Effect of the GLP-1 Receptor Agonist Exenatide on Impaired Awareness of Hypoglycemia in Type 1 Diabetes: A Randomized Controlled Trial

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Context: Impaired awareness of hypoglycemia (IAH), resulting from habituation to recurrent hypoglycemia, can be reversed by strict avoidance of hypoglycemia. Adjunctive treatment with glucagon-like peptide-1 receptor agonists may reduce glucose variability, hence lower the risk of hypoglycemia and improve awareness. The aim of our study was to investigate the effect of exenatide on awareness of hypoglycemia in patients with type 1 diabetes and IAH.

Methods: This was a randomized double-blind, placebo-controlled crossover trial. Ten patients with type 1 diabetes and IAH were included [age, 38.5 ± 4.4 years; 40% males; glycated hemoglobin 7.2% ± 0.4% (55.2 ± 4.8 mmol/mol)]. Patients were treated with exenatide 5 μg twice daily (first two weeks), followed by 10 μg twice daily (remaining four weeks) or matching placebo, with a four-week washout period. Patients wore blinded glucose sensors in the final weeks and modified hyperinsulinemic normoglycemic-hypoglycemic glucose clamps (nadir 2.5 mmol/L) were performed at the end of each treatment period.

Results: Treatment with exenatide caused body weight to decrease compared with placebo (−3.9 ± 0.9 vs 0.6 ± 1.2 kg, $P = 0.047$). Exenatide did not change mean 24-hour glucose levels (8.3 ± 0.4 vs 8.5 ± 0.3 mmol/L, exenatide vs placebo, $P = 0.64$), median (interquartile range) percentage of time spent in hypoglycemia [15.5 (4.5, 25.5) vs 7.8 (4.4, 17.1)%, $P = 0.11$] and frequency of hypoglycemia (15.8 ± 3.7 vs 12.1 ± 3.5, $P = 0.19$). Symptom scores in response to clamped hypoglycemia were similar between exenatide [median change 1.0 (−1.5, 7.0)] and placebo [4.5 (1.5, 5.8), $P = 0.08$].

Conclusions: Six weeks of treatment with exenatide did not improve awareness of hypoglycemia in patients with type 1 diabetes and IAH. (***J Clin Endocrinol Metab*** **104: 4143–4150, 2019)**

Iatrogenic hypoglycemia is the most frequent acute complication of insulin therapy in patients with type 1 diabetes (1). Patients with type 1 diabetes experience on average two to three hypoglycemic events per week and one severe event requiring external assistance every year (2, 3). Accurate and timely recognition of the typical symptoms of decreasing plasma glucose levels are of pivotal importance to prevent severe hypoglycemia. Approximately 25% of patients with type 1 diabetes have lost the ability to detect hypoglycemia, a condition referred to as impaired awareness of hypoglycemia (IAH) (4, 5), which increases the risk for severe hypoglycemia up to sixfold (6). IAH is usually the end result of a process of brain adaptation to recurrent hypoglycemia. Meticulous avoidance of hypoglycemia for two to four weeks can reverse this process, thus ameliorating symptomatic awareness of hypoglycemia (7, 8). Not uncommonly, marked glucose variability and (too aggressive correction

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Abbreviations: BMI, body mass index; CGM, continuous glucose monitor; GLP, glucagon-like peptide; HbA_{1c}, glycated hemoglobin; IAH, impaired awareness of hypoglycemia.

of) recurrent hyperglycemia are at the basis of the hypoglycemic burden as a whole, thus contributing to both the development and the persistence of IAH (9–11).

Exenatide was the first glucagon-like-peptide-1 receptor agonist (GLP-1RA) to be used for the treatment of type 2 diabetes. GLP-1RAs improve glycemic control by several mechanisms, including suppressed glucagon release, delayed gastric emptying, and decreased food intake (because of early satiety) (12–15). By virtue of their pharmacology, these agents have their most profound glucose-lowering effect on postprandial glucose excursions (16), but do not increase the risk of hypoglycemia (17). More stability in day-to-day glucose control with reduced need to (over)correct hyperglycemia may decrease hypoglycemic exposure, which would particularly benefit patients with IAH. GLP-1 and GLP-1RAs have a neutral effect on counterregulatory hormone and symptom responses to hypoglycemia, both in healthy subjects and in patients with type 1 or type 2 diabetes (17–20). However, the effect of GLP1-RAs on these responses has not been examined in patients with type 1 diabetes and IAH. Furthermore, their effect on the recovery from and in particular the glucose excursion after hypoglycemia has not been examined. We posited that reduced exposure to hypoglycemia during treatment with GLP-1RAs will improve awareness of and recovery from hypoglycemia in patients with type 1 diabetes and IAH, whereas the pharmacology of GLP-1RAs will limit hyperglycemic glucose excursions following hypoglycemia. The aim of this study was to investigate the effect of exenatide (GLP-1RA) treatment on symptom scores in response to insulin-induced hypoglycemia in patients with type 1 diabetes and IAH.

Materials and Methods

Study design

This was an investigator-initiated randomized double-blind, placebo-controlled crossover intervention trial that was performed at the Radboud University Medical Center in Nijmegen, Netherlands. The study was approved by the local institutional review board and performed according to the principles of the Declaration of Helsinki. All participants provided written informed consent. This research was conducted with support from AstraZeneca BV, Netherlands.

Study population

Patients with type 1 diabetes were recruited from the outpatient diabetes clinic of the Radboud University Medical Center between January 2017 and March 2018. Patients were eligible for participation when they met the following criteria; type 1 diabetes mellitus for one year or more; age between 18 and 75 years; glycated hemoglobin (HbA_{1c}) 6% to 9% (42 to 75 mmol/mol); insulin treatment according to basal-bolus insulin regimen; body mass index (BMI) 19 to 40 kg/m^2; and the presence of IAH as assessed by a score of three or more on the Dutch version of the Clarke questionnaire (21). Key exclusion criteria were current treatment with or known intolerance to incretin-based therapy, treatment with coumarin derivates or antibiotics, treatment with glucose- or immune-modifying agents, history of cardiovascular disease, diabetes-related complications (except for background retinopathy and asymptomatic peripheral neuropathy), and total daily insulin dose requirements <20 units unless on pump treatment.

Study procedure

Participants were asked to come to the outpatient clinic for a medical screening, including medical history and standard physical examination (including weight, height, blood pressure, pulse rate, and screening for peripheral neuropathy). We also determined kidney function (serum creatinine) and HbA_{1c} if this had not been done within the last six months.

After inclusion, patients were randomly assigned to treatment with exenatide or placebo for six weeks in a crossover fashion, with a washout period of four weeks in between. Randomization was done by a computer program with the use of blocks of two subjects, to ensure that equal numbers of subjects would be treated with exenatide or placebo first. Random allocation sequence was done using a computer software program that generated the random sequence. Participants were enrolled by the investigator and were assigned to exenatide or placebo treatment first according to a randomization list that was managed by the pharmacy department of our hospital, ensuring that participants and investigators were blinded to treatment assignment. After the start of the study medication, patients were instructed to reduce prandial insulin levels by 20%. Participants were asked to perform four-point daily blood glucose profiles and to keep a glucose diary for the duration of the study. Insulin doses were adjusted according to the glucose profiles, aiming for fasting and premeal blood glucose levels of 4 to 7 mmol/L without the occurrence of hypoglycemia. Exenatide and placebo injections were dosed 5 μg twice daily for the first two weeks of the study, and when tolerated, the dose was increased to 10 μg twice daily for the remaining four weeks. Insulin doses were then decreased by another 20% and adjusted according to the glucose profiles. In weeks one, two, and four, insulin dose adaptations and potential side effects were documented by telephone consultation. Patients recorded any hypoglycemic event in their glucose diary and whether they needed help from someone. During the final week of each treatment period, subjects completed seven-point glucose profiles, and wore a blinded continuous glucose monitor (CGM) (Dexcom G4; Dexcom Inc., San Diego, CA) for five days.

At the end of each treatment period, subjects underwent a hyperinsulinemic euglycemic hypoglycemic clamp (nadir 2.5 mmol/L). Participants presented at 8:00 AM at the clinical research facility after an overnight fast, having abstained from alcohol, caffeine, and smoking for 24 hours and from strenuous exercise for 48 hours. They received instructions to avoid (nocturnal) hypoglycemia the day before the clamp by reducing basal insulin dose during the night and an extra blood glucose measurement at 2:00 AM. In the case of hypoglycemia, the clamps were rescheduled. When the patients arrived at the research facility, two intravenous cannulas were inserted into the antecubital vein of each forearm. One forearm was placed

in a heated box (55°C) so that arterialized venous blood could be obtained to measure glucose levels every five minutes. The cannula in the contralateral arm was used for infusion of glucose 20% (Baxter B.V., Deerfield, IL) and insulin (insulin aspart; Novo Nordisk, Bagsvaerd, Denmark). Glucose levels were determined using Biosen C-Line (EKF Diagnostics, Cardiff, UK) (22). Baseline hyperglycemia was corrected as needed with a small bolus of insulin. Subsequently, a hyperinsulinemic (60 $mU \cdot m^{-2} \cdot min^{-1}$) euglycemic (5.0 mmol/L) hypoglycemic (2.5 mmol/L) glucose clamp was initiated. Blood samples for the measurement of catecholamines, insulin, glucagon, cortisol, and GHs were obtained at baseline, after 30 minutes of euglycemia, twice during hypoglycemia (after 20 and 45 minutes), and after recovery from hypoglycemia (45 minutes after hypoglycemia). After the euglycemic phase (30 minutes), glucose levels were allowed to decrease to 2.5 mmol/L over ~35 minutes and were maintained there for another 45 minutes. At the end of the hypoglycemic phase, participants were asked to estimate their current glucose levels, and to eat as much as they thought would be necessary to recover from hypoglycemia. Insulin infusion was stopped at that moment and glucose infusion was tapered until cessation over 35 minutes. Glucose levels were measured until 45 minutes after hypoglycemia, unless patients were still hypoglycemic at that point, then measuring of glucose levels continued until euglycemic glucose levels were reached.

Participants were asked to rate hypoglycemic symptom scores by a validated questionnaire (21) at baseline, once during euglycemia, twice during hypoglycemia, and once after recovery from hypoglycemia. Symptoms were divided into autonomic symptoms (trembling, palpitations, anxiety, sweating, hunger, and tingling), neuroglycopenic symptoms (difficulty speaking, confusion, fatigue, blurred vision, feeling faint and difficulty thinking), general symptoms (nausea, headache, dry mouth, and weakness), and dummy symptoms (pain in the legs and yellow vision). Symptoms were scored from 0 (none) to 6 (severe) (21, 22). Differences in symptom scores were calculated between baseline and the second hypoglycemic time point (after 45 minutes of hypoglycemia). Participants also completed a questionnaire about appetite scores at the same time points during the clamp. This questionnaire consisted of a visual analog scale (0 to 100 mm) on which patients rated hunger, fullness, prospective consumption, desire to eat, and thirst (maximal score 500 mm) (23).

Study outcomes

The primary end point of this study was the symptom score in response to insulin-induced hypoglycemia, measured during the hyperinsulinemic hypoglycemic clamps after treatment with exenatide or placebo. Secondary end points were changes in plasma levels of counterregulatory hormones in response to insulin-induced hypoglycemia, time until recovery from hypoglycemia (defined as a glucose level above 4.0 mmol/L), maximal glucose excursion post-hypoglycemia, self-reported appetite scores during and after hypoglycemia, amount of carbohydrates and calories consumed after hypoglycemia, glucose variability, mean 24-hour glucose levels, and time spent in low glucose (<4.44 mmol/L) on CGM during the final treatment weeks, glucose infusion rates during the hyperinsulinemic clamp, and HbA_{1c} levels. Time in range was defined as glucose levels between 4.44 and 7.21 mmol/L, according to predefined Dexcom G4 settings.

Measurements

Plasma insulin was assessed by an in-house radioimmunoassay (24). Plasma glucagon was measured by radioimmunoassay (Eurodiagnostica, Malmö, Sweden). Plasma GH and cortisol were determined using a routine analysis method with an electrochemiluminescent immunoassay on a Modular Analytics E170 (Roche Diagnostics, GmbH, Mannheim, Germany). Plasma adrenaline and noradrenaline were analyzed by HPLC combined with fluorometric detection (22). HbA_{1c} was measured by the TOSOH G8 HPLC-analyzer (Sysmex Nederland B.V., Etten-Leur, Netherlands).

Statistical analysis

A power calculation aimed at finding a 40% increase in symptom score in response to hypoglycemia with a power of 80% yielded a total number of participants of 10, where dropouts would be replaced. Data were analyzed using IBM SPSS statistics version 25. We tested for normality using the Shapiro-Wilk test and QQ plots. Paired Student *t* tests were used to analyze differences in means within groups, and Wilcoxon signed rank tests were used when data were not normally distributed. Serial data were analyzed by two-way repeated-measures ANOVA. All data are expressed as the mean ± SEM, unless otherwise specified. A P value < 0.05 was considered statistically significant. Missing data were imputed if possible.

Results

A total of 13 patients with type 1 diabetes and IAH were recruited between January 2017 and November 2017, with a follow-up period between February 2017 and March 2018. One patient withdrew after six days of exenatide treatment because of nausea and vomiting. One patient withdrew after five weeks, while on placebo treatment, because of diabetic ketoacidosis not related to the study. One other patient assigned to placebo treatment withdrew after six weeks, because her endocrinologist disagreed with her participation in this study, although he/she was informed about the participation before start of the study and did not disagree at that time. As a result, a total of 10 patients were included and analyzed; baseline characteristics are shown in Table 1. Four patients, already using CGM, continued using this device in unblinded setting during the study. None of the results in this group differed from those on blinded CGM (data not shown but available on request).

Treatment periods

Glucose variability

Mean 24-hour glucose levels averaged 8.3 ± 0.4 mmol/L during the final week of treatment with exenatide and 8.5 ± 0.3 mmol/L during the final week of treatment with placebo (difference, −0.24 mmol/L, $P = 0.64$). Median percentage of time in range was comparable between exenatide and placebo treatment [30.4% (22.9, 30.4) vs 29.1% (22.3, 29.1), $P = 0.45$]. Glucose

Table 1. Baseline Characteristics

	n = 10
Age, y	38.5 ± 14.0
Male, n (%)	4 (40)
Weight, kg	78.1 [68.5, 106.3]
BMI, kg/m^2	25.4 [23.7, 31.7]
Abdominal circumference, cm	94.8 ± 16.6
Score on modified Clarke questionnaire	3.5 [3.0, 4.25]
Complications, n (%)	
Retinopathy	1 (10)
Neuropathy	1 (10)
Nephropathy	0 (0)
Duration of diabetes, y	21.7 ± 13.5
Insulin therapy, n (%)	
CSII	8 (80)
MDI	2 (20)
Insulin dose, IU/d	46.9 ± 20.6
HbA_{1c}, % (mmol/mol)	7.2 ± 0.4 (55.2 ± 4.8)
Creatinin, μmol/L	69.1 ± 6.0

Data are presented as number (%), mean ± SD or median [IQR].

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

variability, defined as the mean SD, also did not differ between the two treatment periods (3.7 ± 0.3 mmol/L vs 3.6 ± 0.3 mmol/L, exenatide vs placebo respectively, P = 0.82). HbA_{1c}-levels did not change in either group.

Insulin dose

Total daily bolus insulin doses were numerically lower during treatment with exenatide (15.8 ± 1.9 IU) compared with treatment with placebo (18.6 ± 2.8 IU), but this difference did not reach statistical significance (P = 0.20). Daily basal insulin doses were approximately similar between the two treatment periods (21.6 ± 3.2 IU vs 22.2 ± 3.4 IU, exenatide vs placebo respectively, P = 0.43). Two patients were on multiple daily insulin injections, with insulin glargine as basal insulin. Evening meal bolus insulin doses were numerically lower with exenatide treatment when compared with placebo, however there was no statistically significant difference (difference, −1.5 ± 0.7 IU, P = 0.061).

Hypoglycemia

The frequency of hypoglycemic episodes during the six-week treatment did not differ according to the treatment regimen (15.8 ± 3.7 episodes vs 12.1 ± 3.5 episodes per person, P = 0.19). The frequency of severe hypoglycemia was 1.5 ± 2.5 episodes per person during exenatide treatment and 0.4 ± 1.0 episodes per person during placebo treatment. Median percentage of time spent in low glucose on CGM was numerically higher during the final week of treatment with exenatide compared with placebo [15.5% (4.5, 25.5) vs 7.8% (4.4, 17.1), P = 0.11], but this difference was not statistically significant.

Weight and BMI

There was a substantial change in body weight after treatment with exenatide compared with placebo treatment (−3.9 ± 0.9 kg vs 0.6 ± 1.2 kg, respectively, P = 0.047). BMI also changed after treatment with exenatide compared with placebo (−1.2 ± 0.3 kg/m^2 vs 0.2 ± 0.3 kg/m^2, P = 0.043).

Adverse effects

Five participants experienced nausea during treatment with exenatide; in two cases this was self-limiting and predominantly occurred directly after starting the medication. The other three participants used antiemetic drugs because of nausea and vomiting. In one other participant, nausea and vomiting were reasons to withdraw from study participation a few days after start of the treatment. One serious adverse event (diabetic ketoacidosis) occurred during placebo treatment, which was judged to be unrelated to the investigational medicinal product. Patients did not experience any other adverse effects during treatment with placebo.

Hypoglycemic glucose clamps

Glucose and insulin levels

Mean glucose levels during the two clamps are shown in Fig. 1. Nadir plasma glucose levels were 2.4 ± 0.0 mmol/L during exenatide treatment and 2.5 ± 0.0 mmol/L after placebo treatment (difference between groups 0.1 ± 0.0 mmol/L, P = 0.046). Mean glucose infusion rates did not differ during hypoglycemia (3.8 ± 0.5 vs 3.7 ± 0.3 mg·kg^{-1}·min^{-1}, exenatide vs placebo, P = 0.67) or during recovery after hypoglycemia (3.2 ± 0.3 vs 2.9 ± 0.2 mg·kg^{-1}·min^{-1}, respectively, P = 0.62) (Fig. 1). Glucose levels after 45 minutes of hypoglycemia averaged 2.8 ± 0.1 mmol/L during exenatide treatment and 2.9 ± 0.1 mmol/L during placebo treatment. Patients estimated their lowest glucose levels as 3.6 ± 0.3 mmol/L after exenatide treatment and as 3.4 ± 0.3 mmol/L after placebo treatment. Mean time until glycemic recovery was 35.0 ± 5.2 minutes after exenatide treatment and 31.9 ± 3.4 minutes after placebo treatment (P = 0.66). Median serum insulin concentrations were 72.1 (60.6, 100.0) mU/L after exenatide treatment, and 63.9 (53.6, 156.3) mU/L after placebo treatment (P = 0.80).

Hypoglycemic symptoms and counterregulatory hormone responses

Mean symptom scores during the glucose clamps are shown in Fig. 2. Symptom scores in response to clamped hypoglycemia were not different after treatment with

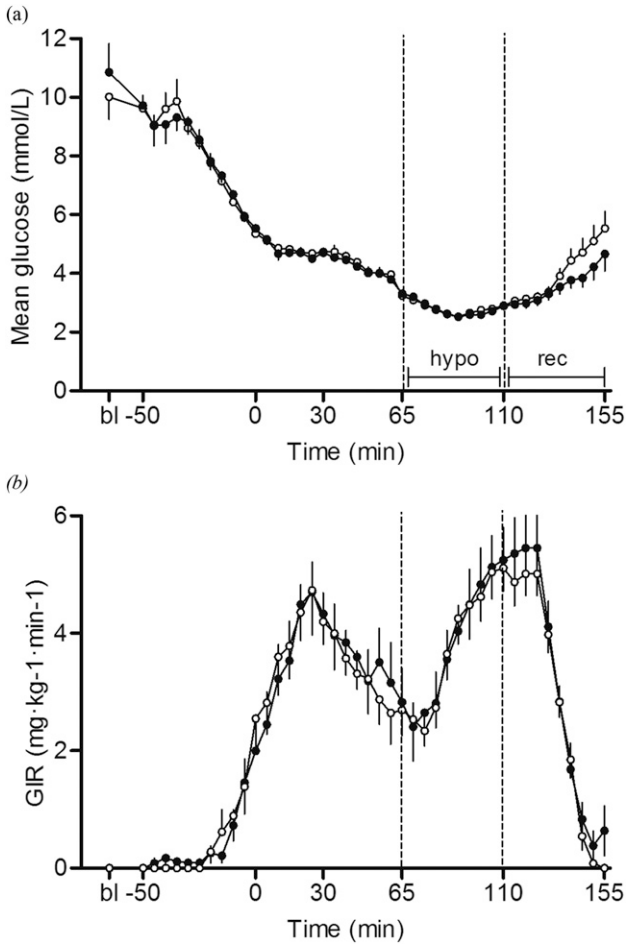

Figure 1. (a) Glucose levels and (b) glucose infusion rate during hyperinsulinemic euglycemic hypoglycemic clamps after exenatide treatment (closed circles) and after placebo treatment (open circles). GIR, glucose infusion rate; bl, baseline; Hypo, 45 min hypoglycemic phase; Rec, 45 min recovery period after hypoglycemia.

exenatide compared with treatment with placebo [median change from baseline 1.0 (−1.5, 7.0) vs 4.5 (1.5, 5.8), respectively, $P = 0.08$].

Treatment with exenatide did not change adrenaline or noradrenaline responses to hypoglycemia compared with placebo treatment. GH levels increased in response to hypoglycemia after both exenatide and placebo treatment, with no between-group differences. There were no differences in cortisol and glucagon levels between exenatide and placebo treatment (Fig. 3).

Appetite scores during clamp

Mean appetite scores were higher during hypoglycemia than after recovery from hypoglycemia, both after exenatide treatment (204.0 ± 28.9 vs 130.4 ± 11.3 mm, $P = 0.016$) and after placebo treatment (204.5 ± 26.8 vs 120.9 ± 13.5 mm, $P = 0.004$). However, there were no differences between the two treatment periods (−73.6 ± 24.8 vs −83.6 ± 21.8 mm, exenatide vs placebo, $P = 0.56$).

Discussion

The main finding of this study is that six weeks of treatment with exenatide does not improve awareness of hypoglycemia in patients with type 1 diabetes and IAH. Although exenatide reduced body weight and BMI, no differences occurred in mean blood glucose levels, glucose variability, frequency of hypoglycemic events, or symptom scores in response to experimental hypoglycemia between exenatide and placebo treatment. Exenatide also did not affect the recovery from hypoglycemia.

Our data are largely in agreement with two previous studies examining the effect of GLP-1 receptor agonists on responses to hypoglycemia in people with type 1 diabetes. Pieber *et al.* (20) showed that four weeks of

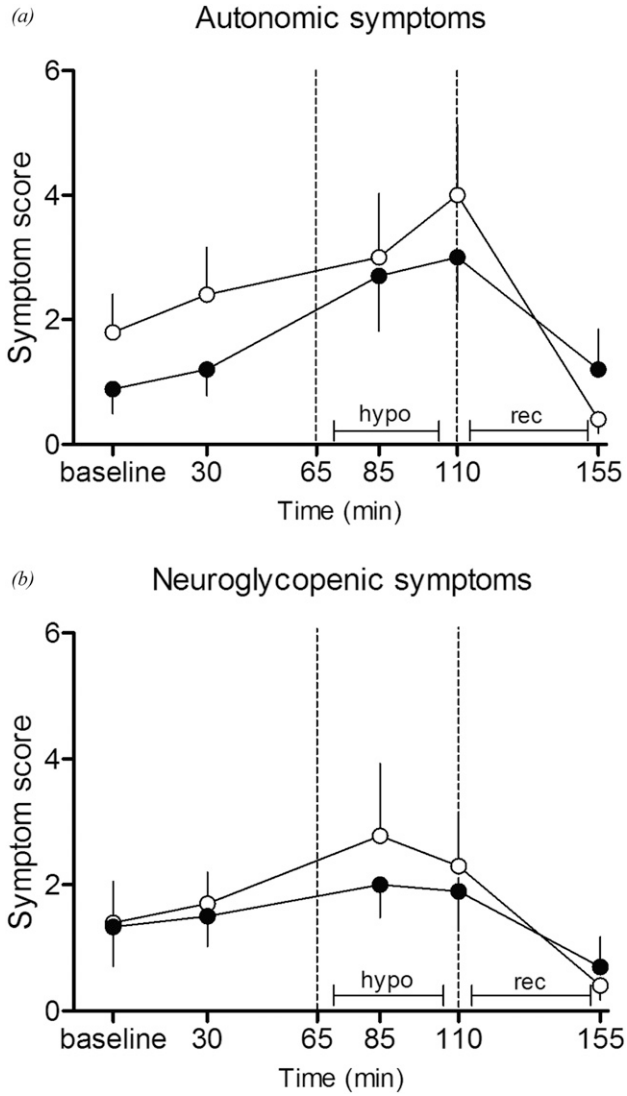

Figure 2. (a) Autonomic and (b) neuroglycopenic symptom responses to hypoglycemia during hyperinsulinemic euglycemic hypoglycemic clamps after exenatide treatment (closed circles) and after placebo treatment (open circles). Hypo, 45 min hypoglycemic phase; Rec, 45 min recovery period after hypoglycemia.

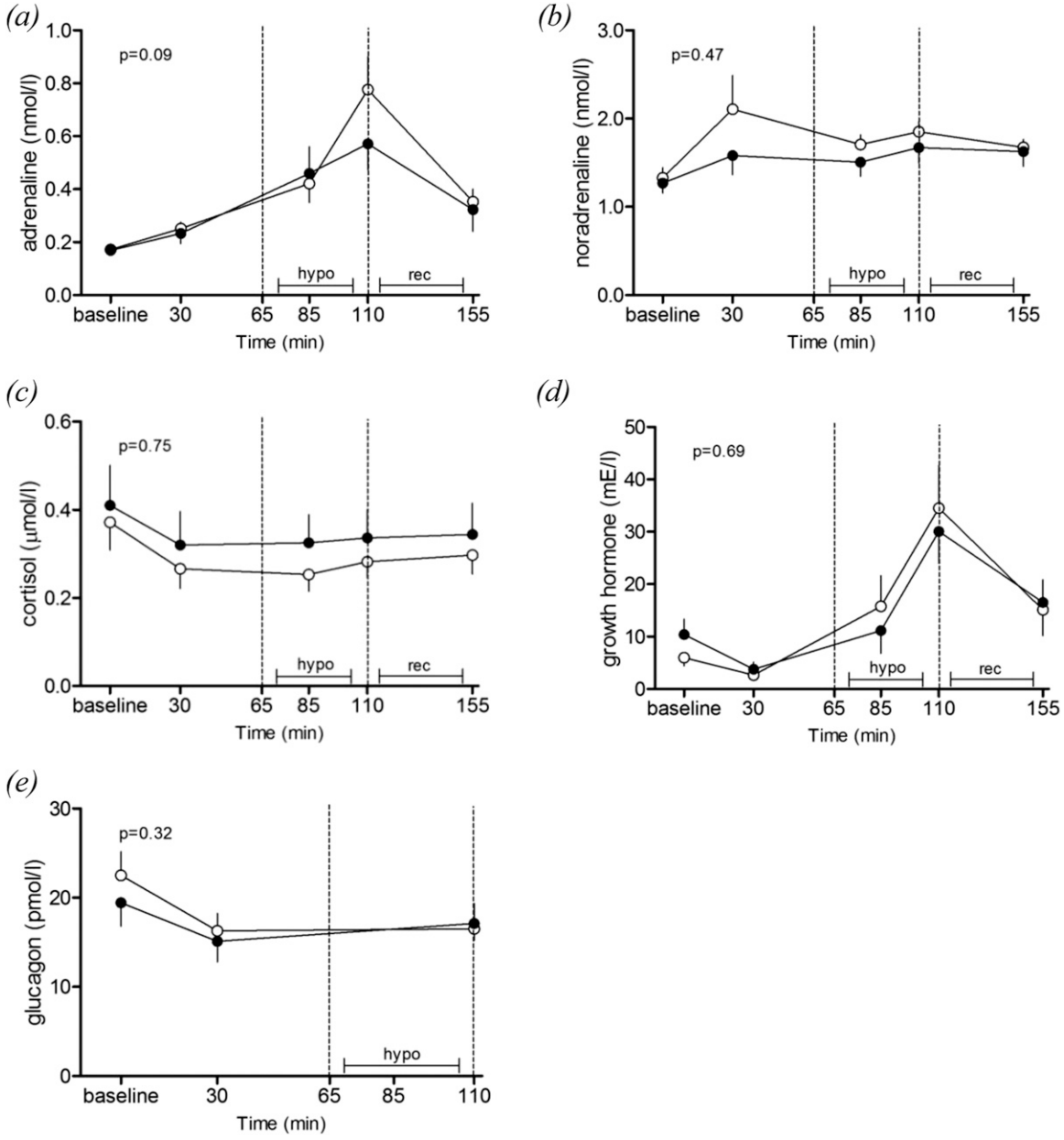

Figure 3. (a-e) Levels of counterregulatory hormones during hyperinsulinemic euglycemic hypoglycemic clamps after exenatide treatment (closed circles) and after placebo treatment (open circles). Hypo, 45 min hypoglycemic phase; Rec, 45 min recovery period after hypoglycemia.

treatment with liraglutide did not affect symptom or counterregulatory hormone responses to hypoglycemia in people with type 1 diabetes and intact awareness of hypoglycemia, although glucose infusion rates were lower. Another study conducted among patients with poor glycemic control ($HbA_{1c} > 8\%$) reported similar results after 12 weeks of treatment with liraglutide 1.2 mg group compared with placebo (25). Our study, using a different GLP-1RA, extends these data to patients with IAH.

Previous studies that formed the rationale for the current study showed less glucose variability (26, 27) and lower frequency of hypoglycemia (26) after treatment with the GLP-1RA, liraglutide, in people with type 1 diabetes. In our study, however, treatment with exenatide did not affect the rate of or time spent in hypoglycemia. This discrepancy may be in part related to the short duration of follow-up and the study design. Other studies also found no differences in overall hypoglycemia event rate between liraglutide and placebo, using treatment periods of 12 or 4 weeks (20, 25, 27). Patients even seemed to experience fewer hypoglycemic events during placebo than during exenatide treatment, probably because the double-blind study design necessitated the adjustment of the insulin doses at fixed time points in both study arms. Despite subsequent adjustment based on glucose values, this may still have resulted in slightly lower insulin doses than needed in the placebo group and

slightly higher than needed in the intervention group and may have resulted in slightly decreased vs slightly increased risks of hypoglycemia. Both changes jeopardize the possibility of identifying a potential positive effect of exenatide on symptom scores in response to the hypoglycemic clamp between exenatide and placebo treatment.

Strengths of our study include the randomized, double-blind placebo-controlled study design, the use of CGM, and the use of glucose clamps to measure awareness of hypoglycemic symptoms. Our study also has limitations. The data should be interpreted in the context of IAH at elevated rate of hypoglycemia, which limits generalizability to the broader diabetes population. The number of participants in this study, although based on power calculation, was relatively low. Although we may have failed to detect more subtle differences between treatments, it is unlikely that a larger number of participants would have disclosed a clinically relevant benefit of exenatide. By design, we reduced insulin doses in both study arms at initiation and titration of study medication, which led to a small, albeit nonsignificant, difference in hypoglycemia exposure in favor of the placebo study arm. In hindsight, the treatment periods of six weeks, chosen because avoidance of hypoglycemia for two to four weeks has been shown to reverse the process of impaired awareness of hypoglycemia (7, 8), may have been too short. A study with longer exposure to study drug is needed to disclose whether more extensive use of exenatide may be beneficial in the treatment of impaired awareness of hypoglycemia. We found a small difference between exenatide and placebo arms in mean glucose levels during 45 minutes of recovery after hypoglycemia, but this failed to reach statistical significance. It is possible that a longer follow-up period would have resulted in a more pronounced separation.

In conclusion, six weeks of treatment with exenatide does not improve awareness of hypoglycemia in patients with type 1 diabetes and IAH. Based on the current study findings, the adjunctive use of GLP-1RA cannot be recommended for use in patients with type 1 diabetes to improve impaired awareness of hypoglycemia. Various strategies exist for the management of IAH, including educational programs, behavioral therapy, and technological interventions. Despite proven effectiveness of several of these approaches (28), however, this condition can still be extremely difficult to reverse in daily clinical practice, particularly when the patient's concern about it is low (29). Future research should focus on additional means to sustainably decrease the frequency of hypoglycemic events and consequently restore awareness of hypoglycemia in patients with type 1 diabetes and IAH.

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Author Contributions: H.M.R., C.J.T., and B.E.d.G. designed the study. L.A.v.M. and H.M.R. performed the experiments and collected the data. L.A.v.M. analyzed the data and wrote the first version of the manuscript. All authors discussed the results and implications and commented on the manuscript at all stages. The guarantor accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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