Effect of liraglutide on anthropometric measurements, sagittal abdominal diameter and adiponectin levels in people with type 2 diabetes treated with

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ORIGINAL ARTICLE

Effect of liraglutide on anthropometric measurements, sagittal abdominal diameter and adiponectin levels in people with type 2 diabetes treated with multiple daily insulin injections: evaluations from a randomized trial (MDI-liraglutide study 5)

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Summary

Aim

Use of the glucagon-like peptide 1 receptor agonist liraglutide has been shown to reduce weight. Different types of anthropometric measurements can be used to measure adiposity. This study evaluated the effect of liraglutide on sagittal abdominal diameter, waist circumference, waist-to-hip ratio and adiponectin levels in people with type 2 diabetes (T2D) treated with multiple daily insulin injections (MDI).

Materials and methods

In the multicentre, double-blind, placebo-controlled MDI-liraglutide trial, 124 individuals with T2D treated with MDI were randomized to either liraglutide or placebo. Basal values of weight, waist circumference, waist-to-hip ratio, sagittal abdominal diameter and adiponectin were compared with measurements at 12 and 24 weeks after randomization.

Results

Baseline-adjusted mean weight loss was 3.8 ± 2.9 kg greater in liraglutide than placebo-treated individuals ($p < 0.0001$). Waist circumference was reduced by 2.9 ± 4.3 cm and 0.2 ± 3.6 cm in the liraglutide and placebo groups, respectively, after 24 weeks (baseline-adjusted mean difference: 2.6 ± 4.0 cm, $p = 0.0005$). Corresponding reductions in sagittal abdominal diameter were 1.1 ± 1.7 cm and 0.0 ± 1.8 cm (baseline-adjusted mean difference: 1.1 ± 1.7 cm, $p = 0.0008$). Hip circumference was reduced in patients randomized to liraglutide (baseline-adjusted mean difference between treatment groups: 2.8 ± 3.8 cm, $p = 0.0001$), but there was no significant difference between the groups in either waist-to-hip ratio (baseline-adjusted mean difference: 0.0 ± 0.04 cm, $p = 0.51$) or adiponectin levels (baseline-adjusted mean difference: 0.8 ± 3.3 mg L^{-1}, $p = 0.17$). Lower HbA1c and mean glucose levels measured by masked continuous glucose monitoring at baseline were associated with greater effects of liraglutide on reductions in waist circumference and sagittal abdominal diameter.

Conclusions

In patients with T2D, adding liraglutide to MDI may reduce abdominal and hip obesity to a similar extent, suggesting an effect on both visceral and subcutaneous fat. Liraglutide had greater effects on reducing abdominal obesity in patients with less pronounced long-term hyperglycaemia but did not affect adiponectin levels.

Keywords: Adiponectin, anthropometric measurements, liraglutide, predictive variable.

Introduction

Type 2 diabetes (T2D) is a chronic disease defined by elevated blood glucose levels (1). The American Diabetes Association and European Association for the Study of Diabetes have published position statements regarding hyperglycaemia management in T2D (2–4), which include use of multiple daily insulin injections (MDI) as an advanced option for glycaemic control. However, MDI does not guarantee that a glycaemic target of HbA1c <53 mmol mol^{-1} ($<7.0\%$) will be obtained (4), and the treatment is generally associated with weight gain, greater insulin resistance likely due to increased visceral abdominal fat and possible hypoglycaemia (2–4). Accordingly, combining MDI with a weight-reducing agent such as a glucagon-like peptide 1 (GLP-1) receptor agonist has been proposed as another option in the management of hyperglycaemia (4).

Liraglutide, a GLP-1 receptor agonist, added to MDI in individuals with T2D is associated with lower blood glucose values, insulin doses and body weight (5), and lower HbA1c levels at baseline are associated with greater weight loss (6). Different types of anthropometric measurements can be used to measure adiposity, and the effects of liraglutide on sagittal abdominal diameter, waist circumference, hip circumference and waist-to-hip ratio have not been evaluated.

Additionally, obesity, insulin resistance and T2D are associated with low levels of adiponectin (7), a peptide hormone derived from adipose tissue produced by adipocytes, which decreases insulin resistance and indirectly inhibits gluconeogenesis. This effect results in increased muscle glucose transport and fat combustion (8). Whether GLP-1 receptor agonists affect adiponectin levels in patients with uncontrolled T2D treated with MDI is unknown.

The primary aim of this study was to evaluate the effects of liraglutide added to MDI on sagittal abdominal diameter, hip circumference, waist circumference, waist-to-hip ratio and adiponectin levels in patients with T2D enrolled in the MDI-liraglutide trial (5,6). The hypotheses of the present study were that liraglutide reduces both hip and abdominal obesity and increases adiponectin levels in persons with T2D treated with MDI.

Materials and methods

Cohort

The design of the MDI-liraglutide trial has been described in detail (5,9). In brief, persons with T2D treated with MDI were randomized 1:1 to liraglutide 1.8 mg daily or placebo for 24 weeks. The study was carried out at 14 sites in Sweden. All individuals gave written and verbal informed consent. Patients with body mass index (BMI) 27.5–45.0 kg m^{-2}, HbA1c $\geq$58 mmol mol^{-1} (7.5%) and $\leq$102 mmol mol^{-1} (11.5%), fasting C-peptide $\geq$0.1 nmol L^{-1} and ongoing treatment with MDI were included. MDI was defined as separate basal and meal-time insulin components including at least two daily meal-time insulin doses. Other inclusion and exclusion criteria have been described previously (9).

Overall study procedures

Patients were examined at baseline and every 6 weeks during treatment. Among other variables, HbA1c, blood pressure, weight, insulin doses and concomitant medications were recorded at each follow-up visit. Waist circumference, sagittal abdominal diameter, hip circumference, waist-to-hip ratio and adiponectin levels were measured at baseline and weeks 12 and 24 after randomization.

Blood glucose levels were measured by masked continuous glucose monitoring (CGM) using the DexCom G4 Platinum system at baseline, week 12 and either week 23 or 24 after randomization. All study variables and measurement time points have been described in detail (9).

Weight was measured in the fasting state on calibrated scales, namely, using the same scale for each patient throughout the trial. Patients were weighed without shoes, in underwear with emptied urinary bladder. Waist circumference was recorded at the umbilicus with the patient in the standing position after a regular expiration. Hip circumference was measured at the widest point of the hip at the level of the greater trochanter. From these two parameters, waist-to-hip ratio was calculated. Sagittal abdominal diameter ('abdominal height') was measured with a standardized sliding beam caliper with the patient in the supine position with bent knees at the highest point of the abdomen after a regular expiration. All blood samples including adiponectin levels were measured at a central laboratory (Karolinska University Hospital, Stockholm, Sweden). Fasting adiponectin levels were measured using a commercially available RIA-kit (#HADP-61HK, Millipore Corporation, Linco Research, Inc.), which was semi-automated and thereby standardized in the laboratory. In the full analysis set, all patients with any valid information on variables during follow-up (122 of 124 randomized patients) were used, which was also used in the primary effect analysis (5).

HbA1c was measured in accordance with the International Federation of Clinical Chemistry method in mmol mol^{-1} and converted to National Glycosylation Standardisation Program (NGSP) values for dual reporting (10). The study was approved by the ethics committee of

the University of Gothenburg, Gothenburg, Sweden (Diary number 596-12).

Statistical methods

Data are presented as mean ± standard deviation, median (interquartile range) and minimum and maximum for continuous variables and as number (per cent) for categorical variables. Baseline comparisons between groups were performed with Fisher's exact test for dichotomous variables and Fisher's non-parametric permutation test for continuous variables.

Efficacy analyses were the changes from baseline to 24 weeks in weight, waist circumference, hip circumference, waist-to-hip ratio, sagittal abdominal diameter and adiponectin levels between liraglutide and placebo on the full analysis set using analysis of covariance with the effect variable at baseline as the covariate. The full analysis set consisted of all randomized patients who received at least one dose of study medication and had at least one follow-up measurement. The last observation carried forward from 6 weeks was used to account for missing follow-up data. Measurements obtained after rescue therapy were excluded in all efficacy analyses.

In addition to overall effects between liraglutide-treated and placebo-treated patients, possible predictors were evaluated for the effects on sagittal abdominal diameter, waist circumference and adiponectin levels. The following baseline variables were evaluated: age, sex, BMI, mean and standard deviation of glucose levels measured by masked CGM, diabetes duration, metformin use, fasting C-peptide, fasting pro-insulin, HbA1c, per cent meal insulin of total insulin, total daily insulin dose, sagittal abdominal diameter, adiponectin level, waist circumference, waist-to-hip ratio and weight.

Prediction analyses of the changes in sagittal abdominal diameter, waist circumference and adiponectin levels were performed using linear regression, with the baseline variables analysed one at a time. Explanatory variables were treatment group and the baseline predictor, also including an interaction between treatment and baseline predictor to evaluate whether the predictors were significantly stronger in the liraglutide than placebo group and to eliminate study-related spurious correlations. Statistical tests for the effects of baseline predictors were performed in the liraglutide group, and tests for treatment with predictor interactions were performed only for statistically significant predictors in the liraglutide group. Post hoc multivariable analyses were also performed including the statistically significant predictors in the liraglutide group.

All statistical tests were performed at $p < 0.05$ significance level. All analyses were performed with SAS version 9.4.

Results

Patient characteristics

Baseline patient characteristics are shown in Table 1. A total of 122 of 124 patients enrolled in the trial had at least one valid follow-up visit and were randomized (63 to liraglutide and 59 to placebo). The mean age was 63.8 ± 8.2 years, and 36.5% were female in the liraglutide group. In the liraglutide and placebo groups, mean weight was 98.8 ± 14.1 kg and 99.8 ± 14.8 kg, respectively. Waist and hip circumference, sagittal abdominal diameter, waist-to-hip ratio and adiponectin levels were numerically similar at baseline between groups.

Effects of liraglutide and placebo on various anthropometric measurements

Descriptive data for the different anthropometric measurements at baseline and week 24 are presented in Table 2, as well as changes from baseline to week 24 in liraglutide-treated and placebo-treated patients and baseline-adjusted differences between groups. Weight decreased on average by 3.8 ± 3.1 kg in the liraglutide group, while there was no change in the placebo group. Sagittal abdominal diameter decreased on average by 1.1 ± 1.7 cm in the liraglutide group compared with no reduction in the placebo group ($p = 0.0008$ for treatment effect). Waist circumference decreased by 2.9 ± 4.3 cm in liraglutide group versus 0.2 ± 3.6 cm in the placebo group ($p = 0.0005$ for treatment effect). Hip circumference decreased by 2.3 ± 4.1 cm in patients receiving liraglutide but increased by 0.6 ± 3.6 cm in the placebo group ($p = 0.0001$ for treatment effect). BMI was also reduced in persons treated with liraglutide ($p < 0.0001$ for treatment effect), whereas there was no change in waist-to-hip ratio ($p = 0.51$). There was a significant change in adiponectin levels within the liraglutide group but not when compared with placebo.

As shown in Figure 1, reductions in sagittal abdominal diameter, waist circumference and hip circumference in the liraglutide group were evident at week 12 and persisted until week 24.

Predictors of change on sagittal abdominal diameter

Baseline characteristics evaluated as potential predictors of changes in sagittal abdominal diameter are shown in Table S1. In the liraglutide group, mean glucose levels ($p = 0.016$), glycaemic variability ($p = 0.043$) and HbA1c levels ($p = 0.021$) were associated with reductions in sagittal abdominal diameter, with lower baseline values predicting greater reductions. Mean glucose level

Table 1 Demographics and baseline characteristics

Variable	Liraglutide (n = 63)	Placebo (n = 59)	p-value
Age (years)	63.8 (8.2)	63.6 (7.7)	0.88
	66.3 (44.1, 78.0)	65.0 (38.9, 77.3)	
	n = 63	n = 59	
Female	23 (36.5%)	20 (33.9%)	0.91
Diabetes duration (years)	17.3 (7.7)	17.0 (8.2)	0.88
	16.0 (4.0, 40.0)	16.0 (2.0, 35.0)	
	n = 63	n = 59	
Total daily basal insulin dose (units)	57.2 (25.9)	59.3 (26.4)	0.66
	54.0 (12.0, 130.0)	60.0 (18.0, 130.0)	
	n = 63	n = 59	
Total daily meal insulin dose (units)	48.1 (25.6)	46.3 (26.6)	0.70
	40.0 (12.0, 114.0)	40.0 (8.0, 165.0)	
	n = 63	n = 59	
Total daily meal and basal insulin (units)	105.3 (44.9)	105.6 (41.5)	0.97
	100.0 (28.0, 228.0)	100.0 (42.0, 230.0)	
	n = 63	n = 59	
Meal insulin/total insulin	0.457 (0.121)	0.435 (0.135)	0.34
	0.452 (0.196, 0.750)	0.439 (0.082, 0.750)	
	n = 63	n = 59	
Metformin user	43 (68.3%)	43 (72.9%)	0.72
HbA1c (IFCC) (mmol mol^{-1})	74.6 (10.8)	74.4 (12.0)	0.92
	73.0 (53.0, 103.0)	73.0 (54.0, 101.0)	
	n = 63	n = 59	
HbA1c (NGSP) (%)	8.98 (0.99)	8.96 (1.10)	0.91
	8.83 (7.00, 11.58)	8.83 (7.09, 11.39)	
	n = 63	n = 59	
CGM (SD) (mmol L^{-1})	2.98 (0.71)	2.97 (0.79)	0.94
	2.95 (1.64, 4.84)	2.77 (1.72, 5.80)	
	n = 62	n = 57	
CGM (mean) (mmol L^{-1})	10.9 (2.3)	10.7 (2.2)	0.56
	10.5 (5.7, 16.6)	10.0 (6.9, 16.7)	
	n = 62	n = 57	
Sagittal abdominal diameter (cm)	27.9 (3.5)	27.8 (3.5)	0.78
	27.5 (20.5, 36.9)	27.2 (22.0, 36.7)	
	n = 63	n = 58	
Waist circumference (cm)	116.1 (10.2)	115.7 (10.6)	0.81
	116.0 (95.0, 135.5)	113.0 (101.0, 144.8)	
	n = 61	n = 57	
Hip circumference (cm)	112.9 (9.4)	111.6 (9.6)	0.46
	111.0 (97.0, 138.0)	110.3 (94.0, 139.0)	
	n = 60	n = 58	
Waist-to-hip ratio	1.03 (0.07)	1.04 (0.06)	0.54
	1.04 (0.82, 1.16)	1.04 (0.90, 1.22)	
	n = 60	n = 57	
Adiponectin (mg L^{-1})	4.47 (2.17)	4.39 (2.21)	0.84
	4.20 (1.70, 11.00)	3.85 (2.00, 15.00)	
	n = 63	n = 58	
Weight (kg)	98.8 (14.1)	99.8 (14.8)	0.70
	100.0 (69.0, 134.9)	96.0 (72.5, 139.2)	
	n = 63	n = 59	
BMI (kg m^{-2})	33.7 (4.3)	33.5 (4.0)	0.75
	33.3 (27.3, 44.0)	33.5 (27.7, 43.0)	
	n = 63	n = 59	

Continues

Table 1. *Continued*

Variable	Liraglutide (n = 63)	Placebo (n = 59)	p-value
Fasting C-peptide (nmol L^{-1})	0.651 (0.477) 0.560 (0.090, 3.100) n = 63	0.727 (0.494) 0.620 (0.100, 2.600) n = 59	0.39
Fasting pro-insulin (pmol L^{-1})	18.9 (23.4) 12.0 (3.3, 136.0) n = 63	21.4 (22.2) 15.0 (3.3, 99.0) n = 58	0.56
Smoker	8 (12.7%)	7 (11.9%)	1.00
Number of daily insulin injections	4.46 (0.88) 4.00 (3.00, 9.00) n = 63	4.42 (0.62) 4.00 (3.00, 6.00) n = 59	0.89
Height (cm)	171.3 (10.4) 172.0 (148.0, 192.0) n = 63	172.7 (10.0) 173.0 (145.0, 194.0) n = 59	0.47
Systolic blood pressure (mmHg)	137.9 (16.8) 139.0 (101.0, 180.0) n = 63	133.7 (13.7) 134.0 (104.0, 157.0) n = 59	0.14
Diastolic blood pressure (mmHg)	73.5 (12.7) 74.0 (45.0, 103.0) n = 63	74.9 (8.5) 76.0 (54.0, 97.0) n = 59	0.48
Fasting low-density lipoprotein cholesterol (mmol L^{-1})	2.22 (0.79) 2.10 (0.20, 4.40) n = 61	2.28 (0.96) 2.30 (0.50, 4.80) n = 53	0.70
Fasting high-density lipoprotein cholesterol (mmol L^{-1})	1.12 (0.23) 1.10 (0.70, 1.80) n = 63	1.07 (0.32) 1.00 (0.60, 2.80) n = 58	0.39
Fasting triglycerides (mmol L^{-1})	1.87 (1.11) 1.60 (0.59, 6.50) n = 63	2.15 (1.59) 1.65 (0.56, 9.60) n = 58	0.27
Fasting total cholesterol (mmol L^{-1})	4.18 (0.92) 4.10 (2.70, 7.90) n = 63	4.24 (1.00) 4.10 (2.40, 6.80) n = 58	0.73
Fasting plasma glucose (mmol L^{-1})	9.96 (3.17) 9.40 (4.20, 17.90) n = 63	9.41 (2.55) 9.40 (2.50, 19.60) n = 59	0.30
Mean postprandial glucose level (mmol L^{-1})	12.0 (3.0) 11.7 (6.7, 20.6) n = 59	11.2 (3.0) 11.2 (5.9, 19.8) n = 57	0.20

For categorical variables, n (%) is presented. For continuous variables, mean (SD)/median (min, max)/n is presented. For comparison between groups, Fisher's exact test was used for dichotomous variables and Fisher's non-parametric permutation test for continuous variables. BMI, body mass index; CGM, continuous glucose monitoring; IFCC, International Federation of Clinical Chemistry; SD, standard deviation.

(p = 0.022) and HbA1c (p = 0.016) were stronger predictors of reduced sagittal abdominal diameter than in the liraglutide group. The effects of liraglutide and placebo in reducing sagittal abdominal diameter in relation to baseline mean glucose and HbA1c levels are shown in Figure 2.

Predictors of change on waist circumference

Baseline characteristics evaluated as potential predictors of changes in waist circumference are shown in Table S2. In the liraglutide group, lower sagittal abdominal diameter (p = 0.022), lower mean glucose levels (p = 0.023) and lower HbA1c (p = 0.0065) at baseline were associated with greater effects in reducing waist circumference. Comparing their effects between treatment groups, only HbA1c remained significant (p = 0.028). The effects of liraglutide and placebo treatments in reducing waist circumference in relation to baseline HbA1c are shown in Figure 2.

Predictors of change on adiponectin levels

Baseline characteristics evaluated as potential predictors of changes in adiponectin levels are shown in Table S3. In the liraglutide group, older age (p = 0.016), absence of

Table 2 Change in weight measurements and adiponectin levels between the groups receiving liraglutide and placebo from baseline until week 24

	Liraglutide (n = 63)			Placebo (n = 59)			Liraglutide–placebo baseline-adjusted difference***	
Variable	Baseline*	24 weeks*	Change**	Baseline*	24 weeks*	Change**	Mean (SD) 95% CI	p-value
Abdominal sagittal diameter (cm)	27.9 (3.5) 27.5 (20.5, 36.9) n = 63	26.8 (3.9) 26.5 (20.0, 36.5) n = 63	−1.11 (1.70) (−1.54, −0.68)	27.8 (3.5) 27.2 (22.0, 36.7) n = 58	27.7 (3.4) 27.2 (22.5, 35.6) n = 59	−0.01 (1.81) (−0.48, 0.47)	−1.09 (1.74) (−1.72, −0.46)	0.0008
Adiponectin (mg L^{-1})	4.47 (2.17) 4.20 (1.70, 11.00) n = 63	5.97 (4.79) 4.30 (1.30, 25.00) n = 59	1.43 (3.80) (0.44, 2.42)	4.39 (2.21) 3.85 (2.00, 15.00) n = 58	4.99 (3.28) 3.95 (1.70, 19.00) n = 54	0.56 (2.53) (−0.13, 1.26)	0.85 (3.26) (−0.37, 2.06)	0.17
BMI (kg m^{-2})	33.7 (4.3) 33.3 (27.3, 44.0) n = 63	32.4 (4.5) 32.7 (25.2, 42.8) n = 63	−1.32 (1.10) (−1.59, −1.04)	33.5 (4.0) 33.5 (27.7, 43.0) n = 59	33.5 (4.0) 33.4 (27.4, 44.8) n = 59	0.02 (0.92) (−0.22, 0.26)	−1.33 (1.02) (−1.70, −0.97)	<0.0001
Hip circumference (cm)	112.9 (9.4) 111.0 (97.0, 138.0) n = 60	110.5 (9.7) 108.3 (94.0, 133.0) n = 62	−2.34 (4.05) (−3.40, −1.28)	111.6 (9.6) 110.3 (94.0, 139.0) n = 58	112.3 (9.6) 111.1 (95.0, 140.0) n = 58	0.57 (3.62) (−0.39, 1.53)	−2.84 (3.82) (−4.24, −1.43)	0.0001
Waist circumference (cm)	116.1 (10.2) 116.0 (95.0, 135.5) n = 61	113.1 (10.9) 113.0 (87.0, 135.0) n = 63	−2.88 (4.32) (−3.99, −1.77)	115.7 (10.6) 113.0 (101.0, 144.8) n = 57	115.3 (10.6) 114.0 (95.0, 145.0) n = 59	−0.24 (3.63) (−1.20, 0.73)	−2.63 (4.01) (−4.09, −1.16)	0.0005
Waist-to-hip ratio	1.03 (0.07) 1.04 (0.82, 1.16) n = 60	1.02 (0.06) 1.03 (0.85, 1.18) n = 62	−0.002 (0.042) (−0.013, 0.009)	1.04 (0.06) 1.04 (0.90, 1.22) n = 57	1.03 (0.07) 1.03 (0.87, 1.17) n = 58	−0.008 (0.040) (−0.018, 0.003)	0.005 (0.039) (−0.010, 0.019)	0.51
Weight (kg)	98.8 (14.1) 100.0 (69.0, 134.9) n = 63	95.1 (15.1) 96.4 (61.5, 137.0) n = 63	−3.77 (3.10) (−4.55, −2.99)	99.8 (14.8) 96.0 (72.5, 139.2) n = 59	99.9 (14.8) 97.5 (73.1, 145.3) n = 59	0.06 (2.74) (−0.66, 0.77)	−3.81 (2.94) (−4.87, −2.76)	<0.0001

*Mean (SD)/median (min, max)/n is presented.
**Mean (SD)/95% CI is presented.
***Comparison between groups were made with ANCOVA, adjusting for baseline values.
BMI, body mass index; CI, confidence interval; SD, standard deviation.

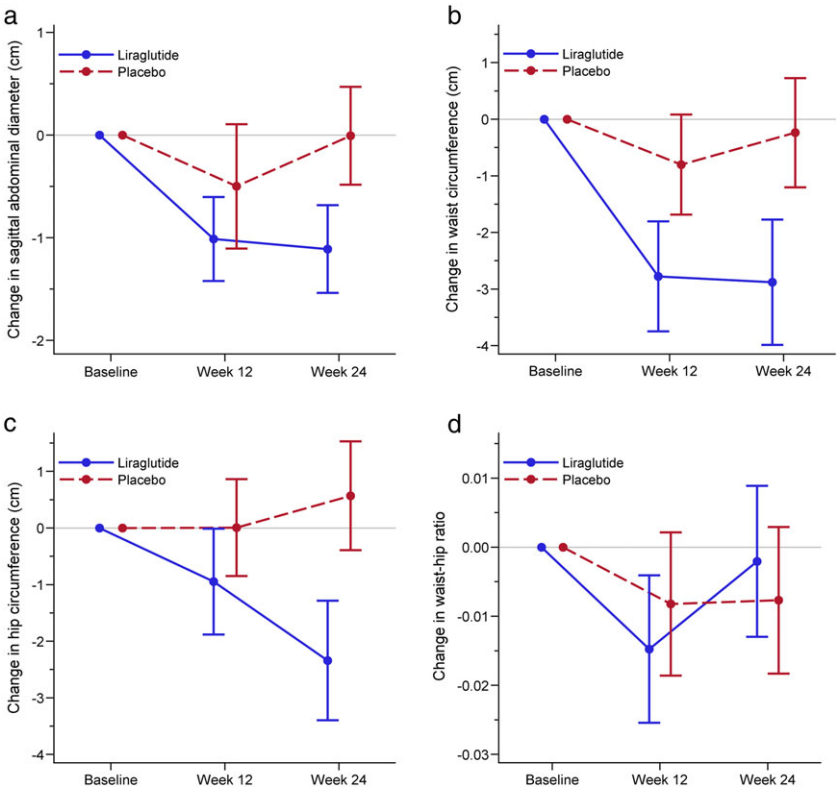

Figure 1 Change in sagittal abdominal diameter, waist circumference, hip circumference and waist-to-hip ratio among patients treated with liraglutide and placebo during 24 weeks of follow-up.

metformin use (p = 0.029) and smaller waist-to-hip ratio (p = 0.017) were associated with greater increases in adiponectin levels. However, none remained significant when effects were compared between treatment groups.

Post hoc multivariable analysis

HbA1c, sagittal abdominal diameter and mean glucose as measured masked CGM were evaluated further for prediction of change in waist circumference in multivariable analyses. HbA1c remained a significant predictor in the liraglutide group (p = 0.013) and on the borderline of significance when evaluated versus placebo (p = 0.053), adjusting for sagittal abdominal diameter. No adjustment for CGM mean was performed, because of multicollinearity issues. No significant interactions between sagittal abdominal diameter or CGM and treatment were observed in multivariable analyses.

Multivariable analyses of predictors for change in sagittal abdominal diameter were not performed, because of multicollinearity between the predictors identified in univariable analyses. Neither were multivariable analyses performed for predictors of change adiponectin levels, as no predictors were found in the univariable placebo-controlled evaluation.

Discussion

In this analysis from a randomized double-blind placebo-controlled trial, treatment with liraglutide was associated with reductions in both abdominal and hip obesity. In contrast, there were no changes in waist-to-hip ratio or adiponectin levels. Patients with lower baseline mean blood glucose levels and HbA1c also had greater reductions in abdominal obesity as opposed to patients with higher baseline levels.

Earlier analyses from this population showed significant reductions in HbA1c (−1.1% or −12.3 mmol mol^{-1}) and weight loss (−3.8 kg) when liraglutide was added to MDI compared with placebo (5). Previous studies, meta-analyses included, have also shown that GLP-1 receptor agonists cause weight loss (11–13) and reduction in waist circumference (14–17). The present study expands upon these findings in that sagittal abdominal diameter, hip circumference and waist-to-hip ratio were reduced when liraglutide was added to patients with MDI who usually gain weight due to the addition of insulin.

Both sagittal abdominal diameter and waist circumference correlate with visceral adipose tissue volume (18,19). The overall effect of liraglutide on weight loss

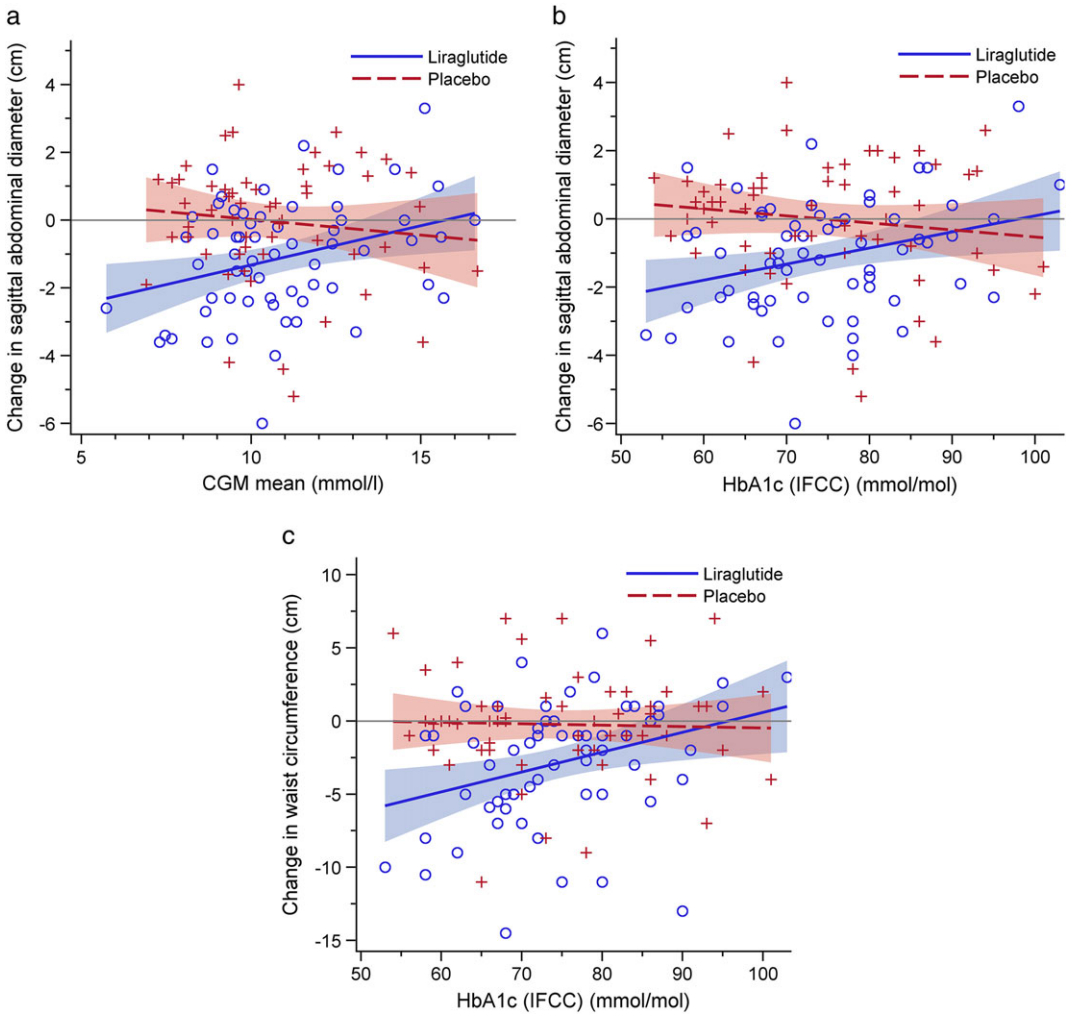

Figure 2 Change in sagittal abdominal diameter predicted by continuous glucose monitoring (CGM) mean and HbA1c at baseline and change in waist circumference predicted by HbA1c at baseline, among liraglutide-treated and placebo-treated patients. A significant reduction in sagittal abdominal diameter was seen among liraglutide-treated patients for CGM mean levels below 11.5 mmol L^{-1} and HbA1c levels below 80.5 mmol mol^{-1} (9.5%), when compared against placebo-treated patients. Similarly, liraglutide treated with baseline HbA1c levels below 81 mmol mol^{-1} (9.6%) experienced a significantly greater reduction in waist circumference compared with placebo-treated patients. IFCC, International Federation of Clinical Chemistry.

(and in particular abdominal obesity) may be due to appetite suppression and lower food intake as well as increased energy expenditure (20,21). It is well known that abdominal obesity is associated with insulin resistance (22), thus liraglutide's effects on abdominal obesity may be related to more efficient use of insulin. In the present study, liraglutide seemed to reduce not only visceral fat depots but also subcutaneous fat, as measured by hip circumference. Notably, in patients with poor glycaemic control, abdominal obesity was not reduced to the same extent as compared with patients with lower mean blood glucose and HbA1c levels at baseline. Nevertheless, abdominal obesity was reduced in patients randomized to liraglutide, likely resulting in lower insulin resistance and better cellular absorption of glucose. The smaller reduction in abdominal obesity among patients with very poor glycaemic control when liraglutide was added may be explained by improved metabolism, reduced glycosuria and, therefore, better uptake of glucose into the cells. Earlier analyses showed that patients responding to HbA1c reductions are different from patients who respond to weight reductions (6). Guidelines from the National Institute for Health and Care Excellence in the UK recommend continued use of GLP-1 receptor agonists if the patients have lost 1.0% (11 mmol mol^{-1}) in HbA1c and 3% in body weight in 6 months (23). The present results suggest that clinicians might consider not only severity of hyperglycaemia but also insulin resistance and therefore abdominal obesity, when

deciding whether to add GLP-1 receptor agonists to MDI. Moreover, the likelihood of weight loss in this patient population will increase as insulin doses are reduced (5), which would be beneficial in the long run.

It is also known that adiponectin levels are lower in individuals with obesity, T2D and insulin resistance (24). Animal models have shown both liraglutide and other GLP-1-receptor agonists to be associated with increased adiponectin levels (25,26), while there are few data from clinical studies (27–29). Because patients treated with liraglutide had reduced abdominal obesity, one could expect to find increased levels of adiponectin. Previous studies of liraglutide and adiponectin levels among persons with T2D have shown conflicting results. A double-blind, double-dummy active-controlled study showed that patients with T2D had increased levels of adiponectin when liraglutide, compared with glimepiride, was added to metformin (27). In contrast, an open-label, randomized trial showed no significant change in adiponectin levels when patients were switched from an inadequately controlled DPP4 inhibitor-based regimen to liraglutide (28), and a retrospective study showed a decrease in adiponectin levels (29). The present study is the first randomized, placebo-controlled trial studying the effects of liraglutide on adiponectin levels in patients receiving MDI and showed an increase in adiponectin levels in liraglutide group, albeit not significant compared with placebo. A possible explanation might be that the slight decrease in HbA1c in the placebo group caused a slight increase in adiponectin levels, possibly caused by increased visits and inclusion in a study. Another possible explanation for this finding is that adiponectin expression is already up-regulated by insulin treatment; thus, add-on therapy with liraglutide results in no further increase. These results suggest that further clinical studies are needed to determine how liraglutide affects adiponectin levels in patients with T2D because the effect of liraglutide may depend on patient characteristics (27–29).

A strength of this study is the randomized design where the different body measurements and adiponectin were evaluated between patients randomized to liraglutide or placebo. Moreover, baseline blood glucose was measured in two different ways and then related to these parameters. This is also the first known study to investigate the effect of liraglutide added to MDI on weight parameters. Another strength was the use of placebo controls in the prediction analyses, which by evaluation of predictor with treatment interactions allowed us to test whether predictors were significantly stronger in the liraglutide than placebo group. Generally, when predictors are only studied in the active group, there is a risk that they may be related to other factors than treatment *per se* (30).

Limitations include the relatively small study size. For example, adiponectin levels were slightly but not significantly higher in the liraglutide than placebo group, whereas a significant difference may have been observed if more patients had been included. Correspondingly, a few predictors existed within the liraglutide group that where non-significant when compared with the placebo group; thus, it cannot be discounted that minor effects could be found for these or other variables in larger patient cohorts. Another limitation is the relatively short duration of the study, although extending the study duration may have raised ethical issues because patients had poor glycaemic control. Finally, this study was also limited by the absence of information on patient dietary habits during the trial, which potentially influenced treatment effects to some extent.

Conclusions

In patients treated with MDI, the addition of liraglutide was associated with reductions in both abdominal and hip obesity but not with change in adiponectin levels. Patients with better glycaemic control showed reductions in abdominal obesity to a greater extent as opposed to those with very poor glycaemic control. Patients with high HbA1c levels most likely respond better to glucose-lowering effects. Abdominal obesity leading to insulin resistance may partly explain why this group of MDI patients may benefit from using liraglutide. These findings suggest that individualized therapy with liraglutide may be warranted in patients with T2D in which weight measurements may be biomarkers of responsiveness to treatment.

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Authorship

M. L., I. H. and J. T. designed the study. S. D., K. F. and M. L. were involved in carrying out the study. H. I. analysed the data; all authors took part in interpreting the data. H. D. and S. S. A. wrote the first draft of the manuscript. All authors revised the manuscript and approved the final version.

Conflict of Interest Statement

S. S. A.'s institution received grants from Novo Nordisk during the conduct of the study. K. F. has been a consultant or speaker for Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Astra Zeneca and Sanofi and acted as an advisory board member for MSD, NovoNordisk and AstraZeneca. I. H. has been a consultant for Abbott Diabetes Care, Roche, Bigfoot and Becton Dickinson and has received grants from Medtronic Diabetes. J. T. has received grants from Bayer Pharma, Boehringer Ingelheim, Merck Serono and MSD outside the submitted work, and has acted as a consultant, advisory board member or speaker for Merck Serono, Orion Pharma, Renova and MSD, and is a share owner in Orion Pharma. B. A. has received lecture fees from Novartis, Merck, Sanofi and Novo Nordisk and has received grants from Novartis and Merck outside the submitted work. S. S. has occasionally been a consultant and received honorariums from Eli Lilly, Sanofi-Aventis, Novo Nordisk, Abbot Scandinavia, AstraZeneca and Merck, Sharp & Dohme and has participated in advisory boards for Sanofi-Aventis, AstraZeneca and Eli Lilly. M. L.'s institution received grants from Novo Nordisk during the conduct of the study. M. L. has received honoraria or been a consultant for AstraZeneca, DexCom, Eli Lilly and Novo Nordisk, participated in advisory boards for MSD and Novo Nordisk and received research grants from AstraZeneca and Dexcom outside the submitted work. S. S. A., H. D., S. D., S. I., H. I. and T. G. have no conflict of interest to declare.

Trial registration number

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Predictors of change on sagittal abdominal diameter (cm)
Table S2. Predictors of change on waist circumference (cm)
Table S3. Predictors of change on adiponectin levels (mg/l)