

The Effect of Liraglutide, a Long-Acting Glucagon-Like Peptide 1 Derivative, on Glycemic Control, Body Composition, and 24-h Energy Expenditure in Patients With Type 2 Diabetes

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OBJECTIVE — Glucagon-like peptide (GLP)-1 is a gut hormone that exerts incretin effects and suppresses food intake in humans, but its therapeutic use is limited due to its short half-life. This was a randomized, double-blind, parallel-group, placebo-controlled trial investigating the effect of the long-acting GLP-1 derivative liraglutide (NN2211) on glycemic control, body weight, body composition, and 24-h energy expenditure in obese subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Thirty-three patients (mean \pm SD) aged 60.0 ± 9.5 years, with HbA_{1c} $7.5 \pm 1.2\%$ and BMI 36.6 ± 4.1 kg/m², were randomized to treatment with a single daily subcutaneous dose of 0.6 mg liraglutide ($n = 21$) or placebo ($n = 12$) for 8 weeks. In addition to weight and glycemic parameters, body composition was assessed by dual-energy X-ray absorptiometry (DEXA) scanning and 24-h energy expenditure in a respiratory chamber.

RESULTS — After 8 weeks, liraglutide reduced fasting serum glucose (liraglutide, -1.90 mmol/l, and placebo, 0.27 mmol/l; $P = 0.002$) and HbA_{1c} (liraglutide, -0.33% , and placebo, 0.47% ; $P = 0.028$) compared with placebo. No change in body weight was detected (liraglutide, -0.7 kg, and placebo, -0.9 kg; $P = 0.756$). There was a nonsignificant trend toward a decrease in total fat mass (liraglutide, -0.98% , and placebo, -0.12% ; $P = 0.088$) and toward an increase in lean body mass (liraglutide, 1.02% , and placebo, 0.23% ; $P = 0.118$) in the liraglutide group compared with the placebo group. Twenty-four-hour energy expenditure was unaffected by the treatment (liraglutide, -12.6 kJ/h, and placebo, -13.7 kJ/h; $P = 0.799$).

CONCLUSIONS — Eight weeks of 0.6-mg liraglutide treatment significantly improved glycemic control without increasing weight in subjects with type 2 diabetes compared with those on placebo. No influence on 24-h energy expenditure was detected.

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Glucagon-like peptide (GLP)-1 has several effects that make it a potential candidate molecule for the treatment of type 2 diabetes. GLP-1 is a peptide hormone secreted from the L-cells in the lower gut, i.e., the distal jejunum, ileum, and colon/rectum, in response to ingestion of carbohydrates, lipids, and

mixed meals (1–3). GLP-1 stimulates postprandial insulin secretion and acts as an incretin hormone, thus potentiating glucose-stimulated insulin release. The incretin effect refers to the increased insulin response elicited by oral glucose compared with the response resulting from an isoglycemic intravenous infusion (4). In addition, GLP-1 has a suppressive effect on glucagon release and hepatic glucose output (5).

Treatment of hyperglycemia in type 2 diabetic patients with GLP-1 has received much attention, but additional therapeutic indications could be envisioned. Within the last few years, the ability of GLP-1 to decrease appetite and energy intake has been established (6). A reduced food intake would support weight reduction attempts in patients with type 2 diabetes. The appetite-reducing effect might partly be related to the ability of GLP-1 to decrease gastric emptying and reduce gastric motility (2). The mechanisms involved in the regulation of appetite and food intake are, however, complex and not fully understood; this also applies for the mechanisms mediating the anorectic effects of GLP-1. Furthermore, GLP-1 receptors have been found in various tissues, such as pancreas, stomach, intestine, brain, and heart (7). The anorectic effect of GLP-1 has been shown in both healthy lean and obese people as well as in type 2 diabetic patients (6,8–12). This effect has been reported from studies (13,14) of up to 2 days in duration. In addition, obese subjects have been shown (10) to have an attenuated GLP-1 release in response to meals. A study (15) in obese type 2 diabetic subjects with continuous infusion of GLP-1 using insulin pumps demonstrated that, aside from a glucose-lowering effect, GLP-1 also exhibited weight-reducing properties. After 6 weeks, GLP-1-treated subjects experienced a significant weight

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Abbreviations: AUC, area under the curve; DEXA, dual-energy X-ray absorptiometry; GLP, glucagon-like peptide; HOMA, homeostasis model assessment; OHA, oral hypoglycemic agent; VAS, visual analog score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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loss of 1.9 kg compared with baseline; the weight loss was, however, not significant when compared with placebo (15).

It is estimated that >80% of type 2 diabetic patients are obese, and even more might be overweight, with abdominal fat accumulation, and hence benefit from weight loss. It would be desirable if peripherally administered GLP-1 was able to reduce energy intake and thereby induce weight loss. A major disadvantage is that native GLP-1 has a very short half-life in plasma due to rapid degradation by dipeptidyl-peptidase IV ($t_{0.5} < 1.5$ min after intravenous injection) (16), which is why modifications are needed for clinical use. Liraglutide (NN2211) is a long-acting GLP-1 derivative developed for the treatment of type 2 diabetes. Liraglutide has a prolonged action ($t_{0.5} = 13$ h) suitable for once-daily injection. The mechanism of protraction is a combination of albumin binding and self-association, resulting in slow absorption from subcutis, stability against dipeptidyl-peptidase IV, and a long plasma half-life. The aim of the present study was to examine if liraglutide administered subcutaneously once daily for 8 weeks in obese type 2 diabetic subjects would decrease body weight and total fat mass and have an effect on 24-h energy expenditure, in addition to improvement of glycemic control.

RESEARCH DESIGN AND METHODS

— Thirty-five type 2 diabetic patients (age 60.0 ± 9.5 years [mean \pm SD]) were recruited from the investigators' own patient files and/or advertisement in local newspapers and screened medically for their eligibility for the trial. Inclusion criteria were 1) diet treated and/or subjects in monotherapy with sulfonylurea or repaglinide (NovoNorm); 2) HbA_{1c} for diet-treated subjects of 7–12%, both inclusive; 3) HbA_{1c} for sulfonylurea-treated subjects $\leq 10\%$; and 4) BMI ≥ 27 kg/m². The key exclusion criteria were 1) New York Heart Association class III and IV heart failure, 2) uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 105 mmHg), 3) serum creatinine >150 μ mol/l, and 4) alanine aminotransferase three or more times the upper-normal range. Twenty patients were treated with sulfonylureas, 3 with NovoNorm, and 12 with diet only. The protocol (file no. 02-024/01) was approved by the Ethical Committee of Fre-

deriksberg and Copenhagen. The trial was performed in accordance with the Helsinki II Declaration. Written consent was obtained from each participant before beginning the study.

The study was double blind and placebo controlled with two parallel arms. The subjects attended a screening visit to assess their eligibility. Eligible subjects on oral hypoglycemic agents (OHAs) were asked to discontinue current OHA treatment for a 2-week washout period before the start of dosing. Eligible subjects were randomized to receive a single daily dosing of liraglutide (0.6 mg) or placebo for 8 weeks (long term). The trial product was administered as a subcutaneous injection in the abdomen or in the thigh in the morning using a NovoPen (1.5 with Novofine 30-gauge 0.3- to 8-mm needle) as the dispensing device. The 24-h energy expenditure was measured in a respiratory chamber before the intervention period (baseline) and again after 3 days on liraglutide or placebo. The 24-h energy expenditure was performed after 3 days (short term) only to avoid confounding due to possible weight loss later in the intervention period. Thus, no long-term energy expenditure assessment was done. To assess appetite and spontaneous energy intake, three meal tests were conducted through the intervention period. Two were carried out following each respiratory chamber visit, and the third one was conducted at the end of the intervention period (8 weeks). Subjective appetite ratings were assessed by visual analog scores (VASs) in connection with the fixed-energy breakfast meal (17). Spontaneous energy intake was assessed in connection to an ad libitum lunch meal 4 h after the fixed-energy breakfast meal. Body composition (assessed by dual-energy X-ray absorptiometry [DEXA] scan) was evaluated at baseline and after 8 weeks (end of intervention).

Analytical determinations

HbA_{1c} was analyzed using a high-performance liquid chromatography, ion-exchange chromatography assay (normal range 4.3–5.8%; Tosoh). Serum concentrations of liraglutide, insulin, and C-peptide were analyzed by enzyme-linked immunosorbent assay methods. Serum concentration of glucose was measured using an enzymatic glucose oxidase method (normal range [fasting] 3.9–6.6 mmol/l). Plasma glucagon was analyzed

by MDS Pharma Services, Switzerland, using a radioimmunoassay (Linco Research, St. Charles, MO). Standard laboratory analyses were performed by a central laboratory (if not otherwise stated): Capio Diagnostik, Copenhagen, Denmark. Homeostasis model assessment (HOMA) analysis: An estimate of β -cell function (HOMA-S) and of insulin resistance (HOMA-R) was calculated by HOMA: β -cell function (%) = $20 \times \text{insulin}/(\text{glucose} - 3.5)$ and insulin resistance = $\text{insulin}/(22.5 \times e^{\ln(\text{glucose})})$ (18).

Meal test

A venflon catheter was inserted in an antecubital arm vein. After a 10-min rest, fasting blood samples were taken. Immediately thereafter the subjects took a single dose of either liraglutide or placebo, then the standard breakfast meal consisting of 2.5 MJ (carbohydrate 50 E%, protein 13 E%, and fat 37 E%) was served and consumed within 30 min. Paracetamol (15 mg/kg) dissolved in 150 ml of water was administered to the subjects at initiation of the breakfast meal for assessment of the gastric emptying rate. Blood samples were collected regularly over the 240 min after starting the meal for analysis of plasma paracetamol, glucose, insulin, glucagon, C-peptide, and lipid profile. Ratings for appetite were made on 100-mm VASs, with the text expressing the most positive and the most negative rating anchored at each end. VAS was used to assess satiety, hunger, fullness, prospective food consumption, and thirst. The ratings were recorded immediately before the meal and throughout a 4-h period after the meal.

An ad libitum lunch meal consisting of carbohydrate 49.5 E%, protein 13.3 E%, and fat 37.2 E% was served ~ 4.5 h after completion of the breakfast meal. The lunch meal should be completed within 30 min. To reduce participants' awareness of the amount of food being consumed, food was served in excess. The quantity of food and fluid consumed was measured, and the total energy intake was calculated.

DEXA scan

Body composition was assessed before treatment by DEXA scan in all subjects and again after the 8-week intervention period. A dual-energy X-ray absorptiometer (Lunar Radiation, Madison, WI) was used. All scans were performed in the

Table 1—Baseline characteristics of patients

	Liraglutide	Placebo
<i>n</i>	21	12
Demographics		
Men/women	11/10	1/11
Age (years)	59.9 ± 11.0	60.1 ± 6.7
Anthropometrics		
BMI (kg/m ²)	36.8 ± 4.6	36.1 ± 3.4
Diabetes		
Duration (years)	4.5 ± 6.4	3.3 ± 3.4
HbA _{1c} (%)	7.4 ± 1.0	7.7 ± 1.6
Fasting plasma glucose (mmol/l)	10.7 ± 2.4	10.4 ± 2.8
Previous diabetes treatment		
Diet	4 (19)	7 (58)
OHA	17 (81)	5 (42)

Data are means ± SD or *n* (%).

slow mode on fasting subjects. The following parameters were assessed: lean tissue mass, fat mass, and total body weight.

Respiratory chamber

The 24-h energy expenditure was measured in an open-circuit indirect calorimetry respiratory chamber as described elsewhere (19). The measurement started at 9:00 A.M. and continued for 24 h. Basic metabolic rate was measured during the last hour of the stay. Subjects arrived at the department at 10:00 P.M. the evening before the examination and stayed in the chamber overnight. This procedure was chosen for the subject to adapt to the chamber, thereby minimizing stress during the 24-h measurement period. During the 24-h stay, subjects followed a standard protocol, including two periods of 10 min of bicycle exercise (75 watts) and two periods of walking back and forth in the chamber (with a total distance of 182.5 m each time).

Safety assessments

Adverse events, hematology, blood chemistry, and urine values were monitored throughout the study period. In addition, electrocardiograms and blood pressure were measured. Subjects were also supplied with a diary and asked to record information on home measurements of blood glucose, any changes in concomitant medication, concomitant illness, and hypoglycemic episodes.

Statistical analysis

All statistical tests were two sided at a 5% significance level. The model used was an

ANOVA with treatment as a fixed factor and baseline value as a covariate. The main comparison was after 8 weeks of treatment (long-term assessment). In addition, the end points were assessed after 2–4 days of treatment (short-term assessment) and for the period between the long and short terms. The latter was only done for the within-group comparison. This model was applied to all efficacy end points. Safety end points were summarized by descriptive statistics (number of observations, mean, SE, minimum, and maximum) or listed.

RESULTS—Thirty-five patients were randomized. Thirty-three patients completed the intervention, 21 assigned to the liraglutide group and 12 to the placebo group. One subject was withdrawn from the trial due to claustrophobia and one subject due to difficulties with blood drawing, both of whom withdrew before the trial drug was administered. There was an unbalanced distribution of sex in the two treatment groups. However, this uneven distribution has been analyzed and no statistical significant effect was seen. Clinical characteristics of the enrolled patients are shown in Table 1.

Total body weight and body composition

After 8 weeks, no significant difference in total body weight change was observed between liraglutide and placebo treatments (liraglutide, -0.7 kg, and placebo, -0.9 kg; $P = 0.756$) (Fig. 1 and Table 2). Although nonsignificant, the results from the DEXA scan indicated that fat mass (as

a percentage) decreased (liraglutide, -1.0% , and placebo, -0.1% ; $P = 0.088$) and that lean tissue mass increased after treatment with liraglutide compared with placebo (liraglutide, 1.0% , and placebo, 0.2% ; $P = 0.118$) (Table 2).

Glycemic control and lipids

Table 2 shows changes from baseline within each group and a comparison of changes from baseline between groups. Liraglutide improved glycemic control, and this effect was significant after the first week and persisted throughout the study period (difference in fasting serum glucose between liraglutide and placebo after 8 weeks: 2.17 mmol/l [95% CI -3.50 to -0.83], $P = 0.002$). At the end of the study, liraglutide showed a significant decrease in HbA_{1c} level compared with placebo (-0.80% [-1.50 to -0.09], $P = 0.028$). Liraglutide treatment suggested an improved β -cell function compared with placebo as indicated by increased HOMA-S (liraglutide, 17.2% , and placebo, -15.2% ; $P = 0.015$), whereas insulin resistance (HOMA-R) was not affected (liraglutide, -1.9 , and placebo, -0.8 , $P = 0.530$). Liraglutide had no effect on lipid parameters compared with placebo (data not shown).

Meal tests

The absolute area under the curve (AUC) for serum glucose was significantly suppressed in the liraglutide group compared with placebo both after 3 days (short term) (liraglutide, -530.6 mmol \cdot l⁻¹ \cdot min⁻¹, and placebo, -113.9 ; $P = 0.002$) and after 8 weeks (long term) of treatment (liraglutide, -554.7 , and placebo, 11.5 ; $P = 0.004$). No difference was detected for the incremental AUC for serum glucose in either the short term (liraglutide, 0.23 mmol/l, and placebo, -0.20 mmol/l; $P = 0.441$) or the long term (liraglutide, -0.05 mmol/l, and placebo, -0.84 mmol/l; $P = 0.128$). Gastric emptying was unaffected as measured by mean change in postprandial plasma paracetamol concentrations after both 3 days' and 8 weeks' treatment. Neither short- nor long-term treatment with liraglutide changed the subjective appetite sensations during the meal test according to the VAS. Food intake during the ad libitum lunch meal after 3 days and 8 weeks of treatment was not affected by liraglutide compared with placebo (short

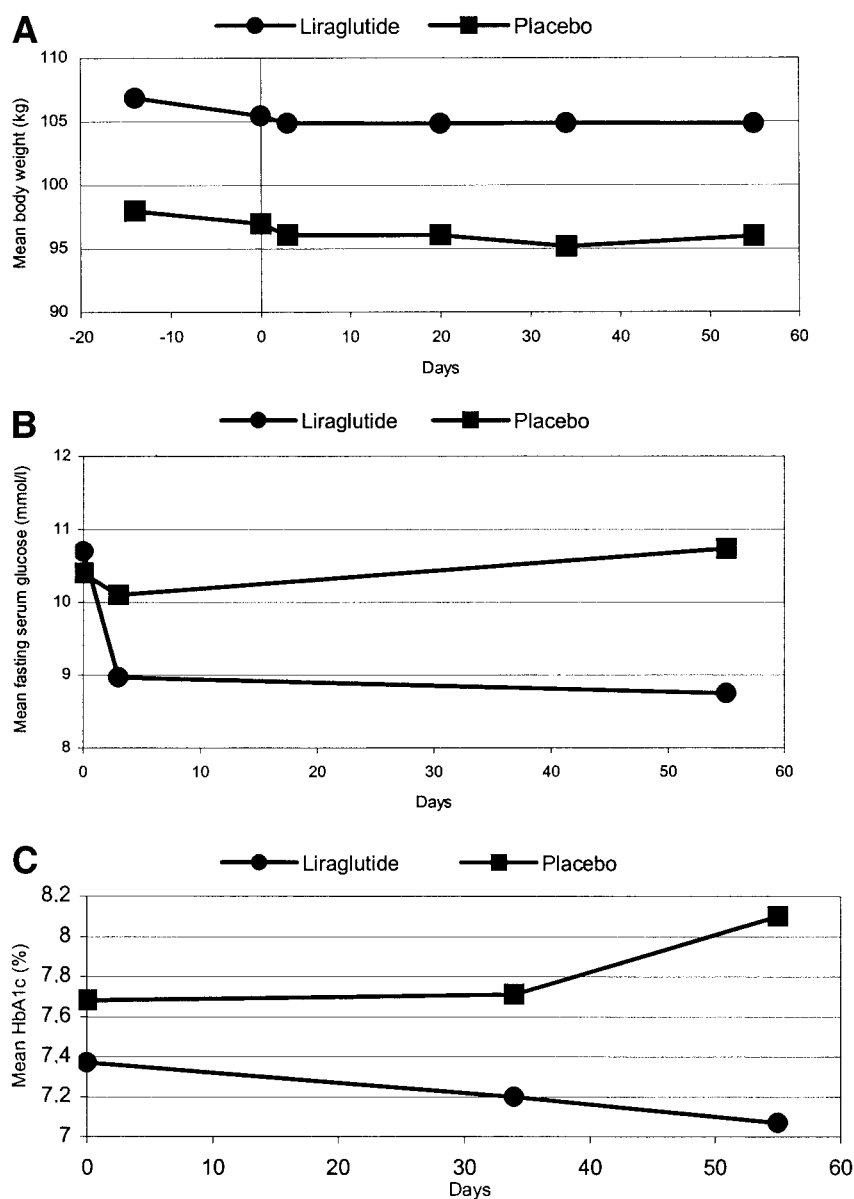


Figure 1—Mean body weight (A), fasting serum glucose (B), and HbA_{1c} (C) over 8 weeks in type 2 diabetic patients treated with liraglutide 0.6 mg/kg versus placebo for 8 weeks.

term: liraglutide, 5 g, and placebo, -1 g, $P = 0.883$; long term: liraglutide, 21 g, and placebo, 7 g, $P = 0.766$).

Twenty-four-hour energy expenditure

Liraglutide had no short-term effect on energy balance as the mean change in 24-h energy expenditure from before to after 3 days' treatment did not differ significantly between the groups (liraglutide, -12.6 kJ/h, and placebo, -13.7 kJ/h; $P = 0.799$). The substrate oxidation was not affected by treatment with liraglutide as the change in 24-h nonprotein respiratory quotient from before to after

treatment did not differ significantly between the groups ($P = 0.548$).

Safety assessments

Eight weeks' treatment with the subcutaneous injection of liraglutide (single daily dose of 0.65 mg) was well tolerated. No hypoglycemic episodes occurred during the study. In the liraglutide group, 76% (16 of 21) of the subjects reported adverse events, whereas 58% (7 of 12) of the placebo-treated subjects reported adverse events. Nausea and diarrhea were the most frequent events; however, these were transient episodes.

CONCLUSIONS— This clinical trial of 8 weeks' treatment with subcutaneous liraglutide in patients with type 2 diabetes shows that 0.65 mg liraglutide, self-administered once daily before breakfast for 8 weeks, compared with placebo improves glycemic control by decreasing fasting glucose by 2.2 mmol/l and HbA_{1c} by 0.8% in this group of relatively well-controlled type 2 diabetic patients, without inducing weight gain. Weight gain associated with improved glycemic control is common in treatment with sulfonylureas, insulin, or thiazolidinediones and often occurs when HbA_{1c} levels are significantly reduced. This effect has been reported in the intensively treated cohorts of the Diabetes Control and Complications Trial (20) and the U.K. Prospective Diabetes Study (21). Weight gain is an undesirable effect as it is often associated with increased insulin resistance, especially if the additional fat is deposited in the abdominal region (22). In the present study, we failed to see any weight loss produced by liraglutide, and in accordance with this observation there were no detectable effects on appetite sensation, gastric emptying, or energy intake at the ad libitum test meals in connection with administration of liraglutide. However, there was a trend to a reduction in fat mass, which results from a daily negative energy balance of a magnitude that would not be picked up by the meal tests or the appetite sensations. The trend in reduction of fat mass suggests that liraglutide actually may have the potential to induce weight loss, and we speculate that larger doses and a longer study period might be required to produce an effect on appetite and weight loss (23). Further studies are needed to fully elucidate the weight profile of liraglutide. Preclinical studies in nondiabetic animals have shown a potential for lowering food intake and body weight with liraglutide. In one study, a dose of 0.2 mg/kg has been shown to markedly decrease food intake and body weight in normal-weight and obese rats (24). Doses of liraglutide needed in rats are larger than in humans, also for blood glucose lowering (25).

In addition, treatment with lira-

Table 2—Body weight, body composition, and glycemic control parameters before and after 8 weeks' intervention

Variable	Liraglutide	Placebo	P
n	21	12	
Weight (kg)			
Before	106.9 ± 2.9	98.0 ± 3.8	
After	104.8 ± 3.0	96.0 ± 4.0	
Change	−0.7 (−1.6 to 0.3)	−0.9 (−2.2 to 0.4)	0.756
Waist circumference (cm)			
Before	114.6 ± 2.0	108.6 ± 2.0	
After	114.0 ± 2.0	107.8 ± 2.4	
Change	−0.5 (−1.6 to 0.6)	−1.1 (−2.6 to 0.4)	0.505
Fat mass (kg)			
Before	41.4 ± 2.3	39.3 ± 1.9	
After	39.8 ± 2.1	38.6 ± 2.0	
Change	−1.0 (−1.8 to −0.3)	−0.7 (−1.7 to 0.4)	0.590
Lean mass (kg)			
Before	59.6 ± 2.5	49.7 ± 1.9	
After	60.2 ± 2.6	49.5 ± 2.1	
Change	0.7 (−0.1 to 1.6)	0.2 (−1.4 to 1.1)	0.259
Fat mass (%)			
Before	39.5 ± 1.8	42.7 ± 1.2	
After	38.5 ± 1.7	42.4 ± 1.0	
Change	−1.0 (−1.6 to −0.4)	−0.1 (−0.9 to 0.7)	0.088
Lean mass (%)			
Before	57.0 ± 1.8	54.1 ± 1.2	
After	58.1 ± 1.6	54.5 ± 1.1	
Change	1.0 (0.5 to 1.6)	0.2 (−0.6 to 1.0)	0.118
Fasting serum glucose (mmol/l)			
Before	10.7 ± 0.5	10.4 ± 0.8	
After	8.8 ± 0.5	10.7 ± 1.0	
Change	−1.9 (−2.7 to −1.1)	0.3 (−0.8 to 1.3)	0.002
HbA _{1c} (%)			
Before	7.37 ± 0.21	7.68 ± 0.47	
After	7.07 ± 0.24	8.10 ± 0.47	
Change	−0.33 (−0.75 to 0.09)	0.47 (−0.09 to 1.03)	0.028
Fructosamine (μmol/l)			
Before	298.5 ± 10.9	293.8 ± 18.6	
After	272.8 ± 9.0	313.4 ± 16.1	
Change	−25.0 (−41.2 to −8.9)	18.3 (−3.1 to 39.6)	0.003
Insulin (pmol/l)			
Before	124.8 ± 14.2	147.2 ± 53.4	
After	118.7 ± 16.7	122.8 ± 48.7	
Change	−7.8 (−38.1 to 22.5)	−21.5 (−61.6 to 18.5)	0.581
C-peptide (nmol/l)			
Before	1.48 ± 0.13	1.64 ± 0.39	
After	1.52 ± 0.13	1.53 ± 0.35	
Change	0.02 (−0.22 to 0.26)	−0.09 (−0.41 to 0.23)	0.592

Data are means ± SE or mean change values (95% CI). All change values are adjusted for differences in baseline values between groups.

glutide did not result in any hypoglycemic episodes. Therapy with sulfonylureas and insulin is associated with the risk of hypoglycemia (26), whereas the insulinotropic action of GLP-1 is attenuated as ambient glucose levels fall. This glucose-dependent mode of action is mediated by intracellular signaling mechanisms de-

pendent on a high ATP-to-ADP ratio, which is generated by the glucose-glycolysis signaling pathway (27,28). Thus, treatment with the long-acting GLP-1 derivative potentially conveys a low risk of drug-related hypoglycemia. This glucose-dependent mechanism has been confirmed for liraglutide in a glu-

cose-ramp study (29), where liraglutide only enhanced insulin secretory response under graded glucose infusion when plasma glucose was >6 mmol/l. In the present study, the placebo-corrected fasting plasma glucose was reduced by 2.2 mmol/l to an average of 8.8 mmol/l, and a corresponding significant placebo-

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