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A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

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ABSTRACT

BACKGROUND

Obesity is a chronic disease with serious health consequences, but weight loss is difficult to maintain through lifestyle intervention alone. Liraglutide, a glucagon-like peptide-1 analogue, has been shown to have potential benefit for weight management at a once-daily dose of 3.0 mg, injected subcutaneously.

METHODS

We conducted a 56-week, double-blind trial involving 3731 patients who did not have type 2 diabetes and who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30 or a BMI of at least 27 if they had treated or untreated dyslipidemia or hypertension. We randomly assigned patients in a 2:1 ratio to receive once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (2487 patients) or placebo (1244 patients); both groups received counseling on lifestyle modification. The coprimary end points were the change in body weight and the proportions of patients losing at least 5% and more than 10% of their initial body weight.

RESULTS

At baseline, the mean (±SD) age of the patients was 45.1±12.0 years, the mean weight was 106.2±21.4 kg, and the mean BMI was 38.3±6.4; a total of 78.5% of the patients were women and 61.2% had prediabetes. At week 56, patients in the liraglutide group had lost a mean of 8.4±7.3 kg of body weight, and those in the placebo group had lost a mean of 2.8±6.5 kg (a difference of −5.6 kg; 95% confidence interval, −6.0 to −5.1; P<0.001, with last-observation-carried-forward imputation). A total of 63.2% of the patients in the liraglutide group as compared with 27.1% in the placebo group lost at least 5% of their body weight (P<0.001), and 33.1% and 10.6%, respectively, lost more than 10% of their body weight (P<0.001). The most frequently reported adverse events with liraglutide were mild or moderate nausea and diarrhea. Serious events occurred in 6.2% of the patients in the liraglutide group and in 5.0% of the patients in the placebo group.

CONCLUSIONS

In this study, 3.0 mg of liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight and improved metabolic control. (Funded by Novo Nordisk; SCALE Obesity and Prediabetes NN8022-1839 ClinicalTrials.gov number, NCT01272219.)

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THE INCREASE IN THE RATE OF OBESITY, a chronic disease with serious health consequences, largely explains the recent tripling in the prevalence of type 2 diabetes.[1,2] Weight loss of 5 to 10% has been shown to reduce complications related to obesity and improve quality of life[3-7]; however, weight loss is difficult to maintain with lifestyle intervention alone.[8]

Liraglutide, a glucagon-like peptide-1 analogue with 97% homology to human glucagon-like peptide-1, is approved for the treatment of type 2 diabetes at doses up to 1.8 mg once daily.[9] Weight loss with liraglutide is dose-dependent up to 3.0 mg once daily[10,11] and is mediated by reduced appetite and energy intake rather than by increased energy expenditure.[12]

A Quick Take summary is available at NEJM.org

This 56-week, randomized, placebo-controlled trial aimed to evaluate the efficacy and safety of 3.0 mg of liraglutide, injected subcutaneously once daily, as an adjunct to a reduced-calorie diet and increased physical activity, for weight management in overweight or obese adults who did not have diabetes at baseline.

METHODS

STUDY OVERVIEW

We conducted the study from June 1, 2011, through March 18, 2013, at 191 sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia. The trial protocol was approved by local ethics committees or institutional review boards and is available with the full text of this article at NEJM.org. The trial was conducted in accordance with the principles of the Declaration of Helsinki[13] and Good Clinical Practice guidelines.[14] A 2-year extension of the trial involving patients with prediabetes that was designed to evaluate whether liraglutide is associated with delayed onset of type 2 diabetes was recently completed. All the authors were involved in the design or conduct of the study and the preparation of the manuscript, including the decision to submit it for publication, and all attest to the accuracy and completeness of data and the data analyses. The sponsor, Novo Nordisk, planned and performed the statistical analyses, provided editorial and writing assistance, and provided the trial drugs.

PATIENTS

The trial enrolled patients 18 years of age or older who had stable body weight and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, or 27 or higher if the patient had treated or untreated dyslipidemia or hypertension (Table S1 in the Supplementary Appendix, available at NEJM.org). All the patients provided written informed consent before participation. Key exclusion criteria were type 1 or 2 diabetes, the use of medications that cause clinically significant weight gain or loss, previous bariatric surgery, a history of pancreatitis, a history of major depressive or other severe psychiatric disorders, and a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. Details of the eligibility and exclusion criteria are provided in the Supplementary Appendix.

STUDY DESIGN AND TREATMENTS

Randomization was performed with the use of a telephone or Web-based system provided by the sponsor. Eligible patients were randomly assigned, in a 2:1 ratio, to receive once-daily subcutaneous injections of liraglutide, starting at a dose of 0.6 mg with weekly 0.6-mg increments to 3.0 mg, or placebo; both groups received counseling on lifestyle modification (Fig. S1 in the Supplementary Appendix). Patients were stratified according to prediabetes status at screening[15] and according to BMI (≥30 vs. <30). Patients, investigators, and the sponsor were unaware of the study-group assignments. Liraglutide and placebo were provided in FlexPen devices (Novo Nordisk). After 56 weeks, patients in the liraglutide group who did not have prediabetes at screening were randomly assigned in a 1:1 ratio to continue receiving liraglutide or to switch to placebo for 12 weeks to assess whether efficacy was maintained after discontinuation of liraglutide treatment and whether there were safety issues related to discontinuation. Patients in the placebo group continued to receive placebo.

STUDY PROCEDURES AND END POINTS

Patients were evaluated every 2 weeks until week 8; thereafter, patients were evaluated every 4 weeks until week 44 and were evaluated again

at weeks 50, 56, 58, 60, 64, 68, and 70. All patients received standardized counseling on lifestyle modification approximately monthly (see the Supplementary Appendix).[11] Patients who withdrew early were asked to return at week 56 for measurement of their weight and recording of adverse events.

The three prespecified coprimary end points, assessed at week 56, were weight change from baseline, the proportion of patients who lost at least 5% of their baseline body weight, and the proportion of patients who lost more than 10% of their baseline body weight. Secondary end points included changes from baseline in BMI, waist circumference, glycemic control variables, cardiometabolic biomarkers, and health-related quality of life. The timing of assessments is described in the Methods section in the Supplementary Appendix. Health-related quality of life was assessed with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; in which higher scores indicate better quality of life)[16] and the Impact of Weight on Quality of Life–Lite[17] (in which higher scores indicate better quality of life) and Treatment Related Impact Measure–Weight[18] (in which higher scores indicate better quality of life) questionnaires. The proportion of patients who modified their use of lipid-lowering or antihypertensive medications was also assessed. Additional methods are described in the Supplementary Appendix.

Specific attention was given to types of adverse events that have an increased prevalence among obese persons or that were relevant to the drug class of liraglutide: of 17 types of adverse events, 9 were prospectively assessed by independent medical experts who were unaware of the study-group assignments (Table S2 in the Supplementary Appendix). We report adverse events that occurred during the main 56-week trial period, with onset on or after the first day of treatment and no later than 14 days after the last day of treatment, unless otherwise stated.

STATISTICAL ANALYSIS

We estimated that with a sample size of 2400 patients assigned to receive liraglutide and 1200 assigned to receive placebo, the study would have more than 99% power to detect a between-group difference in the three coprimary efficacy end points of the main 56-week trial and in the primary end point of the 2-year extension. The power for the first coprimary end point, weight change, was calculated with the use of a two-sided Student's t-test at a 5% significance level. The power for the two categorical coprimary end points was calculated with the use of a two-sided chi-square test, also at a 5% significance level (see the Supplementary Appendix).

The prespecified efficacy analyses used data from the full-analysis set, which included all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline. The safety-analysis set included all patients who were randomly assigned to a study group and had exposure to a study drug. Missing values were imputed with the use of the last-observation-carried-forward method for measurements made after baseline. For weight, only fasting measurements were used. The three coprimary end points were analyzed in hierarchical order. An analysis of covariance model was used to analyze mean changes in continuous end points. The model included treatment, country, sex, BMI stratification, status with respect to prediabetes at screening, and interaction between BMI strata and prediabetes status as fixed effects, with the baseline value of the relevant variable as a covariate. Categorical changes for dichotomous end points were analyzed with the use of logistic regression with the same fixed effects and covariates as the respective analysis of covariance. Sensitivity analyses, performed to assess the robustness of the primary analyses, included repeated-measures and multiple-imputation analyses, which used a model-based approach for missing data (see the Supplementary Appendix). A total of 63 prespecified subgroup analyses were performed to investigate whether prediabetes status had any effect on the primary and secondary end points and whether baseline BMI (in four categories) had any effect on weight or glycated hemoglobin level (see the Methods in the Supplementary Appendix). Results are presented only if an effect was shown.

RESULTS

TRIAL POPULATION

A total of 3731 patients underwent randomization: 2487 to lifestyle intervention plus liraglu-

tide, at a dose of 3.0 mg once daily, and 1244 to lifestyle intervention plus placebo. The baseline characteristics were similar in the two groups (Table 1, and Tables S3 and S4 in the Supplementary Appendix). A total of 1789 patients (71.9%) in the liraglutide group, as compared with 801 patients (64.4%) in the placebo group, completed 56 weeks of treatment (Fig. S2 in the Supplementary Appendix). A larger percentage of patients in the liraglutide group than in the placebo group withdrew from the trial owing to adverse events (9.9% [246 of 2487 patients] vs. 3.8% [47 of 1244]); a smaller percentage of patients in the liraglutide group withdrew from the trial owing to ineffective therapy (0.9% [23 of 2487] vs. 2.9% [36 of 1244]) or withdrew their consent (10.6% [264 of 2487] vs. 20.0% [249 of 1244]).

BODY WEIGHT

After 56 weeks, patients in the liraglutide group had lost a mean (±SD) of 8.0±6.7% (8.4±7.3 kg) of their body weight, whereas patients in the placebo group had lost a mean of 2.6±5.7% (2.8±6.5 kg) of their body weight (Table 2). Weight loss with liraglutide was maintained over 56 weeks and was similar regardless of prediabetes status (Fig. 1A). A greater proportion of patients in the liraglutide group than in the placebo group lost at least 5% of their body weight (63.2% vs. 27.1%), more than 10% of their body weight (33.1% vs. 10.6%), and more than 15% of their body weight (14.4% vs. 3.5%) (Fig. 1B). Overall, approximately 92% of the patients in the liraglutide group and approximately 65% of the patients in the placebo group lost weight (Fig. 1C). The liraglutide group also had a greater reduction than the placebo group in mean waist circumference and BMI (Table 2).

Several sensitivity analyses confirmed the superiority of liraglutide over placebo with respect to the coprimary end points (Table S6 in the Supplementary Appendix). Liraglutide appeared to be less effective in patients with a mean BMI of 40 or higher than in patients with a lower BMI (Fig. S4 in the Supplementary Appendix). Estimated mean changes in body weight and secondary end points are presented in Tables S6 and S8 in the Supplementary Appendix.

GLYCEMIC CONTROL

There was a greater reduction in glycated hemoglobin, fasting glucose, and fasting insulin levels in the liraglutide group than in the placebo group (Table 2). Liraglutide was also associated with a lowering of plasma glucose levels (Fig. 2A) and higher insulin and C-peptide levels relative to placebo during an oral glucose-tolerance test (Fig. S3 in the Supplementary Appendix). The effects of liraglutide on glycated hemoglobin, fasting glucose, and glucose levels during the oral glucose-tolerance test were greater in patients with prediabetes than in those without ($P<0.001$) (Table S9 in the Supplementary Appendix). Measures of insulin resistance and beta-cell function also showed improvement with liraglutide as compared with placebo (Table S10 in the Supplementary Appendix).

The prevalence of prediabetes was significantly lower in the liraglutide group than in the placebo group at week 56 (Fig. 2B), a finding that was consistent with the improvement in glycemic control with liraglutide. Type 2 diabetes developed in more patients in the placebo group than in the liraglutide group during the course of treatment.

CARDIOMETABOLIC VARIABLES

Systolic and diastolic blood pressure decreased more in the liraglutide group than in the placebo group by week 56 (Table 2). All measures of fasting lipid levels (Table 2), as well as levels of high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and adiponectin (Table S8 in the Supplementary Appendix), showed greater improvement in the liraglutide group than in the placebo group.

HEALTH-RELATED QUALITY OF LIFE

Liraglutide treatment was associated with higher scores on the SF-36 for overall physical and mental health, a higher total score (indicating better quality of life) on the Impact of Weight on Quality of Life–Lite questionnaire (Table S7 in the Supplementary Appendix), and more favorable individual domain scores on both instruments (Fig. S5 in the Supplementary Appendix) than was placebo. The total score and the scores for weight management and treatment burden on the Treatment Related Impact Measure–Weight

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Liraglutide (N=2487)	Placebo (N=1244)
Sex — no. (%)		
Female	1957 (78.7)	971 (78.1)
Male	530 (21.3)	273 (21.9)
Age — yr	45.2±12.1	45.0±12.0
Race or ethnic group — no. (%)†		
White	2107 (84.7)	1061 (85.3)
Black	242 (9.7)	114 (9.2)
Asian	90 (3.6)	46 (3.7)
American Indian or Alaska Native	5 (0.2)	4 (0.3)
Native Hawaiian or other Pacific Islander	2 (<0.1)	2 (0.2)
Other	41 (1.6)	17 (1.4)
Hispanic or Latino ethnic group†	259 (10.4)	134 (10.8)
Weight — kg	106.2±21.2	106.2±21.7
Body-mass index‡	38.3±6.4	38.3±6.3
Body-mass index categories — no. (%)‡		
27–29.9: overweight	66 (2.7)	44 (3.5)
30–34.9: obese class I	806 (32.4)	388 (31.2)
35–39.9: obese class II	787 (31.6)	398 (32.0)
≥40: obese class III	828 (33.3)	414 (33.3)
Waist circumference — cm	115.0±14.4	114.5±14.3
Glycated hemoglobin — %	5.6±0.4	5.6±0.4
Fasting glucose — mg/dl	95.9±10.6	95.5±9.8
Fasting insulin — μIU/ml§	16.3±79.8	16.1±89.3
Blood pressure — mm Hg		
Systolic	123.0±12.9	123.2±12.8
Diastolic	78.7±8.6	78.9±8.5
Cholesterol — mg/dl		
Total	193.7±19.1	194.3±18.8
LDL	111.6±27.9	112.2±27.6
HDL	51.4±26.2	51.0±26.4
VLDL	25.1±49.6	25.7±49.4
Free fatty acids — mmol/liter	0.45±40.5	0.46±39.7
Triglycerides — mg/dl	126.2±56.9	128.9±61.0
Prediabetes — no. (%)¶	1528 (61.4)	757 (60.9)
Dyslipidemia — no. (%)‖	737 (29.6)	359 (28.9)
Hypertension — no. (%)‖	850 (34.2)	446 (35.9)

* Plus–minus values are observed means ±SD. For fasting insulin and lipid levels, plus–minus values are geometric means and coefficients of variation. There were no statistically significant differences between the two groups for any characteristic. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.
† Race and ethnic group were self-reported. Patients from France did not report race or ethnic group.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The reference range is 3.0 to 25.0 μIU/mL for both sexes and all ages.
¶ Prediabetes was defined according to American Diabetes Association 2010 criteria.[15]
‖ The diagnoses of dyslipidemia and hypertension were based on self-reported medical history.

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