Original Investigation

Effect of Adding Liraglutide vs Placebo to a High-Dose Insulin Regimen in Patients With Type 2 Diabetes
A Randomized Clinical Trial

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IMPORTANCE An increasing number of patients with type 2 diabetes are treated with high doses of insulin. Such treatment is associated with weight gain, hypoglycemia, and high treatment burden.

OBJECTIVE To assess the effectiveness and safety of adding a glucagon-like peptide 1 receptor agonist to the treatment regimen of patients with type 2 diabetes requiring therapy with high-dose insulin.

DESIGN, SETTING, AND PARTICIPANTS This clinical trial was a double-blind, placebo-controlled, randomized (1:1) study with 6 months of follow-up, conducted from August 13, 2012, to February 9, 2015, at ambulatory clinics at the University of Texas Southwestern Medical Center and Parkland Hospital. Participants were 71 patients with uncontrolled type 2 diabetes (glycated hemoglobin level, 7.5%-11.0%) using more than 1.5 U/kg/d of insulin.

INTERVENTIONS Subcutaneous injection of liraglutide (1.8 mg/d) or matching placebo for 6 months.

MAIN OUTCOMES AND MEASURES The primary outcome was the change in glycated hemoglobin level. Secondary outcomes were changes in weight, hypoglycemia rate, insulin dosage, and quality-of-life measures.

RESULTS Among 71 patients, 45 (63%) were female. The mean (SD) age of patients was 54.2 (7.4) years, with a mean (SD) type 2 diabetes duration of 17.9 (8.4) years and a mean (SD) total daily dose of insulin of 247.0 (95.1) U. Ninety-three percent (66 of 71) of participants completed all scheduled visits. The glycated hemoglobin level improved from a mean (SD) of 9.0% (1.2%) to 7.9% (1.1%) in the liraglutide group ($P < .001$) and remained unchanged (8.9%) in the placebo group, with an estimated treatment difference of 0.9% (95% CI, −1.5 to −0.4) ($P = .002$). Weight decreased from a mean (SD) of 114.6 (21.4) kg to 113.6 (20.8) kg in the liraglutide group vs a mean (SD) increase from 116.1 (26.6) kg to 117.2 (27.2) kg in the placebo group, with a treatment difference of −2.3 kg (95% CI, −4.3 to −0.4 kg) ($P = .02$). The total daily dose of insulin decreased 11.5% (95% CI, −21.8% to −1.1%) in the liraglutide group ($P = .20$). The hypoglycemia rate was higher in the first month after initiation of liraglutide compared with placebo (2.30 vs 0.91 events per person-month, $P = .01$), while the overall hypoglycemia rate over the entire follow-up was similar between groups ($P = .11$). Glycemia control perception, satisfaction with insulin treatment, and willingness to continue insulin use improved more in the liraglutide group.

CONCLUSIONS AND RELEVANCE Liraglutide added to high-dose insulin therapy improved glycemic control, decreased body weight, and enhanced treatment satisfaction in this difficult-to-treat patient population with high-dose insulin requirements. Further studies are warranted to confirm these findings and evaluate the long-term risk and benefit of this treatment option.

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Type 2 diabetes is a progressive disease, characterized by ongoing decline in beta cell function. Ultimately, many patients require insulin to control hyperglycemia, with 30.8% of the estimated 29.1 million people with diabetes in the United States using insulin.[1-3] The main adverse effect of insulin treatment is weight gain, which can lead to increasing insulin dosage requirements. A growing number of insulin-treated patients require high doses of insulin, but unfortunately this treatment strategy has the potential to fuel a vicious cycle where patients attain little glycemic improvement, despite increasing insulin dosages and higher treatment burden.[4] Rarely, these high-dose insulin requirements are due to underlying genetic mutations or endocrine disorders, but in most cases are a function of treatment-related weight gain, lipotoxicity, and unsuppressed glucagon secretion that result in worsening beta cell function, which further promote hyperglycemia.[5,6] Patients requiring treatment with high insulin dosages have longer type 2 diabetes duration, higher body mass index (BMI), and multiple comorbidities and therefore represent a particular treatment challenge.

Glucagon-like peptide 1 receptor agonists have many actions that position them as candidates to break this cycle via their ability to slow gastric emptying, promote satiety, induce weight loss through direct central nervous system action,[7] increase glucose-dependent insulin release and decrease glucagon secretion,[8,9] and improve insulin sensitivity.[10] Potential concerns for their use in patients using high-dose insulin include lack of efficacy given an advanced disease state with minimal residual beta cell function, risk of additive hypoglycemia, and practical aspects like reduced adherence with another injectable diabetes drug when already using a complex insulin regimen and increased cost.[8]

The objective of this study was to investigate whether liraglutide is effective, safe, and feasible when added to an already complex therapeutic regimen using high-dose insulin. We compared the change in glycemic control, weight, insulin dosage, and quality of life, as well as the occurrence of adverse effects, in patients treated with liraglutide vs placebo when continuing the same stable baseline high-dose insulin regimen.

Key Points

Question What are the efficacy and safety of adding a glucagon-like peptide 1 receptor agonist to the treatment regimen of patients with type 2 diabetes requiring therapy with high doses of insulin?

Findings In this randomized clinical trial that included 71 adults, liraglutide significantly reduced glycated hemoglobin A_{1c} levels by 0.9% compared with placebo, while the overall rates of hypoglycemia and adverse events remained similar between groups.

Meaning Liraglutide is a safe and effective treatment option for patients requiring therapy with high doses of insulin to manage their type 2 diabetes.

Methods

Overall Design

This clinical trial was a 6-month, single-center, double-blind, placebo-controlled, randomized (1:1) study that assessed safety, efficacy, and effect on quality of life of adding liraglutide to the treatment regimen of patients with uncontrolled type 2 diabetes requiring high doses of insulin. The University of Texas Southwestern Research Ethics Board approved the trial protocol, and all participants provided written informed consent. The trial protocol can be found in Supplement 1.

Recruitment and Screening

Patients were recruited from Parkland Hospital outpatient clinics. Data were collected from August 13, 2012, to February 9, 2015. Eligible patients had type 2 diabetes, total daily dose (TDD) of insulin exceeding 1.5 U/kg/d, glycated hemoglobin level (HbA_{1c}) of 7.5% to 11.0%, age 18 years or older, and stable doses of all antihyperglycemic agents for at least 3 months before enrollment. Exclusion criteria included history of pancreatic disease (ie, pancreatitis, tumors, or pancreatic surgery), lipase level more than 3 times above normal, creatinine clearance of 30 mL/min/1.73 m^2 or less (to convert creatinine clearance to milliliters per second per meters squared, multiply by 0.0167), use of incretin therapy within the prior 90 days, and decompensated comorbidities. Race/ethnicity was self-reported by patients.

Run-in Period and Randomization

Eligible patients underwent a 10-day placebo-only run-in phase. Stratified (by weight of 104.0 kg and HbA_{1c} level of 8.5%) blocked randomization was performed using computer-generated codes. The study drug was initiated at 0.6 mg/d, was administered subcutaneously daily, and was increased weekly to 1.2 mg/d and to the final dosage of 1.8 mg/d. The active drug and matching placebo were supplied by the manufacturer in identical delivery devices and packaging to ensure the patient and study staff masking. Baseline hypoglycemic medications were continued unchanged during the study period.

Follow-up Schedule and Assessment of Outcomes

Follow-up clinic visits occurred at 1, 2, 4, and 6 months after randomization and were conducted by a study physician (A.V., L.H., or I.L.). All visits included measurement of vital signs (blood pressure, weight, and pulse), adverse event monitoring, review of glucose log, insulin dosage assessment and titration as needed, evaluation of the number of injections administered daily, distribution of trial drug, assessment of compliance, and dietary and lifestyle counseling.

The TDD of insulin and the number of injections administered daily were averaged over the 3 days before each visit. Compliance with the study drug was calculated based on the amount of returned product, while compliance with insulin was estimated by patient recall.

Treatment satisfaction and quality of life were assessed at the run-in visit and the end of the study using a modified Diabetes Quality of Life Clinical Trial Questionnaire (DQOL), with individual domain scores analyzed and reported. The details and rationale have been previously described.[11]

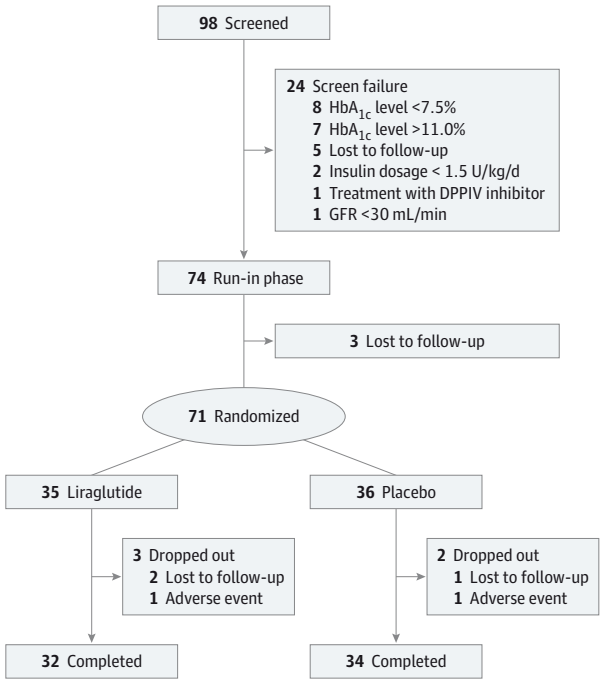
A complete safety assessment was performed at each contact with the patient. Hypoglycemic events were classified as any confirmed hypoglycemia (self-measured blood glucose [SMBG] level, <70 mg/dL irrespective of symptoms) (to convert glucose level to millimoles per liter, multiply by 0.0555), moderate hypoglycemia (SMBG level, <54 mg/dL irrespective of symptoms), or severe hypoglycemia (symptoms of hypoglycemia that required assistance from another individual for treatment regardless of capillary glucose level). The baseline hypoglycemia rate was calculated using the documented events that occurred during the placebo run-in phase.

Blood samples were obtained in fasting state, processed, and shipped immediately. They were analyzed by a commercial laboratory (Quest Diagnostics, Irving, Texas).

Insulin Titration

At randomization, the TDD of insulin was decreased by 20% in patients with an HbA_{1c} level of 8.0% or less. If no hypoglycemia events occurred, the insulin dosage was increased to the baseline dosage at the first in-person visit at 1 month after randomization. The insulin dosage was further titrated only for recurrent hypoglycemia (10% reduction for ≥2 SMBG levels of <70 mg/dL and 20% reduction for an SMBG level of <54 mg/dL), severe hypoglycemia (30% reduction), or symptomatic hyperglycemia (20% increase in the insulin dosage). Patients were asked to monitor capillary glucose levels 4 times a day. Logbooks and meter downloads were reviewed at each visit.

Figure 1. Consolidated Standards of Reporting Trials Diagram



DPPIV indicates dipeptidyl peptidase IV inhibitor; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin.

Statistical Analysis

The sample size was estimated using the results of the only published study[12] about the effect of the addition of liraglutide available at the time of protocol development. In this single-arm study, the addition of liraglutide to a high-dose insulin regimen led to a mean (SD) reduction in HbA_{1c} level from 8.5% (0.8%) to 7.1% (1.1%). Because this study did not have a control arm, we opted for a more conservative approach and estimated the final HbA_{1c} level in the active group to be a mean (SD) of 7.1% (0.9%) in the active intervention group and a mean (SD) of 7.6% (0.9%) in the control group (mean [SD] between-group HbA_{1c} level difference of 0.5% [0.7%]). Based on these assumptions, 32 volunteers per group had to complete the study to yield power of at least 0.80 at the $\alpha = .05$ level of significance.

An intent-to-treat analysis was performed consisting of all randomized individuals who received study medication and had at least 1 postrandomization study visit. The randomization and final month 6 postrandomization measurements plus all available repeated-measures data from the 1-month, 2-month, or 4-month intermediate study visits were included in the analysis models. The month 6 HbA_{1c} level response was compared between groups using mixed-effects model repeated-measures analysis. Secondary continuous end points, such as weight, TDD of insulin, and DQOL measurements, were compared between groups using the same analysis approach. These repeated-measures models included a between-group factor, a repeated factor for study visits, and a group × visit interaction term, and the study participant was modeled as a random effect. The difference in response between treatment groups was assessed via the interaction effect. Pairwise comparisons were made using the least squares contrasts derived from these mixed-effects models. A post hoc analysis used models stratified by the baseline HbA_{1c} level (<9.0% vs ≥9.0%) to assess the effect of the baseline HbA_{1c} level on treatment response. Similar analyses were performed stratifying by metformin use and by insulin regimen (human premixed insulin vs all other regimens). Hypoglycemic event rates were analyzed with Poisson repeated-measures regression models. Categorical variables, such as the occurrence of adverse events, were compared between groups with the Fisher exact test. A 2-sided $P < .05$ was considered statistically significant. Statistical analyses were conducted with a software program (SAS, version 9.4; SAS Institute).

Results

Baseline Characteristics of Participants

We randomized 71 patients (**Figure 1**). Ninety-three percent (66 of 71) of participants completed all scheduled visits.

The volunteers were a mean (SD) of 54.2 (7.4) years old, had long-standing (median duration, 17 years, and using insulin for 8 years) uncontrolled diabetes (mean [SD] HbA_{1c} level, 8.9% [1.1%]), and had a high BMI (calculated as weight in kilograms divided by height in meters squared) (mean [SD], 41.2 [8.7] kg/m2) (**Table 1**). Patients were using the following insulin regimens: 48% (34 of 71) used premixed human insulin, 40% (28 of 71) used a basal-bolus regimen with analogue insulins,

Table 1. Baseline Characteristics and Demographics of Randomized Patients

Variable	All Patients (N = 71)	Liraglutide (n = 35)	Placebo (n = 36)
Age, mean (SD), y	54.2 (7.4)	52.8 (8.1)	55.5 (6.6)
Sex, No. (%)			
Men	26 (37)	12 (34)	14 (39)
Women	45 (63)	23 (66)	22 (61)
Race/ethnicity, No. (%)			
White	26 (37)	15 (43)	11 (31)
Hispanic	18 (25)	9 (26)	9 (25)
African American	26 (37)	11 (31)	15 (42)
Asian	1 (1)	0	1 (3)
BMI, mean (SD)	41.2 (8.7)	40.7 (6.7)	41.6 (10.4)
Weight, mean (SD), kg	115.4 (24.0)	114.6 (21.4)	116.1 (26.6)
Diabetes duration, median (25th to 75th percentile), y[a]	17 (12-24)	16 (12-23)	18 (13-27)
Insulin use duration, median (25th to 75th percentile), y[b]	8 (4-13)	6 (3-12)	8 (5-13)
Hypoglycemia rate, events per person-month[c]	0.77	0.73	0.81
Current smoker, No. (%)	7 (9.9)	6 (17.1)	1 (2.8)
Drug therapy, No. (%)			
Metformin	50 (72)	28 (80)	22 (61)
Statin	60 (85)	28 (80)	32 (89)
Antihypertensive	67 (94)	33 (94)	34 (94)
Alanine aminotransferase level, U/L	30.5 (16.9)	30.7 (15.5)	30.3 (18.4)
Aspartate aminotransferase level, U/L	29.7 (18.2)	31.8 (20.5)	27.7 (15.7)
Amylase level, U/L	40.2 (16.5)	37.1 (16.0)	43.2 (16.6)
Lipase level, U/L	35.6 (22.2)	40.2 (23.0)	31.2 (20.7)
Creatinine level, mg/dL	1.0 (0.3)	0.9 (0.3)	1.0 (0.3)
Hemoglobin level, g/dL	13.2 (1.5)	13.3 (1.5)	13.0 (1.6)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

SI conversion factors: To convert creatinine level to micromoles per liter, multiply by 88.4; glucose level to millimoles per liter, multiply by 0.0555; and hemoglobin level to grams per liter, multiply by 10.0. To convert all other laboratory levels (alanine aminotransferase, amylase, aspartate aminotransferase, and lipase) to microkatals per liter, multiply by 0.0167.

[a] The mean (SD) diabetes duration among all patients was 17.9 (8.4) years.

[b] The mean (SD) total daily dose of insulin among all patients was 247.0 (95.1) U.

[c] Hypoglycemia rate is the number of hypoglycemic events (capillary glucose level of <70 mg/dL) documented during the run-in period regardless of symptoms.

8% (6 of 71) used a human insulin neutral protein hagedorn (NPH) and regular combination, and 4% (3 of 71) used U500 regular human insulin, all equally distributed between the 2 groups. All patients were treated with the maximum tolerated dosage of metformin, unchanged throughout the trial. Slightly more patients were completely metformin intolerant in the placebo group (39% [14 of 36] vs 20% [7 of 35]), while the dosage among metformin users was similar (mean [SD], 1866 [403] mg in the liraglutide group vs 1775 [509] mg in the placebo group). The characteristics (age, BMI, sex, and TDD of insulin) of the screen failure group (n = 24) were similar to those of the randomized group.

Efficacy

The HbA_{1c} level decreased by 0.9% (95% CI, −1.4% to −0.5%) ($P < .001$) in the liraglutide group compared with 0.0% (95% CI, −0.4% to 0.4%) in the placebo group, for an estimated treatment difference of −0.9% (95% CI, −1.5% to −0.4%) ($P = .002$) (**Table 2**, **Table 3**, **Figure 2**A, and eFigure, A in Supplement 2). The target HbA_{1c} level of less than 7.0% was achieved by 22% (7 of 32) of patients in the liraglutide group vs 3% (1 of 34) of patients in the placebo group ($P = .02$). In the liraglutide group, 53% (17 of 32) of patients had an improvement in HbA_{1c} level from baseline without associated weight gain compared with 29% (10 of 34) of patients in the placebo group ($P = .08$). Fasting plasma glucose level improved in the liraglutide group ($P = .05$) but not in the placebo group ($P = .36$).

The subgroup of patients with a baseline HbA_{1c} level of at least 9.0% had a greater improvement in HbA_{1c} level regardless of treatment assignment (mean [SD], −1.1% [1.2%] in the liraglutide group and −0.6% [1.1%] in the placebo group) compared with patients with a baseline HbA_{1c} level of less than 9.0% (mean [SD], −0.7% [0.9%] in the liraglutide group and 0.5% [1.3%] in the placebo group). Furthermore, the treatment effect on HbA_{1c} level was not influenced by baseline use of metformin ($P = .62$ for interaction).

The TDD of insulin and the insulin dosage per kilogram of body weight were not different between groups, but both decreased in the liraglutide group (Table 2, Table 3, and Figure 2C). The number of daily injections (insulin only) did not change significantly in either group, with a mean number of 3.8 injections per day in both groups throughout the study.

Weight decreased by −2.0 kg (95% CI, −3.4 to −0.6 kg) ($P = .007$) in the liraglutide group, while weight increased by 0.4 kg (95% CI, −1.0 to 1.7 kg) ($P = .60$) in the placebo group, for a treatment difference of −2.3 kg (95% CI, −4.3 to −0.4 kg) ($P = .02$) (Table 2, Table 3, Figure 2B, and eFigure, B in Supplement 2). The treatment effect on weight was similar in patients with a baseline HbA_{1c} level of less than 9.0% vs at least 9.0%.

A subanalysis was performed evaluating the interaction of the baseline insulin type (premixed insulin regimens in 48% [34 of 71] of the cohort vs treatment with other insulin regimens [primarily basal-bolus]) and the effect of treatment

Table 2. Effects of Liraglutide Compared With Placebo on Primary, Secondary, and Other Efficacy Outcomes at 6 Months

Variable	Liraglutide			Placebo				
	Mean (SD)		LS Mean (95% CI)	Mean (SD)		LS Mean (95% CI)	Mean (95% CI)	*P* Value for ΔL vs ΔP
	Baseline (n = 35)	Month 6 (n = 32)	ΔL_{M6-B}	Baseline (n = 36)	Month 6 (n = 34)	ΔP_{M6-B}	ΔL-ΔP	
HbA_{1c} level, %	9.0 (1.2)	7.9 (1.1)	−0.9 (−1.4 to −0.5)[a]	8.9 (1.0)	8.9 (1.3)	0.0 (−0.4 to 0.4)	−0.9 (−1.5 to −0.4)	.002
HbA_{1c} level <7.0%, No. (%)	0	7 (22)[b]	NA	0	1 (3)	NA	NA	.02
Weight, kg	114.6 (21.4)	113.6 (20.8)	−2.0 (−3.4 to −0.6)[b]	116.1 (26.6)	117.2 (27.2)	0.4 (−1.0 to 1.7)	−2.3 (−4.3 to −0.4)	.02
BMI	40.7 (6.7)	40.1 (6.3)	−0.7 (−1.2 to −0.2)[b]	41.6 (10.4)	41.9 (10.7)	0.2 (−0.3 to 0.7)	−0.9 (−1.6 to −0.2)	.01
TDD of insulin, median (25th-75th percentile), U	240 (180-292)	200 (163-275)	−37[b,c]	220 (180-288)	218 (160-260)	−10[c]	−28[c]	.06
Insulin dose, median (25th-75th percentile), U/kg/d	2.1 (1.7-2.6)	1.6 (1.4-2.1)	−0.3[b,c]	1.8 (1.6-2.4)	1.7 (1.4-2.4)	−0.1[c]	−0.2[c]	.10
No. of insulin injections per day	3.8 (1.2)	3.7 (1.4)	−0.2 (−0.5 to 0.1)	3.8 (1.4)	3.8 (1.3)	0 (−0.3 to 0.3)	−0.2 (−0.6 to 0.2)	.27
Blood pressure, mm Hg								
Systolic	135 (15)	134 (18)	−1 (−7 to 5)	137 (16)	135 (17)	−3 (−9 to 3)	2 (−7 to 11)	.67
Diastolic	79 (13)	81 (14)	2 (−2 to 6)	76 (13)	74 (10)	−2 (−6 to 2)	4 (−2 to 9)	.21
Pulse, beats/min	81.5 (12.4)	87.4 (12.5)	6 (3 to 10)[a]	77.4 (9.2)	78.1 (10.7)	0.2 (−3 to 4)	6 (1 to 11)	.02
FPG level, mg/dL	217 (69)	179 (75)	−37 (−70 to −4)[b]	213 (77)	197 (98)	−15 (−48 to 17)	−21 (−68 to 25)	.36
Cholesterol level, mg/dL								
Total	171 (41)	154 (41)	−16 (−29 to −2)[b]	150 (31)	152 (42)	2 (−11 to 15)	−18 (−37 to 1)	.07
Low density	98 (38)	84 (37)	−12 (−23 to −1)[b]	80 (28)	76 (28)	−3 (−13 to 8)	−9 (−25 to 6)	.24
High density	38 (10)	37 (10)	−2 (−4 to 1)	37 (7)	38 (10)	1 (−1 to 3)	−3 (−6 to 1)	.11
Triglyceride levels, mg/dL	149 (111-232)	142 (105-216)	−12[c]	169 (108-221)	156 (116-212)	−2[c]	−10[c]	.49

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; LS mean, least squares mean; M6-B, from baseline to 6 months; NA, not applicable; TDD, total daily dose; ΔL, change in the liraglutide group; ΔP, change in the placebo group.

SI conversion factors: To convert cholesterol level to millimoles per liter, multiply by 0.0259; glucose level to millimoles per liter, multiply by 0.0555; and triglyceride levels to millimoles per liter, multiply by 0.0113.

[a] $P < .001$ from mixed-effects model repeated-measures analysis comparing baseline with month 6 response within the treatment arm.

[b] $P < .05$ from mixed-effects model repeated-measures analysis comparing baseline with month 6 response within the treatment arm.

[c] Difference corresponds to the geometric mean.

assignment. We found that the baseline insulin type did not alter the treatment effect on HbA_{1c} level ($P = .70$ for interaction), weight ($P = .50$), or TDD of insulin ($P = .86$).

Hypoglycemia

The percentages of patients experiencing any episodes of hypoglycemia (capillary glucose level, <70 mg/dL) during the study were 85% (30 of 35) in the liraglutide group and 71% (25 of 36) in the placebo group ($P = .25$), while the percentages of patients experiencing moderate hypoglycemia (capillary glucose level, <54 mg/dL) were 55% (18 of 35) in the liraglutide group and 37% (13 of 36) in the placebo group ($P = .22$). The overall rates of any hypoglycemia over the entire study period were 1.44 events per person-month in the liraglutide group vs 0.93 events per person-month in the placebo group ($P = .11$), with a risk ratio of 1.6 (95% CI, 0.9-2.9). The rate of moderate hypoglycemia was 0.47 vs 0.22 events per person-month ($P = .13$), with a risk ratio of 2.0 (95% CI, 0.8-5.1). The rate of any hypoglycemia occurring within the first month after randomization was higher in the liraglutide group (2.30 vs 0.91 events per person-month, $P = .01$), as was the rate of moderate hypoglycemia (0.85 vs 0.15 events per person-month, $P = .002$). The hypoglycemia rate decreased after the first month and was not significantly different between groups at any of the subsequent months (Figure 2D). Two major hypoglycemic events in one patient occurred during the study in the placebo group.

We undertook a post hoc analysis to evaluate if the hypoglycemia rate, especially during the first month after initiation of the intervention, was influenced by the baseline HbA_{1c} level. While the overall group × treatment interaction stratified by the baseline HbA_{1c} level was not significant, the risk ratio of any hypoglycemia during the first month was 1.4 (95% CI, 0.6-3.4) times higher in the liraglutide group if the baseline HbA_{1c} level was less than 9.0% vs at least 9.0%. Furthermore, the risk ratio of any hypoglycemia attributed to liraglutide vs placebo was 2.6 (95% CI,

Table 3. Effect of Liraglutide Compared With Placebo on Patient Reported Outcomes[a]

Variable	Liraglutide			Placebo				
	Mean (SD)		LS Mean (95% CI)	Mean (SD)		LS Mean (95% CI)	Mean (95% CI)	*P* Value for ΔL vs ΔP
	Baseline (n = 35)	Month 6 (n = 32)	ΔL_{M6-B}	Baseline (n = 36)	Month 6 (n = 34)	ΔP_{M6-B}	ΔL-ΔP	
General health perception	3.8 (0.8)	3.1 (0.9)	−0.7 (−1 to −0.4)[b]	4.0 (0.8)	3.6 (0.6)	−0.4 (−0.6 to −0.1)[c]	−0.4 (−0.8 to 0.1)	.09
Current health perception	2.9 (1.1)	2.1 (0.9)	−0.8 (−1.3 to −0.4)[b]	3.1 (0.9)	2.6 (1.0)	−0.5 (−0.9 to −0.1)[c]	−0.3 (−1.0 to 0.3)	.29
Treatment satisfaction	3.1 (0.7)	2.4 (0.8)	−0.7 (−0.9 to −0.5)[b]	3.1 (0.7)	2.7 (0.7)	−0.4 (−0.6 to −0.2)[c]	−0.3 (−0.6 to 0.0)	.06
Treatment impact	2.6 (0.6)	2.3 (0.5)	−0.3 (−0.5 to −0.2)[b]	2.7 (0.7)	2.6 (0.7)	−0.1 (−0.3 to 0.0)	−0.2 (−0.4 to 0.0)	.06
Social or vocational worry	1.7 (0.9)	1.5 (0.7)	−0.1 (−0.3 to 0.2)	1.6 (0.8)	1.8 (0.9)	0.2 (−0.1 to 0.4)	−0.3 (−0.6 to 0.1)	.16
Hypoglycemia fear	1.9 (0.6)	1.9 (0.6)	0.0 (−0.2 to 0.2)	2.0 (0.8)	2.0 (0.8)	0.0 (−0.2 to 0.2)	0.0 (−0.3 to 0.2)	.72
Glycemia control perception	3.6 (1.0)	2.0 (1.0)	−1.6 (−2.1 to −1.1)[b]	3.4 (1.2)	2.9 (1.0)	−0.5 (−1.0 to −0.0)[c]	−1.0 (−1.7 to −0.3)	.004
Lifestyle flexibility	2.5 (0.8)	2.2 (0.9)	−0.3 (−0.6 to −0.0)[c]	2.8 (0.7)	2.6 (0.7)	−0.2 (−0.5 to 0.1)	−0.1 (−0.5 to 0.3)	.58
Social stigma	2.2 (1)	2.5 (1.1)	0.4 (0.0 to 0.7)[c]	2.3 (1.1)	2.4 (1.0)	0.1 (−0.2 to 0.4)	0.3 (−0.2 to 0.7)	.24
Satisfaction with insulin treatment	3.3 (1.2)	1.6 (1.0)	−1.7 (−2.3 to −1.2)[b]	2.8 (1.3)	2.3 (1.3)	−0.5 (−1.0 to 0.1)	−1.2 (−2.0 to −0.4)	.003
Willingness to continue insulin treatment	2.2 (1.4)	1.0 (0.5)	−1.1 (−1.6 to −0.6)[b]	2.0 (1.3)	2.1 (1.3)	0.1 (−0.4 to 0.6)	−1.2 (−1.9 to −0.5)	<.001

Abbreviations: LS mean, least squares mean; M6-B, from baseline to 6 months; ΔL, change in the liraglutide group; ΔP, change in the placebo group.

SI conversion factors: To convert cholesterol level to millimoles per liter, multiply by 0.0259; glucose level to millimoles per liter, multiply by 0.0555; and triglyceride levels to millimoles per liter, multiply by 0.0113.

[a] Quality of life was assessed using a modified Diabetes Quality of Life Clinical Trial Questionnaire.[11]

[b] $P < .001$ from mixed-effects model repeated-measures analysis comparing baseline with month 6 response within the treatment arm.

[c] $P < .05$ from mixed-effects model repeated-measures analysis comparing baseline with month 6 response within the treatment arm.

1.0-6.6) times higher in the group with a baseline HbA_{1c} level of less than 9.0% and 2.4 (95% CI, 0.7-8.5) times higher in the group with a baseline HbA_{1c} level of at least 9.0%.

A similar analysis was performed to explore if the baseline insulin type influenced the hypoglycemia rate. Higher rates of confirmed hypoglycemia and moderate hypoglycemia in the first month after initiation of liraglutide, as well as the entire study period, were observed in patients treated with insulin regimens other than premixed (primarily basal-bolus) (eTable in Supplement 2).

Other Adverse Events

The rate of adverse events was similar in both groups (40% [14 of 35] of patients in the liraglutide group vs 47% [17 of 36] of patients in the placebo group, $P = .39$). There were 2 serious adverse events in the liraglutide group and 6 serious adverse events in the placebo group. One patient in each group discontinued the trial medication owing to adverse events. Gastrointestinal tract adverse events were the most common (37% [13 of 35] of patients in the liraglutide group and 36% [13 of 36] of patients in the placebo group), and most occurred within the first 4 weeks after randomization. Pulse rate increased significantly in the liraglutide group (from a mean [SD] of 81.5 [12.4] to 87.0 [12.5] beats/min, $P < .001$) but not in the placebo group (eFigure, D in Supplement 2).

There were no significant changes in the levels of pancreatic enzymes (amylase and lipase), liver enzymes (alanine aminotransferase and aspartate aminotransferase), hemoglobin, or creatinine between groups, but alanine aminotransferase and aspartate aminotransferase levels decreased in the liraglutide group ($P < .05$). The lipase level increased by a median of 6.5 U/L (from a baseline median of 37 U/L) in the liraglutide group ($P = .06$) (eFigure, C in Supplement 2).

Compliance, Satisfaction, and Quality of Life

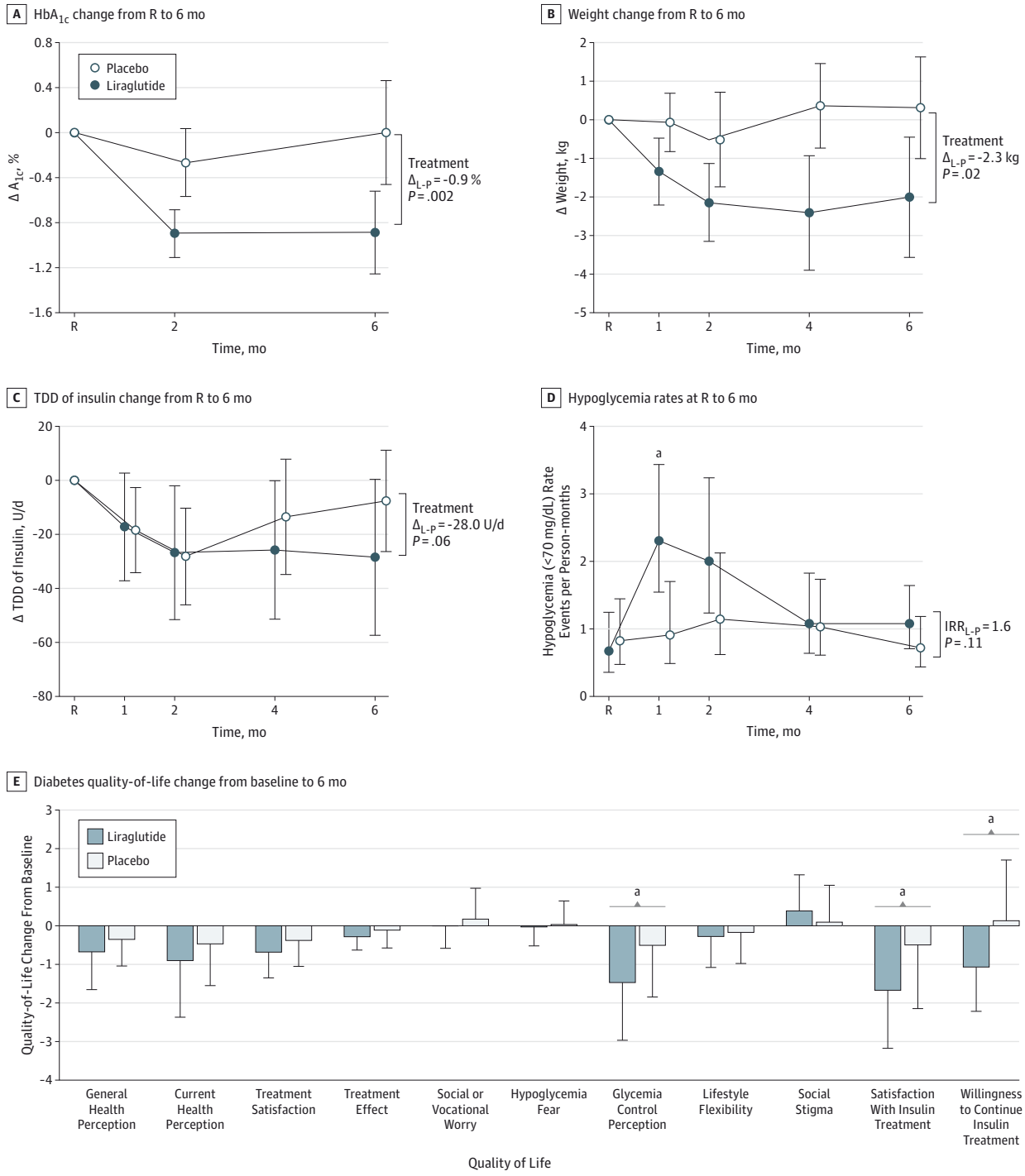
Compliance with the study medication was high at a mean (SD) of 97.6% (6.9%) in the liraglutide group and 94.8% (8.0%) in the placebo group ($P = .02$). The mean (SD) compliance with insulin was 98.7% (2.7%) in the liraglutide group and 97.7% (3.4%) in the placebo group.

The modified DQOL results (Table 3 and Figure 2E) improved in both groups during the study. Patients in the liraglutide group had a greater improvement in the scores exploring glycemic control perception ($P = .004$), satisfaction with insulin ($P = .003$), and willingness to continue insulin ($P < .001$). General health perception ($P = .09$), treatment satisfaction ($P = .06$), and treatment impact ($P = .06$) domains were also improved, but the between-group differences were nonsignificant.

Discussion

The addition of liraglutide compared with placebo in patients with type 2 diabetes requiring high-dose insulin therapy (>1.5 U/kg/d) led to improved glycemic control, weight loss, and

Figure 2. Primary and Main Secondary Study Outcomes



Hypoglycemia is a capillary glucose level of less than 70 mg/dL (to convert glucose level to millimoles per liter, multiply by 0.0555). Quality of life was assessed on a scale of 1-5 using a modified Diabetes Quality of Life Clinical Trial Questionnaire.[11] A negative number represents improvement from baseline.

HbA_{1c} indicates glycated hemoglobin; IRR, incident rate ratio; L-P, ratio of liraglutide to placebo; R, randomization; TDD, total daily dose.

[a] $P < .01$.

enhanced treatment satisfaction. Furthermore, treatment with liraglutide in this group of patients with long-standing type 2 diabetes (mean, 17.9 years) was well tolerated, showed a high compliance rate, and had a high patient satisfaction rating. While the overall hypoglycemia rate over 6 months was not different between treatments, patients randomized to liraglutide experienced a higher hypoglycemia rate in the first month after treatment initiation.

Our results are in line with the only other study[13] performed to date in a similar patient population. Lane at al[13] performed an open-label study that compared treatment with liraglutide (n = 21) vs insulin titration (n = 16) in patients with type 2 diabetes requiring more than 100 U of insulin daily. Compared with their study, we observed herein a smaller weight change and insulin-sparing effect but found a larger decrease in HbA_{1c} level and a higher hypoglycemia rate in the first month after randomization to liraglutide, all of which could be explained by the following differences between the protocols and patient populations. First, we only used insulin dosage adjustments for safety, while Lane et al[13] performed protocol-driven insulin titration in both treatment groups, which led to a larger effect on HbA_{1c} level but a smaller effect on the insulin dosage in our study. Second, the protocol-driven preemptive insulin dosage adjustment was smaller in our study (20% reduction for an HbA_{1c} level of ≤8.0% vs 25% in the study by Lane et al[13]) and likely contributed to the higher hypoglycemia rate and the smaller effect on the insulin dosage in our study. Therefore, we suggest a 25% to 30% preemptive insulin dosage reduction in patients with a baseline HbA_{1c} level of less than 9.0% on initiation of liraglutide therapy.

We enrolled patients regardless of their type of baseline insulin therapy, and most of our patients (48% [35 of 71]) were receiving a premixed insulin regimen. To account for this heterogeneity, we undertook subanalyses to contrast the outcomes in patients receiving premixed insulin vs the others (primarily basal-bolus regimens). We found that the baseline insulin type did not influence the observed results on any of the studied variables except hypoglycemia, such that those treated with mixed regimens had a lower hypoglycemia rate. This finding is unexpected and counterintuitive, yet it was consistent across hypoglycemia definitions and throughout the duration of the study. This result is intriguing and merits reevaluation and confirmation in an independent cohort.

Several limitations of the study are noteworthy. The insulin dosage was kept unchanged during the study, and titration was only performed for safety reasons (symptomatic hypoglycemia or hyperglycemia). As a consequence, the overall change in insulin dosage was small and not significant between groups. The study was designed this way to fully assess the effect of the addition of liraglutide to the drug regimen in this patient population independent of insulin titration, but also based on the premise that the insulin dosage has already been optimized in these patients, who have been followed up in our diabetes clinic, as well as that further insulin uptitration beyond these already high dosages is associated with adverse events but no meaningful improvement in glycemia. This investigation was a relatively small, single-center study; therefore, the results should be interpreted with caution before further validation of these findings. Our study only lasted 6 months, and establishing the long-term durability of this treatment combination is important. Furthermore, it is unknown whether the improved glycemic control translates into any future reduction in the risk of complications or adverse outcomes, including cardiovascular outcomes. Especially in light of the high cost burden of such treatment, this treatment option would have to demonstrate long-term sustainable benefits on glycemic control and comorbidities, as well as quality of life and overall health care spending.

Our investigation has the advantages of representing the largest study to date in this patient population, having a high completion rate, and being masked both to patients and investigators. We recruited our volunteers from a large county hospital system and had a high representation of minority patients with low socioeconomic status; therefore, the findings are applicable irrespective of social or educational barriers. Furthermore, the addition of liraglutide led to clinically meaningful improvements in treatment satisfaction, an important consideration given the chronic nature of this disease and its long-term effect on daily life.

Conclusions

The results of this trial suggest that the addition of liraglutide is an effective treatment option for patients requiring treatment with high-dose insulin to manage their type 2 diabetes. In this difficult-to-treat population with long-standing disease, the addition of liraglutide to a complex insulin regimen led to improvement in glycemic control, weight loss, and treatment satisfaction. The long-term durability of these benefits and the effect on future reduction in the risk of complications or adverse outcomes will be important to establish to justify the significant added cost of this treatment.

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Study concept and design: Harrison, Adams-Huet, Lingvay.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Vanderheiden, Warshauer, Lingvay.
Critical revision of the manuscript for important intellectual content: Harrison, Li, Adams-Huet.
Statistical analysis: Li, Adams-Huet.
Study supervision: Lingvay.

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REFERENCES

1. Mann DM, Woodward M, Ye F, Krousel-Wood M, Muntner P. Trends in medication use among US adults with diabetes mellitus: glycemic control at the expense of controlling cardiovascular risk factors. *Arch Intern Med*. 2009;169(18):1718-1720.

2. Centers for Disease Control and Prevention. Age-adjusted percentage of adults with diabetes using diabetes medication, by type of medication, United States; 1997-2011. http://www.cdc.gov/diabetes/statistics/meduse/fig2.htm. Published 2012. Accessed September 30, 2015.

3. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014: estimates of diabetes and its burden in the United States. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf. Published 2014. Accessed September 30, 2015.

4. Schofield CJ, Sutherland C. Disordered insulin secretion in the development of insulin resistance and type 2 diabetes. *Diabet Med*. 2012;29(8):972-979.

5. Ovalle F. Clinical approach to the patient with diabetes mellitus and very high insulin requirements. *Diabetes Res Clin Pract*. 2010;90(3):231-242.

6. Defronzo RA. Banting Lecture: from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-795.

7. van Bloemendaal L, Ten Kulve JS, la Fleur SE, Ijzerman RG, Diamant M. Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS. *J Endocrinol*. 2014;221(1):T1-T16.

8. Tzefos M, Olin JL. Glucagon-like peptide-1 analog and insulin combination therapy in the management of adults with type 2 diabetes mellitus. *Ann Pharmacother*. 2010;44(7-8):1294-1300.

9. Kielgast U, Krarup T, Holst JJ, Madsbad S. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in type 1 diabetic patients with and without residual beta-cell function. *Diabetes Care*. 2011;34(7):1463-1468.

10. Jinnouchi H, Sugiyama S, Yoshida A, et al. Liraglutide, a glucagon-like peptide-1 analog, increased insulin sensitivity assessed by hyperinsulinemic-euglycemic clamp examination in patients with uncontrolled type 2 diabetes mellitus. *J Diabetes Res*. 2015;2015:706416.

11. Lingvay I, Legendre JL, Kaloyanova PF, Zhang S, Adams-Huet B, Raskin P. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care*. 2009;32(10):1789-1795.

12. Lane W, Weinrib S, Rappaport J. The effect of liraglutide added to U-500 insulin in patients with type 2 diabetes and high insulin requirements. *Diabetes Technol Ther*. 2011;13(5):592-595.

13. Lane W, Weinrib S, Rappaport J, Hale C. The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial. *Diabetes Obes Metab*. 2014;16(9):827-832.