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Liraglutide changes body composition and lowers added sugar intake in overweight persons with insulin pump-treated type 1 diabetes

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Abstract

Aims: To present secondary outcome analyses of liraglutide treatment in overweight adults with insulin pump-treated type 1 diabetes (T1D), focusing on changes in body composition and dimensions, and to evaluate changes in food intake to identify potential dietary drivers of liraglutide-associated weight loss.

Materials and methods: A 26-week randomized placebo-controlled study was conducted to investigate the efficacy and safety of liraglutide 1.8 mg daily in 44 overweight adults with insulin pump-treated T1D and glucose levels above target, and demonstrated significant glycated haemoglobin (HbA1c)- and body weight-reducing effects. For secondary outcome analysis, dual X-ray absorptiometry scans were completed at Weeks 0 and 26, and questionnaire-based food frequency recordings were obtained at Weeks 0, 13 and 26 to characterize liraglutide-induced changes in body composition and food intake.

Results: Total fat and lean body mass decreased in liraglutide-treated participants (fat mass −4.6 kg [95% confidence interval {CI} −5.7; −3.5], $P < 0.001$; lean mass −2.5 kg [95% CI −3.2;-1.7], $P < 0.001$), but remained stable in placebo-treated participants (fat mass −0.3 kg [95% CI −1.3;0.8], $P = 0.604$; lean mass 0.0 kg [95% CI −0.7;0.7]; $P = 0.965$ [between-group P values <0.001]). Participants reduced their energy intake numerically more in the liraglutide arm (−1.1 MJ [95% CI −2.0;-0.02], $P = 0.02$) than in the placebo arm (−0.9 MJ [95% CI −2.0;0.1], $P = 0.22$), but the between-group difference was statistically insignificant ($P = 0.42$). However, energy derived from added sugars decreased by 27% in the liraglutide arm compared with an increase of 14% in the placebo arm ($P = 0.004$).

Conclusions: Liraglutide lowered fat and lean body mass compared with placebo. Further, liraglutide reduced intake of added sugars. However, no significant difference in total daily energy intake was detected between liraglutide- and placebo-treated participants.

1 | INTRODUCTION

A few decades ago, type 1 diabetes (T1D) could be discriminated from other types of diabetes based on phenotype. Most people with T1D were lean or underweight, but today, more than half of the adult population with T1D is overweight or obese.[1,2] Further, despite increasing use of advanced diabetes technologies, the recommended glycaemic goal of glycated haemoglobin (HbA1c) <53 mmol/mol (7.0%) is achieved by only every fifth person with T1D.[3] This means that most T1D treatment should not only address glucose management but also weight management to minimize the risk of diabetes- and obesity-associated morbidity and mortality.[4-8]

A number of add-ons to insulin with the potential to improve glucose levels while sustaining or even reducing body weight has been investigated in open- and closed-loop therapies.[9-12] In particular, the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide has been the target of study in clinical trials in different subgroups of persons with T1D.[13-21] A recent meta-analysis of randomized controlled trials of at least 4 weeks' duration showed that when liraglutide is added to insulin therapy, persons with T1D on average achieve a decrease in HbA1c of 2 mmol/mol (0.2%) and a 3.85-kg weight loss.[12]

Currently, liraglutide is only approved for the treatment of type 2 diabetes, overweight and obesity, and its off-label use for the management of T1D is relatively limited.[2] Nevertheless, the combination of even a modest reduction of HbA1c and a moderate weight loss makes liraglutide an attractive therapeutic option for persons with T1D who struggle with glucose values and a body weight above the recommended levels despite dietary guidance, diabetes education and diabetes technology use.

In a previously published 26-week randomized placebo-controlled study of efficacy and safety of liraglutide in overweight adults with insulin pump-treated T1D and glucose levels above target, the Lira Pump trial, we found greater reductions in HbA1c (−7.3 mmol/mol [−0.7%]) and weight (−6.3 kg) than have been observed in the general T1D population.[18]

In the present paper, we report on secondary outcome analyses, focusing on changes in body composition and dimensions, and we evaluate changes in food intake to identify potential dietary drivers of the liraglutide-associated weight loss.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study is a substudy of the Lira Pump Trial, a 26-week, randomized, double-blind, placebo-controlled, dual-centre study of the effects of liraglutide 1.8 mg once daily in adults with insulin pump-treated T1D who were overweight or obese and had an HbA1c above the recommended level. Details of the primary study have been published elsewhere.[18]

The study was undertaken at Copenhagen University Hospital Hvidovre and Steno Diabetes Center Copenhagen in collaboration with the National Serum Institute (Statens Serum Institut) in Denmark. The study protocol was approved by the Scientific-Ethical Committee of the Capital Region of Denmark (H-3-2014-094), the Danish Medicines Authority (EudraCT 2014–002285-76), and the Danish Data Protection Agency (AHH-2015-002/03497), conducted under the surveillance of the Good Clinical Practice Unit at Copenhagen University Hospital, and registered at ClinicalTrials.gov (NCT02351232).

The study included adults (aged 18-70 years) with T1D and insulin pump use for ≥1 year, body mass index (BMI) > 25 kg/m^2, HbA1c > 58 mmol/mol (7.5%), and consistent use of carbohydrate counting and entry of carbohydrates in the insulin pump bolus calculator. Persons with gastroparesis, inflammatory bowel disease, renal dysfunction (estimated glomerular filtration rate < 60 mL/min/1.73m^2), history of pancreatitis, cancer or other major medical or psychological condition, and concurrent use of corticosteroids or antidiabetic medicine other than insulin were ineligible for participation.

Participants were randomized in a 1:1 ratio to liraglutide or placebo. Study personnel and participants were blinded to the allocation. Liraglutide and placebo injection pens that were indistinguishable from one another were provided by the manufacturer (Novo Nordisk A/S, Måløv, Denmark). The titration methods for the two solutions were identical and as follows: 0.6 mg liraglutide/0.1 mL placebo was injected once daily for the first week, the second week the dose was increased to 1.2 mg liraglutide/0.2 mL placebo, and finally in the third week of study participation the dose was increased to 1.8 mg liraglutide/0.3 mL placebo. The intervals between dose increments could be extended at the discretion of the investigator in case of pronounced gastrointestinal side effects, and if 1.8 mg per day was not tolerated, participants could stay on 1.2 mg per day for the duration of the study.

Participants' insulin pump therapy with rapid-acting insulin analogue was continued during the study and managed according to usual standards based on blood glucose monitoring or continuous glucose monitoring (CGM) values. No dietary guidance or specific guidelines for managing hypoglycaemia were provided. However, at study start—as a safe practice to reduce the risk of hypoglycaemia in participants receiving liraglutide—all insulin basal rates were reduced by 10% and insulin bolus doses were lowered by increasing correction factors and insulin-to-carbohydrate ratios by 15%. Insulin pump settings were subsequently adjusted to appropriate levels by the participants' themselves or by the study personnel at the first telephone contact 1 week later.

Study participation included a screening visit, four visits at the outpatient diabetes clinics (Weeks 0, 3, 13 and 26), and one telephone consultation (Week 1). Insulin pump data were uploaded, evaluated, and adjusted if needed at each contact. Six days of CGM were undertaken with blinded devices (iPro2 [Medtronic, Northridge, California]) four times during the study (Weeks 0, 3, 13 and 26).

The primary study endpoint was difference in change in HbA1c from Week 0 to Week 26 between participants treated with liraglutide and placebo. Differences in change in anthropometry, body composition, self-reported food intake and physical activity level, which are reported in this paper, were among the predefined secondary study endpoints.

2.2 | Anthropometry

At Week 0, height, body weight, waist circumference and hip circumference were measured according to World Health Organization recommendations.[22] The latter three were repeated at Weeks 3, 13 and 26. Subsequently, waist-to-hip ratio and BMI were calculated for each of the timepoints.

2.3 | Body composition

At Week 0 and Week 26, fat and lean body mass were determined by dual X-ray absorptiometry (DXA) scans using a Hologic Discovery A (Hvidovre Hospital: S/N 83487; Steno Diabetes Center Copenhagen: S/N 82800) DXA scanner (Hologic Inc., Marlborough, Massachusetts). Participants were scanned in a fasting state, and during the procedure insulin pumps and continuous glucose monitors were disconnected and removed from the body to avoid artefacts. The android region was defined as the area of the abdomen from a line joining the two superior iliac crests and extended cranially for 20% of the distance to the base of the skull. The gynoid region was defined as the portion of the legs from the greater femoral trochanter, extending caudally to mid-thigh.

2.4 | Food frequency questionnaire

Participants filled out a web-based food frequency questionnaire (FFQ) with a 12-week recall period at Week 0, Week 13 and Week 26. The FFQ was a modified version of the 360-item FFQ used for the Danish National Birth Cohort, which has been validated against 7-day food diaries and selected biomarkers.[23-25] The modifications included conversion from paper to electronic format and updating the questionnaire to cover temporal changes in dietary habits since the initial development for the Danish National Birth Cohort. The amount of foods consumed were then quantified based on reported frequency of consumption and assumptions on standard portion sizes. The amount of nutrients consumed was quantified using the Danish Food Composition table.[26]

2.5 | Physical activity assessment

Participants were asked at Week 0, Week 13 and Week 26 how often they performed exercise causing sweating and an increase in heart and breathing rates for more than 30 minutes. The scale used had five levels: (a) daily; (b) 3 to 4 times per week; (c) 1 to 2 times per week; (d) rarely; and (e) never.

2.6 | Statistical analyses

Measures of body composition, clinical biomarkers and dietary intake of participants at baseline were described using mean and standard deviation or median and interquartile range. Changes over time (Week 0-Week 13-Week 26) within groups (t-test) and between groups (F-test) were modelled using linear mixed-effects models. Changes in physical activity were assessed using Fisher's exact test. All analyses were performed as an intention-to-treat analysis, that is, including all available data for all participants, completers as well as non-completers. The statistical significance level was set at $P < 0.05$. Statistical analyses were conducted in SAS version 9.2.

3 | RESULTS

In February 2015 to April 2016, 171 adults with insulin pump-treated T1D were assessed for eligibility. Of these, 54 were screened, and 44 of them met the inclusion criteria and were randomized to either liraglutide or placebo treatment. Of the 22 participants assigned to the liraglutide study arm, three persons withdrew because of breast cancer, multiple sclerosis and gastrointestinal side effects, respectively. All 22 participants assigned to the placebo study arm completed the study.

Participant characteristics including a summary of primary and selected secondary study endpoints, which have been previously reported, are given in Table 1.[18] In brief, changes in HbA1c were significantly different between participants treated with liraglutide −5 mmol/mol (−0.5%) and participants treated with placebo 2 mmol/mol (0.2%; $P < 0.001$). This was reflected by a significant difference between the two groups in time spent with glucose values in the range 4.0 to 10.0 mmol/L ($P = 0.044$): participants receiving liraglutide increased time in range by 4.6%, that is, by 66 minutes, whereas participants receiving placebo reduced time in range by 4.8%, that is, by 69 minutes. The total daily insulin dose decreased by 4.9 IU in the liraglutide study arm and increased by 2.8 IU in the placebo study arm ($P = 0.008$ for between-group difference). This was mainly driven by a difference in change in total daily bolus insulin dose. Finally, there was a significant 6.8-kg decrease in body weight in participants receiving liraglutide, whereas there was no change in body weight in those receiving placebo ($P < 0.001$ for between-group difference).

The incidence of gastrointestinal symptoms was higher in the liraglutide study arm than in the placebo arm, with nausea being the

TABLE 1 Participant baseline characteristics and changes within and between groups after 26 weeks of treatment with liraglutide or placebo

	Liraglutide			Placebo			ΔLiraglutide vs ΔPlacebo
	Baseline	Change	P value	Baseline	Change	P value	P value
Randomized/female sex, N	22/15			22/15			
Age, years	54 (37-61)			45 (34-52)			
Type 1 diabetes, years	21 (15-34)			20 (15-35)			
Stimulated C-peptide, pmol/L	9 (7-18)			9 (6-12)			
Insulin pump treatment, years	5 (3-7)			6 (5-9)			
rt-CGM use, n	10			6			
Body mass index, kg/m^2	30.2 ± 2	−2.4 (−2.9; −1.9)	<0.001	29 ± 3	−0.2 (−0.7; 0.3)	0.487	<0.001
HbA1c, mmol/mol	66 ± 6	−5 (−8; −2)	<0.001	66 ± 6	2 (0; 5)	0.058	<0.001
HbA1c, %	8.2 ± 0.5	−0.5 (−0.7; −0.2)	<0.001	8.1 ± 0.5	0.2 (0.0; 0.4)	0.058	<0.001
Continuous glucose monitoring data							
Mean glucose, mmol/L	10.0 ± 1.3	−0.7 (−1.4; 0.0)	0.064	10.3 ± 1.5	0.3 (−0.4; 0.9)	0.394	0.053
Coefficient of variation, %	37.9 ± 0.1	0.0 (−3.9; 3.9)	0.983	40.1 ± 6.6	0.8 (−2.8; 4.4)	0.664	0.756
Percentage of time at < 4.0 mmol/L	3.2 ± 3.5	2.5 (0.1; 5.0)	0.044	3.5 ± 3.6	2.1 (−0.2; 4.4)	0.077	0.787
Percentage of time at 4.0 to 10.0 mmol/L	51.3 ± 12.7	4.6 (−2.1; 11.3)	0.178	48.6 ± 12.4	−4.8 (−11.0; 1.5)	0.133	0.044
Percentage of time at > 10.0 mmol/L	45.9 ± 14.0	−7.2 (−14.6; 0.1)	0.053	47.9 ± 13.3	2.7 (−4.1; 9.5)	0.441	0.052
Insulin pump data							
Total daily insulin dose, U	48 ± 15	−4.9 (−9.1; −0.7)	0.021	54 ± 19	2.8 (−1.1; 6.7)	0.164	0.008
Total daily basal insulin dose, U	25 ± 9	−1.8 (−3.3; −0.3)	0.017	28 ± 7	−0.5 (−1.9; 0.9)	0.473	0.214
Total daily bolus insulin dose, U	23 ± 9	−3.1 (−6.8; 0.7)	0.113	26 ± 14	3.3 (−0.3; 6.9)	0.069	0.016
Total daily carbohydrate intake, g	119 ± 39	−6 (−28; 16)	0.578	137 ± 71	14 (−7; 34)	0.184	0.188

Note: Baseline data are mean ± standard deviation and median (interquartile range). Estimated changes within groups are mean (95% confidence interval). P values reflect change over time within each treatment group and difference in change over time between the liraglutide and placebo groups. Time at < 4.0 mmol/L = time spent with sensor glucose values <4.0 mmol/L; time at 4.0 to 10.0 mmol/L = time spent with sensor glucose values; time at > 10.0 mmol/L = time spent with sensor glucose values >10.0 mmol/L.

Abbreviation: rtCGM, real-time continuous glucose monitoring.

FIGURE 1 Fat and lean body mass determined by dual-energy X-ray absorptiometry at Week 0 and Week 26 in participants treated with liraglutide and placebo. NS, not significant
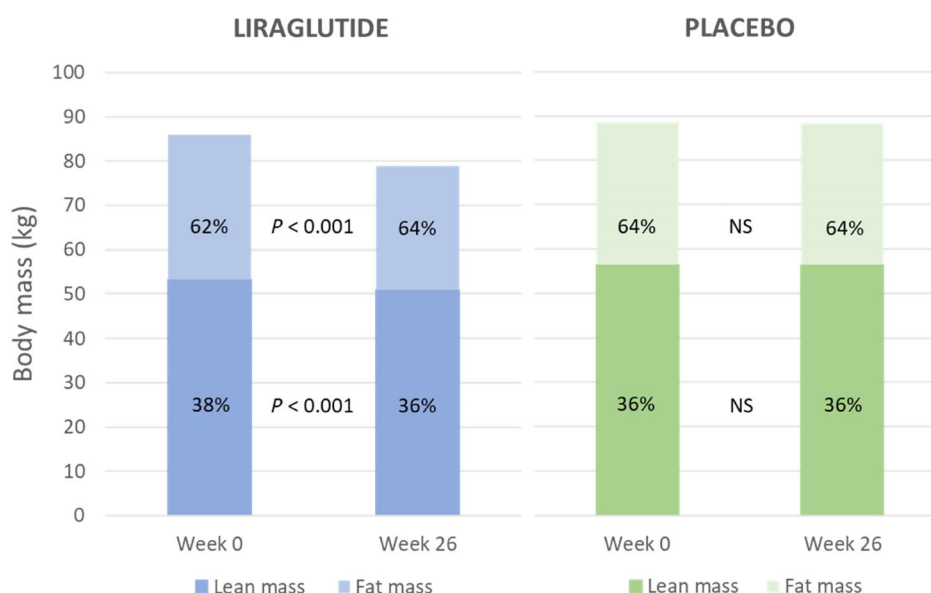
most prevalent. Five persons (23%) receiving liraglutide treatment had to deviate from the titration plan described in the study protocol and postpone the dose escalation from 1.2 to 1.8 mg liraglutide because of gastrointestinal side effects. One of the five persons did not tolerate the end dose and had to stay on 1.2-mg liraglutide daily for the duration of the study.

TABLE 2 Body composition and anthropometric data for participants treated with liraglutide compared with placebo

	Liraglutide			Placebo			ΔLiraglutide vs. ΔPlacebo	
	Baseline	Change	P value	Baseline	Change	P value	P value	P value*
DXA measurements								
Total mass, kg	85.9 ± 10.0	−7.0 (−8.5; −5.5)	<0.001	88.6 ± 12.9	−0.3 (−1.7; 1.1)	0.687	<0.001	<0.001
Total lean mass, kg	53.3 ± 9.5	−2.5 (−3.2; −1.7)	<0.001	56.4 ± 12.7	0.0 (−0.7; 0.7)	0.965	<0.001	<0.001
Total fat mass, kg	32.6 ± 6.2	−4.6 (−5.7; −3.5)	<0.001	32.1 ± 6.1	−0.3 (−1.3; 0.8)	0.604	<0.001	<0.001
Trunk lean mass, kg	26.2 ± 4.8	−1.3 (−1.7; −0.9)	<0.001	27.7 ± 5.8	−0.1 (−0.5; 0.3)	0.556	<0.001	<0.001
Trunk fat mass, kg	14.9 ± 3.5	−2.4 (−3.0; −1.8)	<0.001	14.9 ± 3.1	−0.2 (−0.8; 0.3)	0.430	<0.001	<0.001
Android lean mass, kg	4.2 ± 0.9	−0.2 (−0.3; −0.1)	<0.001	4.3 0.8	0.0 (−0.1; 0.1)	0.471	0.003	0.002
Android fat mass, kg	2.8 ± 0.8	−0.5 (−0.7; −0.4)	<0.001	2.7 ± 0.7	0.0 (−0.1; 0.2)	0.778	<0.001	<0.001
Gynoid lean mass, kg	8.4 ± 1.5	−0.5 (−0.6; −0.3)	<0.001	8.9 1.9	−0.1 (−0.2; 0.1)	0.323	0.001	<0.001
Gynoid fat mass, kg	5.6 ± 1.4	−0.8 (−1.0; −0.6)	<0.001	5.7 ± 1.2	−0.1 (−0.3; 0.1)	0.383	<0.001	<0.001
Android fat mass / Gynoid fat mass	0.53 ± 0.22	−0.04 (−0.06; −0.02)	<0.001	0.48 ± 0.12	0.01 (−0.01; 0.03)	0.182	<0.001	<0.001
Anthropometric measurements								
Waist circumference, cm	98.6 ± 9.8	−7.6 (−9.7; −5.5)	<0.001	98.0 ± 10.1	−1.1 (−3.0; 0.9)	0.272	<0.001	<0.001
Hip circumference, cm	110.6 ± 6.7	−4.1 (−5.5; −2.6)	<0.001	111.5 ± 5.5	0.1 (−1.2; 1.5)	0.845	<0.001	<0.001
Waist / hip ratio	0.89 ± 0.10	−0.04 (−0.06; −0.02)	<0.001	0.88 ± 0.09	−0.01 (−0.03; 0.01)	0.228	0.023	0.018

Note: Baseline data are mean ± standard deviation. Estimated changes within groups are mean (95% confidence interval). *P* values reflect change over time within each treatment group and difference in change over time between the liraglutide and placebo groups.
*Adjusted for sex and age. Android region: the area of the abdomen from a line joining the two superior iliac crests and extended cranially for 20% of the distance to the base of the skull. Gynoid region: the portion of the legs from the greater femoral trochanter, extending caudally to mid-thigh.

TABLE 3 Food recordings for participants treated with liraglutide compared with placebo

	Liraglutide			Placebo			ΔLiraglutide vs. ΔPlacebo
	Baseline	Change	P value	Baseline	Change	P value	P value
Energy, MJ	7.1 ± 2.9	−1.1 (−2.0; −0.02)	0.02	7.5 ± 2.6	−0.9 (−2.0; 0.1)	0.22	0.42
Protein, %E	18.0 ± 3.0	1.2 (−0.3; 2.7)	0.12	18.7 ± 2.7	1.0 (−1.1; 3.1)	0.33	0.24
Total fat, %E	34.3 ± 4.7	1.2 (−1.7; 4.1)	0.40	36.7 ± 6.4	−1.1 (−3.5; 1.2)	0.33	0.37
SFA	12.6 ± 2.2	0.6 (−0.8; 1.9)	0.40	13.3 ± 3.0	0.3 (−0.9; 1.5)	0.58	0.84
MUFA	12.2 ± 2.3	0.7 (−0.8; 2.2)	0.35	12.9 ± 2.6	−0.7 (−1.9; 0.5)	0.01	0.15
PUFA	5.8 ± 0.9	−0.3 (−0.6; 0.1)	0.15	6.1 ± 1.4	−0.1 (−0.6; 0.4)	0.66	0.43
Carbohydrates, %E	42.8 ± 7.8	−3.4 (−7.2; 0.5)	0.08	41.5 ± 7.4	1.1 (−1.1; 3.4)	0.32	0.14
Carbohydrates, g/d	175 ± 95	−42 (−78; −5)	0.03	182 ± 85	−24 (−49; 0.4)	0.05	0.21
Added sugars, %E	4.6 ± 2.7	−1.2 (−2.3; 0.0)	0.05	5.1 ± 4.0	1.0 (−0.8; 2.2)	0.35	0.004
Fibre, g/d	19.7 ± 7.2	−3.4 (−6.7; −0.01)	0.04	21.0 ± 8.6	−3.0 (−6.6; 0.5)	0.09	0.88
Alcohol, g/d	10.8 ± 13.2	0.5 (−1.6; 2.6)	0.65	7.5 ± 11.2	−3.1 (−8.4; 2.1)	0.23	0.09

Note: Baseline data are mean ± standard deviation. Estimated changes within groups are mean (95% confidence interval). *P* values reflect change over time within each treatment group and difference in change over time between the liraglutide and placebo groups.
Abbreviations: MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

The DXA scans showed that the significant weight loss observed in the liraglutide study arm was the result of significant reductions in fat (−4.6 kg) as well as fat-free mass (−2.5 kg), whereas no changes in either of the two tissue types were observed in the placebo study arm (Figure 1). Further details of the DXA scan results are given in Table 2.

Waist circumference and hip circumference decreased significantly in participants treated with liraglutide (−7.6 and −4.1 cm, respectively), but the former more than the latter which is why the waist-hip ratio also decreased. There were no changes in waist and hip circumference in the placebo-treated participants (Table 2).
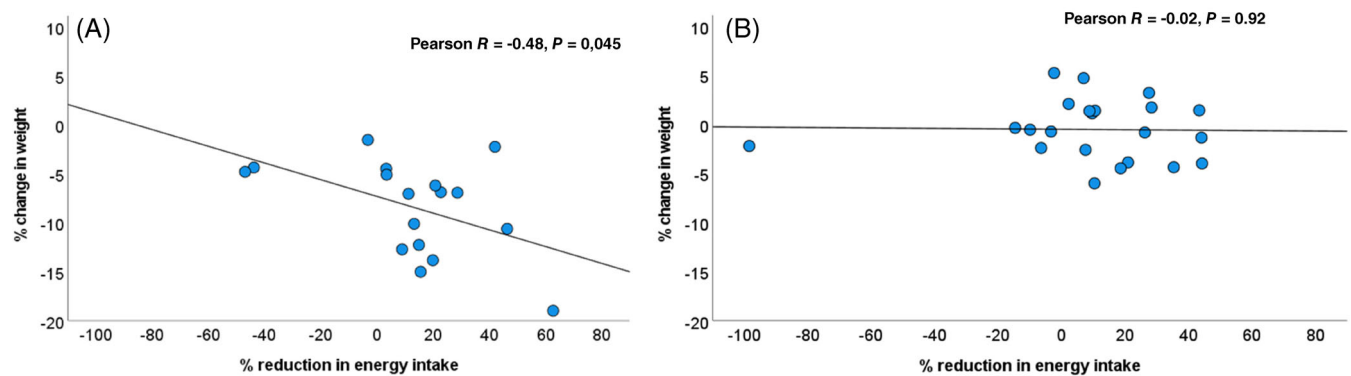
FIGURE 2 Scatter plots of relative change in weight versus relative reduction in energy intake from Week 0 to Week 26. A, Liraglutide-treated participants. B, Placebo-treated participants
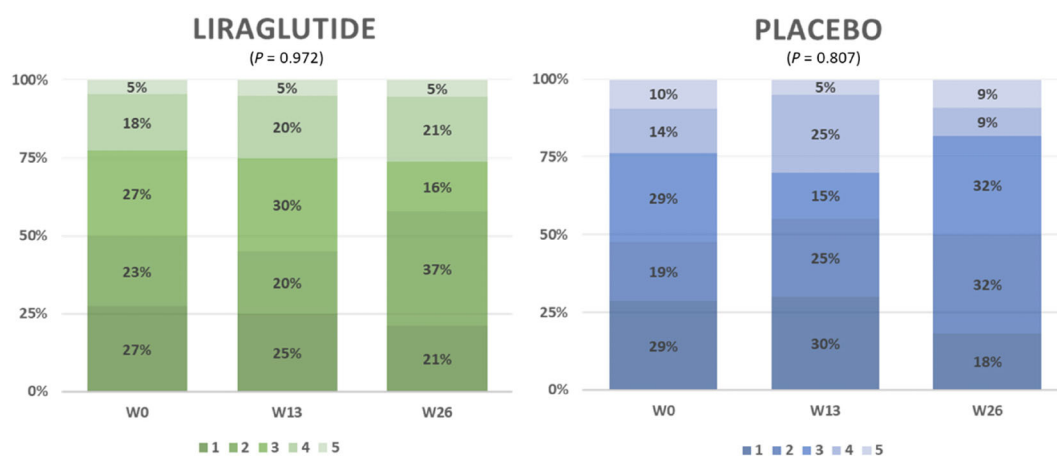

FIGURE 3 Participant-reported exercise level. Exercise causing sweating and an increase in heart and breathing rate > 30 min: 1 = daily; 2 = 3 to 4 times per week; 3 = 1 to 2 times per week; 4 = rarely; 5 = never. P values reflect changes over time within each treatment group. W, week

Baseline energy intake (mean ± SD) was 7.1 ± 2.9 MJ and 7.5 ± 2.6 MJ in the liraglutide and placebo group, respectively (Table 3). During the study period, participants in the liraglutide group reduced their energy intake significantly −1.1 MJ (95% CI −2.0; −0.02), while a numerically similar but statistically insignificant decrease was observed in the placebo group −0.9 MJ (95% CI −2.0; 0.1). There was no difference in change in energy intake between the groups ($P = 0.42$). In liraglutide-treated persons, each 1-MJ decrease in daily energy intake was found to be associated with a 2.0-kg weight loss (95% CI 3.1; 0.9; $P = 0.002$) after adjustment for baseline energy intake, age and sex (Figure 2). In contrast, in placebo-treated persons, a more modest and nonsignificant weight loss of 0.2 kg (95% CI −0.6; 0.9; $P = 0.66$) was observed for each 1-MJ decrease in daily energy intake. The only significantly different change in food intake over time between the two groups was observed for added sugars ($P = 0.004$) where intake decreased in the liraglutide group (∼1% of energy), while intake increased (∼1% of energy) in the placebo group. Further details of the FFQ recordings are given in Table 3.

The majority of participants reported being regularly physically active. There were no significant changes in participant-reported activity level in the two study arms throughout the study (Figure 3).

4 | DISCUSSION

In this secondary endpoint analysis of the 26-week randomized placebo-controlled Lira Pump Trial in overweight adults with insulin pump-treated T1D and glucose levels above target, we demonstrated that the observed liraglutide-induced weight loss was the result of significant reductions in total fat and lean body mass. Both gynoid and android fat mass decreased, but the former proportionally more than the latter, which led to a significant albeit small reduction in the ratio between the two. In parallel, waist-to-hip ratio decreased. The participants' level of physical activity did not change throughout the study. We were unable to identify dietary changes that could explain the pronounced weight loss, however, we did register a significant

reduction in the intake of added sugars when comparing the liraglutide arm with the placebo arm.

The present study is not the first to report changes in body composition in persons with T1D treated with 1.8 mg liraglutide.[19,21] Interestingly, our results differ from the results of the two previously published studies in the sense that, in addition to significant reductions in fat mass, we document clinically and statistically significant reductions in lean mass in the liraglutide arm. The ratio between fat and lean mass reductions in the present study (1.8:1.0) instead resembles what has been reported in studies of liraglutide-treated persons with type 2 diabetes.[27] The most recently published of the two T1D studies has many similarities with the present study, including study design (26-week parallel intervention and placebo arms) and method of assessment of changes in body composition (DXA scans).[19] However, there are also several differences between the two which might explain the differences in outcomes, such as method of insulin therapy (100% insulin pump use vs. 68%) and BMI at baseline (30.2 vs. 33.3 kg/m^2).[19] In the present study we specifically assessed changes in exercise level as a potential contributor to change in tissue mass, but we found no indication of such an association.

It can be debated whether the body composition changes observed in liraglutide-treated participants in the present study should be characterized as beneficial. There is an increasing body of evidence suggesting that losses of fat mass and lean body mass may have oppositely operating effects on mortality—while a reduction in body fat may reduce mortality, a reduction in lean body mass may increase it.[28,29] In this case it would mean that the significant loss of lean body mass could negatively affect health. On the other hand, the lowering of BMI, waist circumference, waist-to-hip ratio, and android fat-to-gynoid fat ratio all contribute to a more favourable cardiometabolic risk profile.[30-32] Finally, from a user perspective, the visible changes in body dimensions were probably viewed as positive, with impact on both physical and emotional well-being.[33]

Dietary changes as an explanatory cause of liraglutide-induced weight loss have not been previously studied in persons with T1D. FFQ scores at Week 0 indicated that, in the 12 weeks prior to study entry, participants' daily energy intake was lower than would be expected for weight maintenance (≈9.0 KJ). Possible explanations for this could be that these overweight and obese persons had already made attempts to lose weight through dietary restrictions, alternatively that they were underreporting their food intake.[34] During the study, there was a trend toward further reductions in participant-reported energy intake. The magnitude of the change in energy intake was not statistically significant between the two study arms, although numerically greater in the liraglutide-treated arm. The absence of a difference in energy intake between liraglutide- and placebo-treated participants is somewhat surprising because GLP-1-based therapies are known to reduce food intake, appetite and hunger and to promote fullness and satiety.[35,36] Further, studies of GLP-1-based therapies in persons with type 2 diabetes have reported reduced food intake when assessed by ad libitum meals.[37,38] In the present study, the association between energy intake at Week 26 and weight loss in the liraglutide arm suggests that absolute energy intake may, at least

partly, explain the observed weight loss. However, lack of significant difference in energy intake between liraglutide- and placebo-treated participants complicates this interpretation. Nevertheless, our results point toward a potentiating effect of liraglutide and energy restriction, that is, those who limit their energy intake the most achieve the greatest weight loss during liraglutide treatment.

Although FFQ responses did not show significant changes between study arms neither in total energy intake nor in macronutrient intake, they did show a difference between liraglutide- and placebo-treated participants in terms of intake of added sugars. Added sugars contributed little to the overall energy intake; however, they may have impacted glucose levels. Thus, the reduced intake of added sugars in the liraglutide arm could, at least partly, explain the previously reported diminished insulin needs and improvements in HbA1c and time spent with continuous glucose monitoring values in the range 4.0 to 10.0 mmol/L.[18,39] Further, the reductions in daily insulin dose may have contributed to the weight loss.[40] Animal studies and some human studies have suggested that treatment with GLP-1 receptor agonists alters individual food preferences and consequently dietary macronutrient composition.[38,41,42] However, further investigations of this association and the potential underlying central and/or peripheral mechanisms are needed to draw firm conclusions.[35]

The present study has both strengths and weaknesses. Data were obtained in a randomized placebo-controlled study setup that met all criteria for good clinical practice. Nevertheless, the presented analyses are secondary, and the outcome variables were not included in study sample size calculations, and therefore we might have dismissed actual differences between treatment groups. We chose to record food intake retrospectively rather than prospectively to avoid the possibility of the ongoing registration affecting participants' food choices during the registration period. However, the rather long recall period (12 weeks) may also have biased the results. In addition, estimation of energy intake by FFQs is limited by a certain inaccuracy, and finally it should be noted that the applied questionnaire has not been validated in this specific population. Physical activity was also assessed using a nonvalidated scale. Objective measures could have been obtained by use of, for example, accelerometers; however, this would have been at the expense of a greater participant device load, and we therefore decided to rely on patient-reported outcomes.

Liraglutide was administered once daily in this study. Today, an alternative strategy for adding a GLP-1 receptor agonist to insulin therapy would be once-weekly administration. However, at the time of protocol development there was only limited availability of and experience with weekly injections of GLP-1 receptor agonists, especially among people with T1D.

In conclusion, we found that 26 weeks of liraglutide treatment resulted in loss of both fat and lean body mass. Loss of lean body mass was not a consequence of a less physically active lifestyle. Proportionally more fat was lost from android than gynoid depots. Parallel reductions in energy intake between the intervention and placebo groups were found by retrospective registration of food intake; however, food frequency recordings indicated that liraglutide treatment led to a diminished intake of added sugars. All in all, this study

contributes to existing knowledge with a further characterization of previously demonstrated glycaemic and weight-reducing effects of liraglutide in persons with T1D.

CONFLICT OF INTEREST

S.S. has served on an advisory panel for Medtronic and has received a research fellowship grant from the Danish Diabetes Academy supported by the Novo Nordisk Foundation. C.S.F. has received research support and lecture fees from Novo Nordisk. T.F.D. has served on advisory panels for Novo Nordisk, has received research support from Novo Nordisk and AstraZeneca and has received lecture fees from Novo Nordisk, AstraZeneca, Sanofi-Aventis and Boehringer-Ingelheim. D.V. is a shareholder in Novo Nordisk. J-E.B.J. has served on advisory panels for Amgen, Eli Lilly, UCB Pharma, and Gedeon Richter, and has received lecture fees from Amgen, Eli Lilly, UCB Pharma, Gilead and Otsuka. S.M. has served on advisory panels for AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Merck Sharp & Dome, Novo Nordisk, Sanofi and Bayer, has received lecture fees from AstraZeneca, Boehringer-Ingelheim, Merck Sharp & Dohme, Novo Nordisk and Sanofi, and has received research grants from Novo Nordisk and Boehringer-Ingelheim. H.U.A. is a shareholder in Novo Nordisk, has served on advisory panels for Abbott, Novo Nordisk and AstraZeneca, and has received lecture fees from Nordic Infucare. K.N. is a shareholder in Novo Nordisk, has received research support from Novo Nordisk, Roche Diagnostics, Medtronic and Zealand Pharma, has received lecture fees from Medtronic, Roche Diagnostics, Rubin Medical, Sanofi, Zealand Pharma, Novo Nordisk and Dexcom, and has served on advisory panels for Medtronic, Abbott and Novo Nordisk. T.H. and S.F.O. have nothing to declare.

AUTHOR CONTRIBUTIONS

Signe Schmidt, Christian Seerup Frandsen, Thomas Fremming Dejgaard, Sten Madsbad, Henrik Ullits Andersen and Kirsten Nørgaard contributed to the study design, data collection and analysis. Kirsten Nørgaard was study sponsor and recipient of the Novo Nordisk A/S study grant. Thórhallur Halldórsson, Sjudur Frodi Olsen and Jens-Erik Beck Jensen contributed to the data collection and analysis. Dorte Vistisen contributed to the data analysis. All authors were involved in the writing of the manuscript and approved the final version of the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of data generated or analysed during this study to preserve patient confidentiality. The corresponding author will, on request, detail the restrictions and any conditions under which access to some data may be provided.

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