ± 0.09% in the exenatide group (p<0.001).

**Conclusion:** Exenatide demonstrates improved glycemic control, reduced body weight, and reduced fasting blood glucose in type II diabetic patients who have failed to achieve glycemic control with traditional oral hypoglycemic medications.

**Keywords:** Diabetes Type II, exenatide, metformin, sulfonylurea, and thiazolidinedione

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A Systematic Review of Exenatide in Glycemic Control

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ABSTRACT

Background: Type II diabetes is characterized by hyperglycemia, insulin resistance or having impairment with insulin secretion. Patients are traditionally treated with oral medication and lifestyle modification before adding insulin to their treatment. Exenatide is an adjunct subcutaneous therapy to improve glycemic control and weight loss.

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Conclusion: Exenatide demonstrates improved glycemic control, reduced body weight, and reduced fasting blood glucose in type II diabetic patients who have failed to achieve glycemic control with traditional oral hyperglycemic medications.

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INTRODUCTION

Background

Diabetes mellitus (DM) is a metabolic disorder that is characterized by impaired insulin secretion and varying degrees of insulin resistance that lead to hyperglycemia. Years of uncontrolled diabetes may result in macrovascular and microvascular complications that affect the heart, kidneys, and eyes. In addition, uncontrolled hyperglycemia can also lead to neuropathic complications that can cause numbing and loss of sensation in distal extremities. In lower extremities, blunted perception of foot trauma from ill-fitting shoes or abnormal weight bearing often leads to foot ulceration and fractures. The increased cardiovascular risk associated with DM contributes to it being the sixth leading cause of death in the US (National Diabetes Information Clearinghouse, 2007). For every 1% increase in glycosylated hemoglobin (HbA\textsubscript{1c}) above 5%, there is a 20% epidemiological increase in cardiovascular risk (Khaw et al., 2004). The financial impact of DM in 2007 was estimated to be US$174 billion (direct medical costs and indirect costs resulting from lack of employee productivity) (American Diabetes Association, 2007). Worldwide, the total number of people with DM is projected to increase from 171 million in 2000 to 366 million in 2030 (Wild, Roglic, Green, Sicree, King, 2004). These important statistics demonstrate that there is a diabetic epidemic on the rise and it is essential that patients are educated about their disease and the proper management of diabetes mellitus.

Diabetes mellitus is treated with diet and exercise, coupled with oral hypoglycemic medications, insulin sensitizers, medications that impede hepatic
production of glucose and prescribed insulin. However, hypoglycemia, gastrointestinal side effects, weight gain, and lack of optimal control of postprandial glucose are limitations that may present with the use of these type II DM treatments, preventing patients from reaching glycemic control. Exenatide, an incretin-mimetic subcutaneous injection, is an adjunct medication that can significantly lower hemoglobin A1c, body weight, and postprandial glucose excursions in humans and significantly improve β-cell function. It has biological effects that slow gastric emptying and decrease appetite (Van Gaal, Gutkin &, Nauck, 2008). This paper comprehensively analyzes research that compares exenatide to traditional oral medications that treat diabetes mellitus type II.

Purpose of the Study

This paper focuses on the current literature on the clinical efficacy and safety of exenatide on the treatment of type II diabetes mellitus and analyzes the medication’s purpose in reducing HbA1c and weight loss. It is a systematic review of the literature that examines exenatide compared to traditional medications that treat DM II. This paper also uses the GRADE criteria to score the strength of evidence of the literatures used in this research.

METHODS

An extensive literature search was conducted for recent studies on exenatide for Type II Diabetes Mellitus. The PubMed, Cochrane, Medline and
CINHAL databases were accessed through the Pacific University Library system. The keywords searched included “diabetes type II”, “exenatide”, “sulfonylurea”, “thiazolidinedione”, and “metformin”. The search was limited to adults; 19+ years, human subjects, the English language, free full text articles, and randomized controlled trials. The initial results included 36 articles. Articles older than the year 2000 were excluded. Only randomized, controlled trials were reviewed. In addition, articles that did not compare exenatide with traditional oral medications for diabetes were excluded. This resulted in three studies to review.

RESULTS

DeFronzo et al. (2005) studied the effects of adding exenatide to metformin to improve glycemic control. The study population was well balanced across the three treatment arms. The intent-to-treat was comprised of 336 subjects with 272 subjects completing the study and 64 withdrawing early. The subjects were between the ages of 19-72 years of age. Inclusion criteria were fasting plasma glucose concentration of < 13.3 mmol/l (<240mg/dl), BMI of 27-45 kg/m2 and HbA1c of 7.1-11.0%. Subjects had to have been using metformin at a dose of equal, to or greater than, 1,500mg/day for at least three months before screening. Stable weight for three months was also a part of the inclusion criteria. Subjects were excluded if they had used sulfonylurea, meglitinides, thiazolinediones, alpha-glucosidase inhibitors, exogenous therapy, weight loss drugs, corticosteroid drugs, drugs known to affect gastrointestinal motility, transplantation medication, or had evidence of clinically significant co-morbid conditions for three months before screening.
The study from DeFronzo et al. (2005) had three treatment arms that analyzed patients on metformin and exenatide or placebo. Metformin was at a stable dose on all three arms. Subjects that were receiving 10mg exenatide arm and 5mg exenatide arm received the study medication twice daily. At week 30, 40% (41 subjects) in 10mg exenatide arm and 27% (27 subjects) in 5mg exenatide arm, with a baseline HbA1c greater than 7%, had reached an HbA1c less than or equal to 7%. The results in the evaluable population also had similar findings. Forty-six percent of the subjects in the 10mg exenatide arm and 32% of subjects in the 5mg exenatide arm had achieved an HbA1c of less than or equal to 7% by week 30. Fasting plasma glucose levels at week 30 were $-0.6 \pm 0.2$ mmol/l ($-10.1 \pm 4.4$ mg/dl; $p=0.0001$) and $-0.4 \pm 0.3$ mmol/l ($-7.2 \pm 4.6$ mg/dl; $p<0.005$) for the 10 mg and 5mg exenatide arms, respectively, compared with $+0.8 \pm 0.2$ mmol/l ($+14.4 \pm 4.2$ mg/dl) for the placebo arm. In addition, body weight on exenatide arms demonstrates progressive weight loss from baseline. The most frequent adverse reaction from the study was mild to moderate in intensity, with the incidence of sever nausea (3.5%, 2.7%, and 1.8% in the 10-mg, 5-mg, and placebo arms, respectively). Nausea was reported to be at a higher incidence during week 0-8 and declined thereafter. There were no cases of severe hypoglycemia. The overall hypoglycemic events were 5.3% (six subjects) in the 10-mg exenatide arm, 4.5% (five subjects) in the 5-mg exenatide arm, and 5.3% (six subjects) in the placebo arm.

Buse et al. (2004) analyzed 377 randomized subjects with uncontrolled type II diabetes that had been treated with sulfonylurea at a maximum dose for
three months. One hundred seventeen of the randomized subjects withdrew due to adverse event, investigator decision, protocol violation, loss to follow-up, or loss of glucose control as defined in the protocol. General inclusion criteria were a screening fasting plasma glucose concentration of <240 mg/dl, BMI 27-45 kg/m², HbA1c 7.1-11.0%, and a stable weight (±10%) for three months. Subjects were excluded from the study if they had prior use of metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, exogenous insulin therapy, or weight-loss drugs within the prior three months.

All of the participating subjects from Buse et al. were treated with sulfonylurea (45% glipizide, 33% glyburide, 1% tolozamide, and 0.3% chlorpropamide). HbA1c values were reduced in all three treatment arms of exenatide 10 mg and exenatide 5 mg administered twice a day. The HbA1c significantly decreased in the first 12 weeks on both of the exenatide arms while the placebo arm had little change. At week 30, the HbA1c changed from a baseline of -0.86 ± 0.11% in the 10 mg exenatide arm and -0.46 ± 0.12% in the 5 mg exenatide arm compared with an increase of 0.12 ± 0.09% in the placebo arm (adjusted P • 0.0002 for pair wise comparisons). The intent-to-treat population at week 30 with baseline HbA1c >7% (n=353), 41 subjects (34.2%) in the 10 mg exenatide arm and 31 subjects (26.7%) in the 5 mg exenatide arm reached an HbA1c • 7%, results that were significantly greater than the placebo arm (9 subjects [7.7%]; P•0.0001 for pairwise comparisons). The evaluable population at week 30 with a baseline HbA1c >7% (n=237), 33 subjects (41.3%) in the 10 mg exenatide arm and 28 subjects (32.6%) in the 5 mg exenatide arm
reached an HbA1c •7%, and these proportions of evaluable population were significantly greater than the placebo group (6 subjects [8.8%]; p• 0.0002 for pairwise comparisons). Fasting glucose concentrations after week 30 in the 10- and 5-mg exenatide arms were reduced by -0.6 ± 0.3 and -0.3 ± 0.2 mmol/l from baseline, respectively, compared with an increase of 0.4 ± 0.3 mmol/l in the placebo arm (P<0.05 vs. placebo for the 10-mg arm only). Weight loss in both the 10- and 5-mg exenatide arms were identified; the 10-mg exenatide arm demonstrated a progressive weight loss over the entire 30 weeks, with an end-of-study weight loss of -1.6± 0.3 kg from baseline (P<0.05 vs placebo). Subjects in the 5-mg exenatide arm experienced a weight loss of -0.9 ± 0.3 from baseline (NS vs placebo). The most frequent adverse event during the study was mild to moderate gastrointestinal symptoms. Nausea was generally described to be mild or moderate in intensity and peaked during the initial weeks of dosing (weeks 0-8), then decreased in incidence thereafter. The incidence of severe nausea was low (5% in the 10-mg exenatide arm, 5% in the 5-mg exenatide arm, and 2% in the placebo arm). There were no severe incidences of hypoglycemic events in this study. The overall incidences of mild to moderate hypoglycemia were 36% in the 10-mg exenatide arm, 14% in the 5-mg exenatide arm, and 3% in the placebo arm.

The Zinman et al. (2007) study was a randomized, double blind study with a sample size of 233 subjects (exenatide group, n=121; placebo group, n=112) with type II diabetes that are sub-optimally controlled with thiazolidinedione (TZD). The study was 16 weeks long with a 2-week, single blind, placebo lead-in
period that resulted in 233 patients who were randomly assigned and analyzed in the intention-to-treat sample. The exenatide and placebo group were similar in age, body weight, duration of disease, and glycemic control. At 16 weeks, results demonstrated a mean HbA1c decrease of 0.89% ± 0.09% in the exenatide group (p<0.001); but a mean of 0.09%±0.10% in the placebo group. The mean-between-group difference in HbA1c 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 A1c levels of 7% or less (p < 0.001), and 30% and 8% of patients, respectively, achieved hemoglobin A1c levels of 6.5% or less (P< 0.001). Mean fasting serum glucose levels decreased more in the exenatide (intention-to-treat sample) group (mean [± SE] change, -1.59 ± 0.22mmol/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) (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 HbA1c levels (P=0.87 for interaction). Patients treated with exenatide and TZD alone (n=27), had mean HbA1c levels that decreased from 7.93% (SD, 0.87%) to 7.15% (SD, 1.05%), and patients treated with exenatide and TZD in combination with 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 HbA1c 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%).

The most common adverse event from the Zinman et al. (2007) study was nausea, which is also the main reason for withdrawal from the study. Approximately 9% of the exenatide group and 1% of the placebo group withdrew from the study because of nausea. Most reports of nausea had occurred after an increase of dosage from 5mg to 10mg of exenatide twice daily; reports of nausea had declined at approximately week 8 from 41 subjects and week 16 from 19 subjects. 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]). No severe hypoglycemia was reported.

**DISCUSSION**

Maximizing medication management to improve glycemic control is important in the treatment of type II diabetes. New medications and treatment regimens are aimed at improving glycemic control and ultimately preventing the variety of complications associated with poorly controlled diabetes. In an effort to evaluate the outcome of adding exenatide to existing medical management regimen, this systematic review studied several published manuscripts.

The outcomes reviewed included HbA1c, fasting plasma glucose, and body weight. DeFronzo et al. (2005), Buse et al. (2004), and Zinman et al.
all observed notable reductions in these measures during their investigations. The study from Defronzo et al. (2005) demonstrated an overall improvement in HbA1c achieving the desired result of less than 7% from nearly 50% of participants who had taken 10-mg of exenatide. Subjects who had taken 5-mg of exenatide also demonstrated a reduction of HbA1c and plasma glucose but it was not as effective in taking 10-mg of exenatide. The 10-mg exenatide arm also demonstrated overall weight loss that was coupled with improved glycemic control. It is important to note that the weight loss that was observed did not plateau during the 30-week study. The most common side effect of exenatide was dose-related nausea, which occurred in only 3% in the 10-mg exenatide arm. Subjects described their nausea to be mild to moderate in intensity, occurring mostly during weeks 4-8. No hypotension was observed in Defronzo et al. (2005) study.

Buse et al. (2004) also demonstrated similar and consistent results with DeFronze et al. (2005) in their 30-week study of exenatide and sulfonylurea. They observed long-term use of exenatide at fixed doses of 5 and 10mg twice a day, greatly improved glycemia in patients failing sulfonylurea therapy. The biggest difference between Buse and Defronzo studies is the hypoglycemic events that occurred more in the Buse et al. (2004) study. It appears that hypoglycemia occurred more readily in subjects who had been taking the 10mg dose of exenatide and sulfonylurea. Events of hypoglycemia were described to be mild to moderate in intensity. It is important to note that when exenatide was used in conjunction with metformin in the DeFronzo et al. (2005) study, no
hypoglycemia was observed. It is possible to speculate that the sulfonylurea itself is what could have caused the hypoglycemic events.

Defronzo et al. (2005) and Buse et al. (2004) both produced adequate data demonstrating a reduction of HbA1c and fasting plasma glucose, however, during the weeks of 24-30 in all three-treatment arms (placebo, 5-mg, and 10mg exenatide) demonstrated a slight increase in HbA1c. No explanations were found in both studies explaining the reason for the increase of HbA1c. It is possible that it was not exenatide related since a slight increase in the placebo group was also identified. The lack of explanation could be potential weakness of both studies.

The 16-week study conducted by Zinman et al. (2007) demonstrated that exenatide in combination with TZD improves HbA1c, fasting blood glucose, and postprandial glucose in patients suboptimally controlled with TZD alone or in combination with Metformin. Reduced weight loss had also been a consequence by the use of exenatide. Subjects reported no clinical hypoglycemic events. The most common adverse event reported by subjects was nausea. The 16-week study is prone to criticism because researchers could not assess sustained reduction of HbA1c, glucose control and weight loss maintenance from exenatide from a short study. However, it is safe to conclude that a reduction in HbA1c is observed in a relatively short study.

The Grading of Recommendations Assessment Development and Evaluation (Grade) was used in this paper to evaluate the quality of evidence and strength of recommendations provided in this study. All literatures chosen from
the DeFronzo et al. (2005), Buse et al. (2004), and Zinman et al. (2007) were randomized control trials, which are a “high” type of evidence according to the GRADE criteria. All studies of exenatide had achieved their desired outcome of decreased HbA1c, fasting glucose and weight loss from a large magnitude of participants. However, higher doses of exenatide demonstrated a greater decrease of HbA1c from all studies. According to these studies that were analyzed, exenatide is an effective medication for type II diabetics who have maximally used traditional oral hyperglycemic medications. It is also important to note that patients could potentially lose weight with this medication and may attract overweight type II diabetics. The only bias that had been identified in this paper is the study from Zinman et al. (2007), which was sponsored by Eli Lilly Company, Indianapolis, Indiana. This bias had downgraded the desired outcomes score to “moderate”. A “moderate” score means that future research could have an important impact on data that may or may not change clinical effects. In addition, further research on dose optimizing regimens could be evaluated. The literatures that were discussed in this research paper only evaluated the clinical effects of 5mg and 10 mg of exenatide. Perhaps a longer study that titrates exenatide from 5mg to 10mg could potentially find an optimized dosing regimen. Ultimately, this medication scored a “moderate” on the overall GRADE of evidence. This means that clinicians who wish to use exenatide have supportive evidence of its safety and clinical efficacy.

In summary, this research paper reviewed clinical trials on adding exenatide to oral hyperglycemic in sub-optimally controlled type II diabetics. Data
demonstrated dose-related subcutaneous administration of exenatide appeared to reduce HbA1c, fasting blood glucose and had a positive effect on weight reduction. The biggest concern of exenatide is dose-related nausea that occurred during the first few weeks, which gradually improved after the 8th week in DeFronzo et al. (2005) and Buse et al. (2004) studies.

REFERENCES


APPENDIX

Table 1. Strength of evidence
<table>
<thead>
<tr>
<th>Evidence</th>
<th>Study Quality</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Large Magnitude</th>
<th>Dose-Response</th>
<th>Confounders</th>
<th>Outcome</th>
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<td>Exenatide vs. traditional oral hyperglycemic medications</td>
<td>Decrease in HbA1c</td>
<td>3 RCT</td>
<td>Decreased HbA1c</td>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Fasting glucose</td>
<td>Decreased fasting glucose</td>
<td>3 RCT</td>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Progressive weight loss</td>
<td>3 RCT</td>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycemic events</td>
<td>No severe hypoglycemic events, but most mild to moderate hypoglycemic events were found in the sulfonylurea study</td>
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