

# The Effect of Glucagon-Like Peptide-1 Receptor Agonist Therapy on Body Mass Index in Adolescents With Severe Obesity

## *A Randomized, Placebo-Controlled, Clinical Trial*

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**Importance:** Medical treatment options for pediatric obesity remain limited. Glucagon-like peptide-1 (GLP-1) receptor agonists induce weight loss by suppressing appetite and increasing satiety, but few studies have evaluated this therapy as a treatment for obesity.

**Objective:** To evaluate the effects of exenatide on body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and cardiometabolic risk factors in adolescents with severe obesity.

**Design:** Three-month, randomized, double-blind, placebo-controlled, multicenter clinical trial followed by a 3-month open-label extension.

**Setting:** An academic medical center and an outpatient pediatric endocrinology clinic.

**Patients:** A total of 26 adolescents (12-19 years of age) with severe obesity (BMI  $\geq 1.2$  times the 95th percentile or BMI  $\geq 35$ ).

**Intervention:** All patients received lifestyle modification counseling and were equally randomized to exenatide or placebo injection, twice per day.

**Main Outcome Measures:** The primary end point was the mean percent change in BMI measured at baseline and 3 months. Secondary end points included absolute

change in BMI, body weight, body fat, blood pressure, hemoglobin A<sub>1c</sub>, fasting glucose, fasting insulin, and lipids at 3 months.

**Results:** Twenty-two patients completed the trial. Exenatide elicited a greater reduction in percent change in BMI compared with placebo ( $-2.70\%$  [95% CI,  $-5.02\%$  to  $-0.37\%$ ];  $P=.03$ ). Similar findings were observed for absolute change in BMI ( $-1.13$  [95% CI,  $-2.03$  to  $-0.24$ ];  $P=.02$ ) and body weight ( $-3.26$  kg [95% CI,  $-5.87$  to  $-0.66$  kg];  $P=.02$ ). Although not reaching the level of statistical significance, reduction in systolic blood pressure was observed with exenatide. During the open-label extension, BMI was further reduced in those initially randomized to exenatide (cumulative BMI reduction of 4%).

**Conclusions and Relevance:** These results provide preliminary evidence supporting the feasibility, safety, and efficacy of GLP-1 receptor agonist therapy for the treatment of severe obesity in adolescents.

**Trial Registration:** clinicaltrials.gov Identifier: NCT01237197

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SEVERE OBESITY AFFLICTS APPROXIMATELY 4% to 6% of the US pediatric population.<sup>1-4</sup> Defined as an age- and sex-specific body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of greater than or equal to 1.2 times the 95th percentile or a BMI of 35 or greater, severe obesity in childhood is associated with profound immediate and long-term consequences. Compared with overweight and obese children and adolescents, children and adolescents with severe obesity have

a more adverse cardiometabolic risk factor profile and are at greatly elevated risk of developing cardiovascular disease and type 2 diabetes mellitus.<sup>2,5</sup> Moreover, adiposity tracks particularly strongly from childhood to adulthood in the severely obese.<sup>2,6</sup>

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Many adolescents with severe obesity achieve only marginal BMI reduction with lifestyle modification alone,<sup>7</sup> and weight

loss maintenance is often poor,<sup>8</sup> highlighting the need for more aggressive and sustainable treatment strategies. While emerging data suggest that bariatric surgery is effective at reducing BMI and other cardiometabolic risk factors,<sup>9-11</sup> significant risks accompany surgery, and few pediatric patients are eligible owing to lack of insurance coverage. Orlistat is the only weight loss medication for adolescents approved by the US Food and Drug Administration, but limited efficacy and notable adverse effects limit its widespread use.<sup>12</sup> Therefore, new pharmacologic approaches are needed for the treatment of severe pediatric obesity.

Glucagon-like peptide-1 (GLP-1) receptor agonists, approved for use in adults with type 2 diabetes mellitus, reduce body weight through enhancing satiety (slowing gastric motility) and suppressing appetite (activation of GLP-1 receptors in the hypothalamus), even in individuals without diabetes.<sup>13-15</sup> Indeed, GLP-1 has been shown to be an endogenous satiety hormone.<sup>16</sup> In a recent feasibility trial,<sup>17</sup> we demonstrated that 3 months of exenatide treatment reduced BMI by approximately 5% and improved markers of insulin resistance and  $\beta$ -cell function in adolescents with severe obesity who did not have diabetes. However, since the study<sup>17</sup> included a small number of patients and was unblinded, we performed a more rigorous evaluation of the effects of GLP-1 receptor agonist therapy in adolescents with severe obesity by conducting a randomized, placebo-controlled, clinical trial. The primary end point was the mean percent change in BMI from baseline to 3 months. Secondary end points included absolute change in BMI, body weight, body fat, blood pressure, hemoglobin A<sub>1c</sub>, fasting glucose, fasting insulin, and lipids at 3 months.

## METHODS

### STUDY DESIGN AND ELIGIBILITY CRITERIA

This was a 3-month, randomized, double-blind, placebo-controlled, multicenter clinical trial followed by a 3-month open-label extension during which time-active medication was offered to all patients. Although the study was primarily designed to evaluate outcomes at 3 months, the open-label extension was included to provide further characterization of the safety profile, to better inform the design of future larger trials, and to enhance recruitment by offering treatment to all patients. Adolescents 12 to 19 years of age with severe obesity (BMI  $\geq 1.2$  times the 95th percentile or BMI  $\geq 35$ ) were recruited from the University of Minnesota, Amplatz Children's Hospital Pediatric Weight Management Clinic in Minneapolis or the McNeely Pediatric Diabetes Center and Endocrinology Clinic, Children's Hospitals and Clinics of Minnesota in St Paul. Exclusion criteria included the following: diabetes mellitus (type 1 or 2), use of medications associated with weight loss/gain within 3 months of screening, history of bariatric surgery, initiation of a new drug therapy within 30 days of screening, psychiatric disorders, current pregnancy/plans to become pregnant, current tobacco use, renal or liver dysfunction, history of pancreatitis, obesity-associated genetic disorders (eg, Prader-Willi syndrome), hypothyroidism, uncontrolled hypertriglyceridemia ( $\geq 300$  mg/dL), and history of an eating disorder.

Trained study coordinators delivered standardized lifestyle modification counseling to all patients throughout the entire trial. The lifestyle modification education materials were

given to patients, and selected sections were discussed at each monthly contact (5 face-to-face sessions and 2 telephone sessions). The curriculum was adapted from "Take Charge of Your Health," a guide for teenagers that was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, and focused on encouraging patients to make healthier food choices and increase levels of physical activity. Pedometers and step-counting logs were given to all patients. Following baseline testing, patients were equally and randomly assigned to exenatide or matching placebo injection for 3 months, followed by a 3-month open-label extension during which all patients received exenatide. The protocol was approved by the University of Minnesota and the Children's Hospitals and Clinics of Minnesota institutional review boards. Consent and assent were obtained from parents and patients, respectively. An investigational new drug exemption was obtained from the US Food and Drug Administration prior to study initiation, and the study was registered on the clinicaltrials.gov website (NCT01237197).

### EXENATIDE AND PLACEBO DOSING, ADMINISTRATION, AND TRACKING

Exenatide was initiated at a dose of 5  $\mu$ g, subcutaneously, twice per day. After 1 month, exenatide was uptitrated to 10  $\mu$ g twice per day for the remaining 2 months of the randomized, placebo-controlled phase. In order to maintain the blind, the same titration protocol was used for the open-label phase. Placebo pens were identical in appearance to the active medication pens. Compliance was assessed by medication logs and inspection of medication/placebo pens. The predetermined threshold of compliance for inclusion in the per-protocol analysis was administration of 80% or more of the required doses.

### MEASUREMENT OF CLINICAL VARIABLES

Clinical variables were obtained at baseline, 3 months, and 6 months. The height and weight of the patient were obtained when the patient wore light clothes and no shoes, using the same site-specific standardized stadiometer and electronic scale, respectively. Three consecutive height and weight measurements were averaged. Waist circumference was obtained (to the nearest 0.1 cm) at end expiration midway between the base of the rib cage and the superior iliac crest. Three consecutive waist measurements were averaged. The percentage of total body fat and the percentage of visceral fat were determined using dual-energy x-ray absorptiometry (iDXA; GE Healthcare) at the University of Minnesota site only (n=17). The measurement of seated blood pressure was obtained after 5 minutes of quiet rest using an automatic sphygmomanometer and appropriately fitted cuff on the right arm. The average of 3 independent blood pressure measurements was used. The Tanner stage (pubertal development) was determined by a trained pediatrician. Fasting ( $\geq 12$  hours) blood samples were analyzed for hemoglobin A<sub>1c</sub>, glucose, insulin, and lipids using standard procedures.

### STATISTICAL ANALYSES

The sample size was based primarily on the preliminary nature of the trial (a pilot study), along with limitations of the funding and recruitment timeline associated with the grant support. Baseline characteristics were tabulated with respect to randomized treatment regimens. Outcomes were evaluated at baseline, 3 months (end of randomized treatment period), and 6 months (end of open-label extension). The primary end point was the mean percent change in BMI at 3 months. Three-month treatment effects were estimated using generalized lin-

ear models to adjust for baseline measurements for added precision.<sup>18,19</sup> The 95% CIs and the *P* values were evaluated based on a *t* distribution and model-based standard errors. A robust variance estimation was not used owing to the small sample size. Because of the incomplete follow-up on all patients who entered the study, the number of measurements for each treatment regimen was unbalanced. The primary analysis followed a prespecified per-protocol analysis in which patients were included if they completed the first treatment phase and missed no more than 20% of the prescribed exenatide doses. An intent-to-treat analysis was also conducted with missing 3-month data imputed using the last available measurement (last observation carried forward). Data were housed in REDCap (a research electronic data capture system),<sup>20</sup> and all statistical analyses were performed using R version 2.12.0 (R Foundation for Statistical Computing).

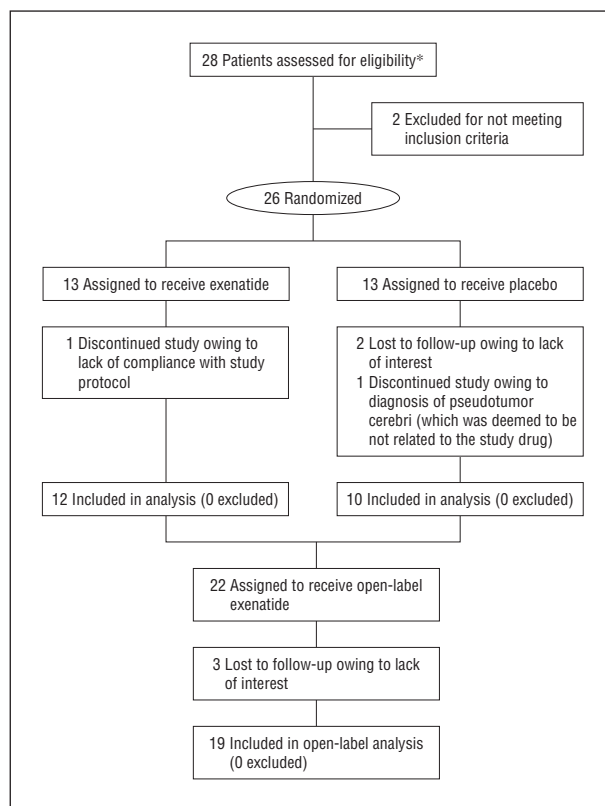
## RESULTS

Enrollment occurred during the period from January to November 2011. **Figure 1** shows the progress of patients throughout the trial. Baseline characteristics of all randomized patients and of those who completed the trial are presented in **Table 1**. Four patients dropped out prior to 3-month follow-up (1 from the exenatide group and 3 from the control group; the reasons are given in Figure 1). All 22 remaining patients achieved the target treatment dose and were compliant with the injection regimen during the first 3-month phase (compliance ranged from 85% to 100% of the required doses; mean compliance rate, 95%). Two participants required a short-term ( $\leq 1$  week) reduction to 5  $\mu\text{g}$  owing to gastrointestinal symptoms but were then able to resume the 10- $\mu\text{g}$  dose without further problems for the remainder of the study. Data from 1 patient during the open-label phase was excluded owing to noncompliance (only data from the first 3-month phase were used).

The change for each end point by group at 3 months for those who completed the trial and the estimated treatment effects are presented in **Table 2**. At 3 months, exenatide elicited a greater reduction in percent change in BMI compared with placebo ( $-2.70\%$  [95% CI,  $-5.02\%$  to  $-0.37\%$ ];  $P = .03$ ) (**Figure 2**). Similar findings were observed for absolute change in BMI ( $-1.13$  [95% CI,  $-2.03$  to  $-0.24$ ];  $P = .02$ ) and body weight ( $-3.26$  kg [95% CI,  $-5.87$  to  $-0.66$  kg];  $P = .02$ ). The treatment effect estimates stemming from the intent-to-treat analysis were not meaningfully different, and the conclusions from the primary analysis remained unchanged for percent change in BMI ( $-2.72\%$  [95% CI,  $-4.68\%$  to  $-0.76\%$ ]) and for absolute change in BMI ( $-1.14$  [95% CI,  $-1.90$  to  $-0.38$ ]) and body weight ( $-2.77$  kg [95% CI,  $-5.09$  to  $-0.44$  kg]). Although not reaching the level of statistical significance, a clinically significant reduction in systolic blood pressure (SBP) was observed with exenatide compared with placebo.

After the open-label extension, the average reduction in BMI from baseline for those initially randomized to exenatide was 4%. For those initially randomized to placebo who switched to exenatide, the average change in BMI from 3 to 6 months was less than 0.25%.

The most common adverse events between baseline and 3 months (all mild-to-moderate and transient events)



**Figure 1.** Consolidated Standard of Reporting Trials flow diagram showing the progress of adolescents with severe obesity throughout the 3-month, randomized, double-blind, placebo-controlled, multicenter clinical trial to evaluate the effects of exenatide on body mass index and cardiometabolic risk factors. \*Defined as patients evaluated at a screening visit.

were nausea (31% of the placebo group and 62% of the exenatide group), abdominal pain (23% of the placebo group and 15% of the exenatide group), diarrhea (31% of the placebo group and 8% of exenatide group), headache (46% of the placebo group and 23% of the exenatide group), and vomiting (8% of the placebo group and 31% of the exenatide group). No patients experienced hypoglycemia or pancreatitis.

## COMMENT

The results of this clinical trial extend the findings of our previous pilot and feasibility study<sup>17</sup> and offer additional evidence, within the context of a randomized, placebo-controlled trial, that treatment with a GLP-1 receptor agonist significantly reduces BMI and body weight in adolescents with severe obesity. The percent BMI reduction achieved with exenatide in 3 months (2.7%) was modest, but the treatment effect was equivalent or better than 3 months of treatment with orlistat<sup>12</sup> or metformin hydrochloride,<sup>21</sup> other medications that have been evaluated for their weight loss effects in youth.

A further reduction in BMI was observed during the open-label phase for those initially randomized to exenatide (cumulative BMI reduction of 4%), which suggests that longer-term use may stimulate further BMI reduction as has been demonstrated in a trial of obese adults.<sup>14</sup> It is interesting to note that the mean

**Table 1. Baseline Characteristics of Adolescents With Severe Obesity Randomized to Either Exenatide or Placebo**

Covariate	Mean (SD)				
	Overall (N = 26)	Randomized		Completed 3-mo Follow-up	
		Exenatide (n = 13)	Placebo (n = 13)	Exenatide (n = 12)	Placebo (n = 10)
Age, y	15.2 (1.8)	14.9 (1.76)	15.5 (1.88)	15.0 (1.82)	15.3 (1.79)
Male sex, No. (%)	10 (38.5)	5 (38.5)	5 (38.5)	5 (41.7)	3 (30.0)
Race/ethnicity, No. (%)					
Non-Hispanic	24 (92.3)	11 (84.6)	13 (100.0)	10 (83.3)	10 (100.0)
Black	4 (15.4)	1 (7.7)	3 (23.1)	1 (8.3)	2 (20.0)
White	20 (76.9)	10 (76.9)	10 (76.9)	10 (83.3)	8 (80.0)
American Indian	1 (3.8)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (3.8)	1 (7.7)	0 (0.0)	1 (8.3)	0 (0.0)
Tanner stage, No. (%)					
3	3 (11.5)	0 (0.0)	3 (23.1)	0 (0.0)	2 (20.0)
4	3 (11.5)	2 (15.4)	1 (7.7)	2 (16.7)	0 (0.0)
5	20 (76.9)	11 (84.6)	9 (69.2)	10 (83.3)	8 (80.0)
BMI	42.5 (6.81)	42.3 (7.08)	42.7 (6.81)	40.8 (4.75)	42.1 (6.67)
Weight, kg	124 (19.3)	123 (18.1)	126 (21.1)	120 (15.4)	121 (20.1)
Waist, cm	130 (14.1)	130 (13.3)	129 (15.5)	128 (10.5)	127 (14.4)
Total tissue fat, kg	61.1 (14.8)	58.0 (14.4)	64.6 (15.4)	54.5 (10.3)	61.6 (13.9)
Blood pressure, mm Hg					
Systolic	122 (11.8)	123 (11.2)	120 (12.7)	121 (9.49)	120 (14.4)
Diastolic	69.2 (8.83)	71.2 (9.25)	67.2 (8.27)	71.2 (9.67)	67.0 (9.39)
Heart rate, beats/min	76.8 (9.08)	76.3 (8.05)	77.4 (10.3)	75.2 (7.4)	77.9 (9.96)
Cholesterol, mg/dL					
Total	173 (31.4)	161 (21.2)	185 (35.9)	160 (21.6)	183 (32.0)
LDL	107 (27.3)	97.4 (19.6)	116 (31.4)	94.8 (18.0)	114 (23.2)
HDL	41.4 (6.95)	39.9 (5.29)	43.0 (8.21)	40.2 (5.39)	42.2 (9.19)
Triglycerides, mg/dL	126 (47.9)	120 (51.0)	132 (45.9)	125 (50.0)	132 (47.2)
Glucose, mg/dL	79.6 (11.1)	79.2 (10.7)	79.9 (12.0)	79.5 (11.1)	79.3 (9.87)
Insulin, $\mu$ U/mL	26.8 (19.6)	31.5 (24.7)	21.8 (10.8)	30.6 (25.6)	20.7 (10.7)
HbA <sub>1c</sub> , %	5.26 (0.28)	5.23 (0.27)	5.29 (0.3)	5.23 (0.28)	5.25 (0.31)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors: To convert total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert glucose to millimoles per liter, multiply by 0.0555; to convert insulin to picomoles per liter, multiply by 6.945; and to convert HbA<sub>1c</sub> to proportion of 1.0, multiply by 0.01.

BMI rebounded slightly at month 4 in this group, which corresponded with the downward titration of exenatide, but subsequently decreased after the higher dose of exenatide was reintroduced (Figure 2). It is possible that had exenatide been maintained at the higher dose for the entire 6 months, an even greater BMI reduction may have been observed. It is unclear why BMI was not reduced during the open-label phase in the group initially randomized to placebo. Perhaps frustration with the lack of weight loss during the first 3 months and/or the unblinded nature of the open-label phase led to altered lifestyle behaviors for the remainder of the study.

Although not reaching the level of statistical significance, exenatide elicited a relatively large reduction, on average, in SBP (−6 mm Hg), which is in line with our previous pediatric trial<sup>17</sup> and with observations from adult studies.<sup>22</sup> The mechanism of SBP reduction with exenatide is currently unknown, but only weak correlations have been observed with weight reduction in adults,<sup>22</sup> which suggests that other mechanisms in addition to weight loss may be responsible. The magnitude of SBP reduction with exenatide is relevant from a clinical perspective since blood pressure levels in youth with se-

vere obesity, although often within the “normal” range, exceed levels observed in overweight and obese children and adolescents.<sup>23,24</sup>

Exenatide was generally well tolerated. The reports of nausea, abdominal pain, diarrhea, headache, and vomiting were transient and mild to moderate in severity and were consistent with reports from the adult literature. None of the patients in the current study discontinued participation owing to gastrointestinal adverse effects, and adherence to the twice-daily injection regimen was excellent.

Other longer-acting GLP-1 receptor agonists, such as exenatide extended release (once weekly) and liraglutide (once daily), require less frequent dosing and may be more attractive to many adolescents and may have a more sustained effect on GLP-1 receptors. The rebound in BMI observed with the downward titration of exenatide at month 4 in the current study suggests the possibility that higher doses might elicit even greater weight loss, but this will need to be examined in subsequent studies.

The primary strength of this study was the randomized, double-blind, placebo-controlled design. The sample size was relatively small, and the treatment period was limited. Therefore, larger studies with longer periods of

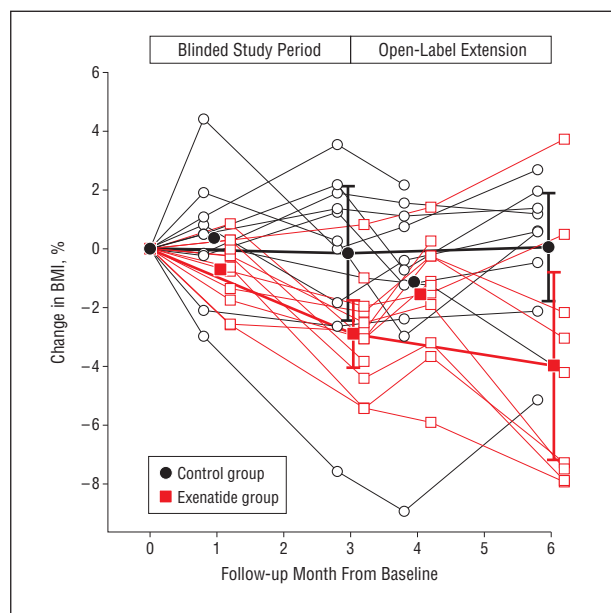


**Table 2. Primary and Secondary End Points of 3-Month, Randomized, Double-blind, Placebo-Controlled, Multicenter Clinical Trial Followed by a 3-Month Open-Label Extension Study of Exenatide**

Covariate	Patients, No.	Mean (SD)				Estimated Treatment Effect (95% CI)	P Value
		3-mo Follow-up		Change From Baseline			
		Exenatide	Control	Exenatide	Control		
% Change BMI	22			−2.90 (1.80)	−0.15 (3.20)	−2.70 (−5.02 to −0.37)	.03
BMI	22	39.64 (4.67)	42.03 (6.95)	−1.18 (0.67)	−0.04 (1.23)	−1.13 (−2.03 to −0.24)	.02
Weight, kg	22	117 (14.85)	122 (20.79)	−2.93 (2.48)	0.32 (3.21)	−3.26 (−5.87 to −0.66)	.02
Waist, cm	22	126 (9.79)	126 (13.45)	−2.04 (2.62)	−1.01 (5.57)	−0.98 (−4.60 to 2.64)	.58
Total tissue fat, kg	15	52.78 (9.50)	60.95 (15.90)	−1.69 (2.41)	−0.65 (2.50)	−0.72 (−3.66 to 2.23)	.61
Visceral fat area, cm²	14	1420 (524.68)	1548 (326.25)	−97.00 (191.22)	−18.17 (178.62)	−78 (−309 to 153)	.47
Blood pressure, mmHg							
Systolic	22	116 (9.03)	122 (7.90)	−5.50 (9.13)	2.00 (13.43)	−6.36 (−13.46 to 0.73)	.08
Diastolic	22	69.67 (5.42)	66.50 (8.17)	−1.50 (9.76)	−0.50 (14.44)	3.37 (−3.02 to 9.76)	.28
Heart rate, beats/min	22	77.25 (8.36)	79.50 (8.95)	2.00 (9.19)	1.60 (11.96)	−1.57 (−9.34 to 6.19)	.68
Cholesterol, mg/dL							
Total	22	160 (19.36)	176 (29.02)	0.08 (13.01)	−6.60 (12.04)	1.98 (−9.48 to 13.44)	.72
LDL	21	91.91 (22.65)	107 (19.17)	−1.45 (9.96)	−7.50 (17.64)	1.52 (−12.81 to 15.86)	.83
HDL	22	39.75 (5.61)	39.20 (8.30)	−0.42 (4.08)	−3.00 (5.12)	2.08 (−1.82 to 5.99)	.29
Triglycerides, mg/dL	22	128 (51.85)	136 (48.98)	2.83 (53.69)	3.90 (44.41)	−4.71 (−45.14 to 35.72)	.81
Glucose, mg/dL	22	80.67 (9.76)	83.90 (7.05)	1.17 (8.19)	4.60 (9.51)	−3.33 (−9.71 to 3.05)	.29
Insulin, µIU/mL	22	22.25 (13.07)	22.80 (9.37)	−8.33 (18.81)	0.67 (7.43)	−2.91 (−10.91 to 5.10)	.46
HbA <sub>1c</sub> , %	22	5.12 (0.26)	5.24 (0.26)	−0.12 (0.16)	−0.01 (0.14)	−0.11 (−0.23 to 0.01)	.07

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SI conversion factors: To convert total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert glucose to millimoles per liter, multiply by 0.0555; to convert insulin to picomoles per liter, multiply by 6.945; and to convert HbA<sub>1c</sub> to proportion of 1.0, multiply by 0.01



**Figure 2.** The percent change in body mass index (BMI) during the randomized, placebo-controlled phase and the open-label phase of the trial. The lighter lines denote individual trajectories (ie, individual patients); the darker lines denote group trajectories (mean percent change in BMI by group at 3 and 6 months, with the errors bars indicating 95% CIs).

treatment will be needed in the future to evaluate the durability of the weight loss effect over time. Finally, the lifestyle modification counseling intervention used in the current study may not have been as comprehensive and/or intensive as what might be typically offered in a specialized pediatric weight management clinic setting. There-

fore, the BMI reduction may have been greater if a multidisciplinary team of pediatric weight management specialists had been used.

In conclusion, data from the current study provide evidence that GLP-1 receptor agonist treatment reduces BMI and elicits a potentially meaningful reduction in SBP in adolescents with severe obesity. Compliance with the required injection regimen was excellent, and exenatide was generally well tolerated. Future clinical trials with GLP-1 receptor agonists should extend treatment beyond 6 months and evaluate changes in other health outcomes such as noninvasive measures of arterial health, insulin sensitivity, and pancreatic  $\beta$ -cell function. In addition, subsequent studies should be designed to evaluate predictors of response to therapy in an attempt to better identify which obese adolescents are most likely to benefit from treatment.

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**Author Contributions:** Dr Kelly had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kelly, Nathan, Fox, Metzger, Fitch, and Abuzzahab. *Acquisition of data:* Kelly, Nathan, Metzger, Fitch, and Abuzzahab. *Analysis and interpretation of data:* Kelly, Rudser, Nathan, Fox, Coombes, Bomberg, and Abuzzahab. *Drafting of the manuscript:* Kelly, Rudser, Fox,

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