One-year exenatide and insulin glargine treatment improves prandial beta-cell response in metformin treated patients with type 2 diabetes

Mathijs C. Bunck, Andrea Mari, Anja Cornér, Bjorn Eliasson, Rimma M. Shaginian, Robert J. Heine, Ulf Smith, Hannele Yki-Järvinen, Marja-Riitta Taskinen, Michaela Diamant

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Chapter 4

Abstract

Background: We recently reported that exenatide twice daily improved hyperglycemic clamp derived measures of beta-cell function, when compared to insulin glargine. Here we report the effect of these therapies on the beta-cell response to a physiological stimulus, i.e. a mixed meal.

Methods: Sixty-nine patients with type 2 diabetes were randomized to exenatide (n=36) or insulin glargine (n=33). Beta-cell function was measured using modeling based on C-peptide deconvolution from a standardized breakfast at t=0h and lunch at t=4h each containing 50g fat, 75g carbohydrates, and 35g protein. Meal tests were performed at baseline, after 51-weeks treatment and at 5 weeks off treatment.

Results: One-year exenatide versus insulin glargine treatment resulted in a greater upward shift in the glucose/insulin dose-response relation (between group geometric LS mean ratio±SEM: 1.41±0.17, P=0.007 (ISR@7.0mM); 1.32±0.16, P=0.025 (ISR@7.5mM) and 1.26±0.15, P=0.060 (ISR@8.0mM)). Additionally, exenatide increased potentiation after both breakfast and lunch compared to insulin glargine (between group geometric LS mean ratio±SEM: 1.26±0.11; P=0.010 and 1.19±0.11; P=0.054, for [170-190min]-to-basal and [240-480min]-to-basal respectively). Both exenatide and insulin glargine treatment equally improved glucose sensitivity. After the 5-week off-drug period, the glucose/insulin dose-response relation remained improved in both treatment groups. All other measures returned to pre-treatment values.

Conclusions: One-year of exenatide versus insulin glargine had a greater effect on both the prandial insulin secretion rate and the potentiation of the glucose/insulin dose-response relation. The beneficial effects on the glucose/insulin dose response relationship were sustained after a 5-week off-treatment period in both the exenatide and insulin glargine treated groups.
Introduction

We previously showed that 52-week exenatide treatment improved various aspects of beta-cell function, as measured during a hyperglycemic clamp in patients with type 2 diabetes treated with metformin, as compared to insulin glargine (1). The hyperglycemic clamp is regarded as gold-standard method for general beta-cell function testing, but the limitation is the non-physiologic nature of the test. In addition the test is demanding and time-consuming, making the technique unsuitable for large-scale follow-up studies. By design, during the hyperglycemic clamp glucose and/or other secretagogues are administered intravenously to test beta-cell function. However, other nutrients and gut derived peptides, and neurological signaling play an important role in beta-cell function in the prandial state (2). By bypassing the gastrointestinal tract, the hyperglycemic clamp may not allow us to fully appreciate the complex physiology of beta-cell function in real-life situations (3).

Recently, we reported exenatide, relative to insulin glargine, to improve postprandial glucose, triglyceride and free fatty acid excursions following an 8-hour, mixed-meal test (4). These findings are consistent with earlier studies with exenatide during a single meal test, and only while on active treatment (5, 6). The design of studies by Heine and co-workers, and Schwartz and colleagues differed substantially from the approach we used (4-6). To simulate the real-life situation we used both a breakfast and lunch meal, and to study whether these effects are sustained, we repeated the meal-test following a 5-week off-therapy period (4).

Data from our hyperglycemic clamp (1) and meal-test (4) study needed additional elucidation. First, the magnitude of the C-peptide response, relative to glucose, during the meal test was increased by both exenatide and insulin glargine administration. Second, the observed rise in postprandial C-peptide in the exenatide treated patients did not appear to be as large as seen following the hyperglycemic clamp (1, 4). This may be secondary to the different physiological principles tested with either procedure. Therefore, evaluation of the effects of exenatide, and insulin glargine on beta-cell function in more physiological conditions, i.e. a mixed-meal test. Finally, no durable effect on C-peptide secretion per se was shown after the cessation of therapy with either the hyperglycemic clamp or mixed-meal test. A more integrated approach may provide additional information on a possible durable effect of beta-cell function of either therapy.

Over recent years, mathematical models have been developed to quantify the beta-cell response following an oral glucose load or standardized mixed meal test. These models describe the dynamic relationship between ambient glucose and insulin/C-peptide concentrations to assess beta-cell function,
independent of the confounding effects of differences in fasting and postprandial plasma glucose concentrations among treatment groups and/or gastric emptying rates (7, 8). Post-hoc analyses of placebo controlled, phase-3, clinical trials showed exenatide to improve these model derived measures of beta-cell function following a mixed meal test (9). These results are consistent with studies using GLP-1 (10), the GLP-1 receptor agonist liraglutide (11), and the DPP-4 inhibitor vildagliptin (12, 13). The aim of the current study was to compare the effects of exenatide or insulin glargine, on model derived measures of beta-cell functioning following two subsequent breakfast and lunch meals, after 51-weeks of treatment. To study a possible sustainable effect of either treatment on beta-cell function, we repeated the meal-test following a 5-week off-drug period.

Research design and methods

Subjects and study design
Details on study design were reported previously (1). Briefly, 69 patients were randomized (using a permuted block randomization scheme stratified by site and baseline HbA₁c stratum (≤ 8.5% or > 8.5%)) at the three study sites, in Finland, Sweden and the Netherlands (Figure 4.1). Sixty patients (exenatide n=30; insulin glargine n=30) completed both the pre-treatment and on-drug meal test and are included in the current analysis (evaluable population); 47 patients participated in the off-drug meal test (exenatide n=25; insulin glargine n=22). Patients randomized to exenatide initiated treatment at a dose of 5 µg twice daily (BID) for a period of 4 weeks, followed by dose increase to 10 µg BID. If needed, exenatide was titrated to a maximum dose of three times (TID) 20 µg, or the maximum tolerated dose, when HbA₁c value at two consecutive visits ranged between 7.1 and 7.4%, or when HbA₁c was >7.4% at any given visit. Patients randomized to insulin glargine started with an initial dosage of 10 IU once daily (QD) at bedtime, followed by self-adjustment of the daily dose according to a fixed-dose treat-to-target (fasting plasma glucose (FPG) <5.6 mmol/l) algorithm, as previously described (14). At 52-weeks the mean±SEM insulin glargine dose used was 33.6±3.5 units per day. The corresponding fasting SMBG in the insulin glargine treated group was 5.6±0.2 mmol/l (1). The study protocol was approved by each site’s ethics review committee and was in accordance to the principles described in the declaration of Helsinki. Patients were recruited at the local sites and through advertising. All participating patients gave their written informed consent prior to screening. This study is registered with ClinicalTrials.gov number NCT00097500.
Exenatide postprandial beta-cell function

Figure 4.1 Protocol flow-chart and patient disposition.

**Standardized mixed meal test**

The overall meal test design is shown in Figure 4.2B. Patients arrived at the study center after an overnight fast. A cannula was inserted into the non-dominant dorsal hand or wrist vein and maintained in a heated box at 50° Celsius for blood collections. Two sequential mixed meal tests were performed prior to randomization, following 51-weeks of treatment, and after a 5-week off-drug period (Figure 4.2A). At the meal visit, each subject received two standardized fat-rich mixed-meals at breakfast (08:30 hours)
and lunch time (12:30 hours). Each meal consisted of 50 g of fat, 75 g of carbohydrates and 35 g of protein. The breakfast consisted of an Egg McMuffin® (McDonald’s), croissant with butter, 200 mL of milk, combined with 20 mL of cream. The lunch consisted of Quarter Pounder® (McDonald’s), croissant with butter, and 200 mL of milk. The subjects were instructed to consume each meal within 15 min. Blood samples for determination of glucose, insulin and C-peptide were collected at times -15, 0, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 250, 255, 260, 270, 285, 300, 330, 360, 420, 480 minutes. During the meal test at week 51, patients received their study medication at the protocol specified time, which were chosen according to the current prescription guidelines. Patients randomized to exenatide were given the study drug 15 minutes prior to breakfast (no exenatide was given prior to the lunch meal) and patients randomized to insulin glargine received their last insulin dose the night before at bedtime. We analyzed the effects on prandial beta-cell function of either therapy on both (breakfast and lunch) meals combined to further match real-life conditions.

**Beta-cell function model**

For each patient the insulin secretion rate (IRS) was calculated from C-peptide deconvolution (15) and expressed per square meter body surface
Exenatide postprandial beta-cell function

area. Pancreatic beta-cell function was assessed with a model that describes the relationship between insulin secretion and glucose concentration, which has been described in detail previously (7, 8). The model expresses insulin secretion (in pmol/min per m² of body surface area) as the sum of two components. The first component represents the dependence of insulin secretion on the absolute glucose concentration at any time point during the meal test and is characterized by a dose-response function relating the two variables. Characteristic parameters of the dose-response are the mean slope within the observed range \( \text{ISR}_{\text{gref}} \) (Insulin Secretion Rate at glucose reference concentration), denoted as beta-cell glucose sensitivity (bGS), and the insulin secretion at a fixed glucose concentration \( \text{ISR}_{gref} \). The dose-response is modulated by a potentiation factor, which accounts for several potentiating signals to the beta-cell (e.g. non-glucose metabolites, incretin hormones and (gut-related) neuronal inputs). The potentiation factor is set to be a positive function of time and to average one during the entire duration of the meal test. It thus expresses a relative potentiation of the secretory response to glucose. The excursion of the potentiation factor was quantified using a ratio between mean values at times 170-190 and 0-10 min for, and is called the potentiation factor ratio (PFR). The second insulin secretion component represents a dynamic dependence of insulin secretion on the rate of change of glucose concentration. This component is termed the derivative component and is determined by a single parameter, denoted as rate sensitivity, which is related to early insulin release (7, 8).

Laboratory analyses

Plasma glucose concentrations were measured at bedside using an YSI 2300 STAT Plus (Yellow Springs Instruments, Yellow Springs, OH) in Sweden and the Netherlands, and using a Beckman Coulter Glucose Analysrer 2 (Beckman Coulter, Fullerton, CA) in Finland. Serum was separated by centrifugation (1300-1500 g) and stored at -80° Celsius until analysis. Insulin and C-peptide samples were analyzed at the VU University Medical Centre using an immunoradiometric assay (Centaur; Bayer Diagnostics, Mijdrecht, the Netherlands). HbA₁c (normal range: 4.3 to 6.1%, DCCT standardized Biorad assay), FPG and serum safety parameters were performed by a central laboratory (Quintiles International, Livingston, United Kingdom).

Statistical analysis

All outcome measures are compared between the two treatment groups using an analysis of covariance (ANCOVA) model. The model includes factors for treatment group (exenatide/insulin glargine), site (NL/SE/FIN),
and baseline HbA1c stratum (≤8.5%/>8.5%), and the pre-treatment variable of the corresponding dependent variable as a covariate. Statistical analysis was done using SPSS 16.0 for Mac OS X (SPSS, Chicago, IL, USA). All inferential statistical tests were conducted at a significance level of 0.05 (two-sided). Unless otherwise stated, data are presented as mean (±SEM).

Results

Patient disposition and pre-treatment clinical characteristics

No between-group differences in patient characteristics were observed at baseline (Table 4.1). Postprandial profiles of glucose, insulin and C-peptide were superimposable prior to treatment with either exenatide or insulin glargine in both treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Exenatide (n=36)</th>
<th>Insulin Glargine (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.4±1.4</td>
<td>58.3±1.3</td>
</tr>
<tr>
<td>Male sex (n (%))</td>
<td>23 (63.9)</td>
<td>22 (66.7)</td>
</tr>
<tr>
<td>Caucasian race (n (%))</td>
<td>36 (100)</td>
<td>32 (97.0)</td>
</tr>
<tr>
<td>Duration of type 2 diabetes (years)</td>
<td>5.7±0.8</td>
<td>4.0±0.6</td>
</tr>
<tr>
<td>Daily metformin dose (mg)</td>
<td>2058±117</td>
<td>1798±147</td>
</tr>
<tr>
<td>Statin use (n (%))</td>
<td>16 (44.4)</td>
<td>20 (60.6)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>90.6±2.1</td>
<td>92.4±2.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.9±0.7</td>
<td>30.1±0.6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.6±0.1</td>
<td>7.4±0.1</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>9.4±0.4</td>
<td>8.9±0.4</td>
</tr>
<tr>
<td>Completed study (n (%))</td>
<td>30 (83.3)</td>
<td>30 (90.9)</td>
</tr>
<tr>
<td>Discontinued study (n (%))</td>
<td>6 (16.7)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Discontinued study due to adverse events (n (%))</td>
<td>5 (13.9)</td>
<td>1 (3.0)</td>
</tr>
</tbody>
</table>

Table 4.1 Pre-treatment characteristics and patient disposition. Data represent mean±SEM or n (%).
Postprandial glucose, insulin, C-peptide and insulin secretion rate

Figure 4.3 depicts post-prandial plasma glucose (Figure 4.3A-B), and serum C-peptide (Figure 4.3C-D) and calculated insulin secretion rate (ISR) (Figure 4.3E-F) concentrations after 1-year of treatment and following a 5-week off-drug period.

As expected, insulin glargine treatment mainly affected fasting plasma glucose concentrations, whereas exenatide predominantly lowered postprandial glucose concentrations (Figure 4.3A). Following one-year treatment mean±SEM incremental glucose AUC0–480min concentrations were 401±80 mmol×min/l for exenatide and 1303±127 mmol×min/l for insulin glargine (between group difference iAUC±SEM change from pre-treatment: -788±126 mmol×min/l, p<0.001). The between group difference in postprandial glucose excursion was mainly attributed to the effect of exenatide on the breakfast (t=0 to 240 minutes) meal (between group difference iAUC±SEM change from pre-treatment: -519±69 mmol×min/l, p<0.0001), whereas no difference in postprandial glucose excursions was found following the lunch (t=240 to 480 minutes) meal (between group difference iAUC±SEM change from pre-treatment: 44±75 mmol×min/l, p=0.559). Both exenatide and insulin glargine treatment significantly increased the glucose adjusted ISR AUC0–480min, with exenatide showing a statistical significant larger increase as compared to insulin glargine (between group AUC±SEM ratio to pre-treatment: 1.14±0.08 mmol×min/l p<0.001).

Model derived measures of beta-cell function

Model derived beta-cell function parameters are presented in Figure 4.4 and Table 4.2. One-year exenatide treatment resulted in a significantly greater upward shift in ISR across the observed range of glucose concentrations (between group geometric LS mean ratio±SEM: 1.41±0.17, P=0.007 (ISR@7.0mM); 1.32±0.16, P=0.025 (ISR@7.5mM) and 1.26±0.15, P=0.060 (ISR@8.0mM). Additionally, exenatide treatment increased the potentiation factor ratio after both breakfast and lunch meals compared to insulin glargine (between group geometric LS mean ratio±SEM: 1.26±0.11; P=0.010 and 1.19±0.11; P=0.054, for [170-190min]-to-basal and [240-480min]-to-basal respectively). Both exenatide and insulin glargine treatment equally improved bGS (median[IQR] change from PT: exenatide: 7.9[2.2-27.5], P<0.001; insulin glargine: 12.8[5.6-29.3], P<0.001, between group comparison P=0.544).
Figure 4.3A-D Plasma glucose and serum C-peptide concentrations during the meals, before and after one-year active treatment (A&C), and after a 5-week off-drug period (B&D). Insulin secretion during the meals, before and after one-year active treatment (E), and after a 5-week off-drug period (F). Data represent mean (SEM). Data represent mean (SEM). Black circles/solid line = exenatide; white circles/hatched line = insulin glargine. Grey line = all subjects (combined exenatide and insulin glargine) pre-treatment.
Exenatide postprandial beta-cell function

After the 5-week off-drug period, $\text{ISR}_{\text{ref}}$ remained improved in both the exenatide and insulin glargine treated patients without a significant difference between the two treatments (Table 4.2). All other model derived beta-cell function measures returned to pre-treatment values.

**Figure 4.4A-D** Beta-cell dose response curve and potentiation factor after one-year active treatment (A&C), and after a 5-week off-drug period (B&D). Data are mean (SEM). Black circles/solid line = exenatide; white circles/hatched line = insulin glargine. Grey line = all subjects pre-treatment.

**Adverse effects and tolerability**
As reported previously, exenatide and insulin glargine treatment was generally well tolerated (1). Mild-to-moderate hypoglycemia (exenatide 8.3%; insulin glargine 24.2%) and nausea (exenatide 50%; insulin glargine 0%) were the most frequently reported adverse events. There were no major hypoglycaemic events observed during this study.
<table>
<thead>
<tr>
<th>ISR at 7.0 mmol/l</th>
<th>PFR breakfast meal</th>
<th>Glucose Sensitivity</th>
<th>Rate Sensitivity</th>
<th>Rate Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Glargine</td>
<td>128.5±16.5</td>
<td>35.3 (25.8-47.8)</td>
<td>38.9 (21.3-46.6)</td>
<td>202.2 (0.0-381.4)</td>
</tr>
<tr>
<td>Exenatide</td>
<td>143.4±18.6</td>
<td>158.6±20.8</td>
<td>115.9±24.1</td>
<td>174.2 (0.0-381.4)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean or median change</td>
<td>164.1±16.8</td>
<td>222.4±21.8</td>
<td>237.1±22.7</td>
<td>342.0 (0.0-381.4)</td>
</tr>
<tr>
<td>P value</td>
<td>0.069</td>
<td>0.006</td>
<td>&lt;0.001</td>
<td>0.063</td>
</tr>
<tr>
<td>Mean or median change</td>
<td>167.7±22.3</td>
<td>216.4±24.0</td>
<td>163.3±26.6</td>
<td>128.9 (0.0-381.4)</td>
</tr>
<tr>
<td>P value</td>
<td>0.106</td>
<td>0.039</td>
<td>0.004</td>
<td>0.527</td>
</tr>
<tr>
<td>Mean or median change</td>
<td>167.7±22.3</td>
<td>1.26±0.15</td>
<td>1.26±0.11</td>
<td>128.9 (0.0-381.4)</td>
</tr>
<tr>
<td>P value</td>
<td>0.007</td>
<td>0.060</td>
<td>0.010</td>
<td>2.2 (-11.6-16.0)</td>
</tr>
<tr>
<td>Mean or median change</td>
<td>13.4 (7.5-23.4)</td>
<td>0.97±0.12</td>
<td>1.03±0.11</td>
<td>0.054</td>
</tr>
<tr>
<td>P value</td>
<td>0.830</td>
<td>0.002</td>
<td>0.650</td>
<td>0.662</td>
</tr>
</tbody>
</table>

Table 4.2 Model derived measures of prandial beta-cell function. Data represent geometric mean±SEM with LS mean ratio±SEM to pre-treatment or median (IQR) change from pre-treatment.
Discussion
Our study demonstrated that exenatide, as compared to the active comparator insulin glargine, improves different aspects of model-derived beta-cell function parameters in patients with type 2 diabetes, as measured during a mixed-meal. One-year treatment with exenatide resulted in a significantly greater increase in the glucose/insulin secretion dose-response relation, as compared to that in insulin glargine treated patients. Since glycemic control was similar for both treatments, this improvement cannot be solely attributed to an improvement of glycemic control, and therefore a GLP-1RA related factor should therefore be considered (1, 16). These findings are consistent with earlier studies with GLP-1 (10), liraglutide (11), and vildagliptin (13), which have all reported an improvement of the glucose/insulin dose-response function. Unfortunately, since these studies used a placebo rather than an active comparator as control, a difference in HbA1c was observed at end-point, which precludes the distinction between a beneficial action of the study drug and the deleterious impact of glucose toxicity in the placebo group, making direct comparison more difficult.
This additional analysis supports our earlier findings showing that exenatide improved hyperglycemic clamp derived measures of beta-cell function as compared to insulin glargine(1). However, there are some important differences. First, in contrast to the clamp study, beta-cell function (measured as the glucose/insulin dose-response relation) was augmented also with insulin glargine. This augmenting effect on beta-cell function in the insulin glargine treated patients was also evident by the substantial reduction in the postprandial glucose levels paralleled by a relatively small change in accompanying C-peptide concentrations. This result, which agrees with a previous study in similar conditions of insulin-induced glucose lowering (17), indicates that the hyperglycemic clamp provides different, information regarding beta-cell function than tests using nutrients or insulin secretagogues administered via the oral route (3). The most likely reason is the route of insulin secretagogue administration, which elicits a cascade of gut-derived hormonal and neural responses that affect islet responses and glucose homeostasis.
Modeling analysis showed that the greater beta-cell function improvement with exenatide compared to insulin glargine concerns in particular a phenomenon referred to as the potentiation factor, which denotes all factors that contribute to the secretion complimentary to circulating glucose. Additionally, a more pronounced upward shift of the beta-cell dose-response, as assessed by insulin secretion at a reference glucose level was observed. The latter effect is likely a consequence of the former; since the model-determined dose-response represents the average relationship between insulin secretion and glucose concentration, a more marked and
sustained potentiation effect, as observed with exenatide, increased the average insulin secretion levels and shifted the relationship upward. Notably, these effects of exenatide versus placebo have been observed in a previous study using similar methodology (9). In addition, these effects are similar to those observed with GLP-1 (10) and the GLP-1RA liraglutide (11), suggesting that the beta-cell function improvement of exenatide compared to insulin glargine is specifically mediated by GLP-1R stimulation, i.e. potentiating effect.

An important novelty of this study is that after five weeks of treatment cessation a modest improvement in some model-derived beta-cell function parameters is still detectable in both the exenatide and insulin glargine treated patients. In particular, the upward shift of the beta-cell dose-response, quantified by insulin secretion at fixed glucose levels, is still present. It has been hypothesized, although human islet-cell biology differs widely from that in rodents, that long-term GLP-1RA treatment may enhance beta-cell mass or health in humans, thereby potentially modifying the progressive course of type 2 diabetes (18). In addition, insulin sensitivity remained improved over pre-treatment values, which may be an effect secondary to the observed reduction in body weight (1). Our finding of a possible sustained effect following the wash-out, is in contrast to our previously reported hyperglycemic clamp results, where all beta-cell parameters returned to pre-treatment values following cessation of treatment (1). In comparison, a large placebo controlled study, 52-week treatment with the DPP-4 inhibitor vildagliptin (50 mg QD) improved several model-derived measures of beta-cell function (13). The effects on beta-cell function and glycemic control were not sustained following a 4-week wash-out period (13, 19). In contrast to our study, the vildagliptin 50 mg QD study by Mari and co-workers did not show a sustained improvement in FPG at the time of the off-drug meal test which may partly explain the observed between study difference (13, 19). GLP-1 receptor agonists stimulate the receptors directly at pharmacological levels, whereas DPP-4 inhibitors affect the endogenous physiological GLP-1 levels, which retain their diurnal pattern (20). Indeed, differences in therapeutic effects between GLP-1RA and DPP-4 inhibitors have been demonstrated previously (21).

The sustained effect following drug cessation is a potentially important finding that may suggest a disease modifying effect. Based on studies in rodents, it has been suggested that the use of GLP-1RA may promote beta-cell mass expansion (22). However, as the observed lasting effect was also found for insulin glargine, this argues a more general mechanism related to alleviation of glucose toxicity (16). Indeed, the persistence of an improvement in beta-cell function after any glucose-lowering treatment, including insulin, has been previously shown several times (23-25).
Interestingly, the present study shows a statistically significant decrease in rate sensitivity in the exenatide-treated patients, when compared to insulin glargine. Rate sensitivity appreciates the relationship between the early, fast rise in plasma glucose concentrations and the subsequent change in insulin secretion. However, in addition to insulin stimulation and glucagon suppression, exenatide lowers postprandial glucose concentrations due to slowing down of gastric emptying. Therefore, exenatide has a profound postprandial glucose lowering effect during the initial period of the meal test. As a result, the observed delta in glucose concentration is negative in the exenatide group. This reduction in postprandial glucose concentration may account for the reduction in rate sensitivity as provided by the model (7, 8). Insulin glargine does not have such an effect on the postprandial glucose concentration, and therefore on rate sensitivity. Our finding is consistent with the observations made in similar experiments with GLP-1 infusion (10) and liraglutide (11). In contrast, no reduction in postprandial glucose and rate sensitivity was observed after vildagliptin administration (12, 13). On the contrary, rate sensitivity has shown to drop dramatically when FPG concentrations exceed 6.4 mmol/l (26). In our study, although no difference was observed in achieved HbA1c at 52 weeks, there was a statistically significant difference in FPG (exenatide 7.8±0.3 mmol/l, insulin glargine 5.85±0.9 mmol/l, p<0.0001) (1). This may therefore, partially, explain the observed between group difference in rate sensitivity after one-year treatment. This idea is strengthened by that after cessation of treatment the between-group difference in FPG disappeared as did rate sensitivity.

Finally, our unique design, with breakfast and lunch meal, mimicking real-life conditions, reveals another interesting observation: the disappearance of the Staub-Traugott effect in both the exenatide and insulin glargine treatment group while on active treatment. The Staub-Traugott effect explains the improvement of carbohydrate tolerance following repeated glucose administration, and the peak glucose excursion following a second meal is expected to be lower when compared to the first stimulus. Glucose potentiation and suppression of endogenous glucose release are the main mechanisms underlying the Staub-Traugott effect (27). Although not statistically significant, we observed a numerical reduction in potentiation following the second meal in the insulin glargine treated patients. Studies using acetaminophen have shown exenatide to slow gastric emptying (28, 29). Late appearance of breakfast meal derived glucose may play a part in the loss of the Staub-Traugott effect in exenatide treated patients (4). Unfortunately, we did not measure gastric emptying or endogenous hepatic glucose production in our study. Interestingly, the Staub-Traugott phenomenon returned when both exenatide and insulin glargine treatment was stopped, suggesting an acute effect of either treatment.
In conclusion, our study demonstrated that one-year exenatide treatment improved model derived measures of postprandial beta-cell functioning when compared to an active comparator [i.e. insulin glargine] tested using a sequential breakfast and lunch mixed-meal in patients with type 2 diabetes, in the presence of similar improvements of glucose control. In addition, after five week of drug cessation, some effect on beta-cell function was still present with both drugs, although impact on glucose control appeared to be small.

Acknowledgments
We thank the patients for participating in the study. This study was sponsored by Amylin Pharmaceuticals, Inc. and Eli Lilly and Company. The study was collectively initiated and designed by the investigators from the three study sites. The investigators had full access to the trial data and had control over the statistical analysis and interpretation of the study results. Parts of this report were presented as an oral presentation at the 45th Annual Meeting of the European Association for the Study of Diabetes, Vienna, Austria, September 29th – October 2nd 2009.
Exenatide postprandial beta-cell function

References


Exenatide postprandial beta-cell function


