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Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue

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Aim: The effect on body composition of liraglutide, a once-daily human glucagon-like peptide-1 analogue, as monotherapy or added to metformin was examined in patients with type 2 diabetes (T2D).
Methods: These were randomized, double-blind, parallel-group trials of 26 [Liraglutide Effect and Action in Diabetes-2 (LEAD-2)] and 52 weeks (LEAD-3). Patients with T2D, aged 18–80 years, body mass index (BMI) $\leq$40 kg/m^2 (LEAD-2), $\leq$45 kg/m^2 (LEAD-3) and HbA1c 7.0–11.0% were included. Patients were randomized to liraglutide 1.8, 1.2 or 0.6 mg/day, placebo or glimepiride 4 mg/day, all combined with metformin 1.5–2 g/day in LEAD-2 and to liraglutide 1.8, 1.2 or glimepiride 8 mg/day in LEAD-3. LEAD-2/3: total lean body tissue, fat tissue and fat percentage were measured. LEAD-2: adipose tissue area and hepatic steatosis were assessed.
Results: LEAD-2: fat percentage with liraglutide 1.2 and 1.8 mg/metformin was significantly reduced vs. glimepiride/metformin ($p < 0.05$) but not vs. placebo. Visceral and subcutaneous adipose tissue areas were reduced from baseline in all liraglutide/metformin arms. Except with liraglutide 0.6 mg/metformin, reductions were significantly different vs. changes seen with glimepiride ($p < 0.05$) but not with placebo. Liver-to-spleen attenuation ratio increased with liraglutide 1.8 mg/metformin possibly indicating reduced hepatic steatosis. LEAD-3: reductions in fat mass and fat percentage with liraglutide monotherapy were significantly different vs. increases with glimepiride ($p < 0.01$).
Conclusion: Liraglutide (monotherapy or added to metformin) significantly reduced fat mass and fat percentage vs. glimepiride in patients with T2D.
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Introduction

The number of overweight and obese people is rising substantially as a result of high-calorie diets and increasingly sedentary lifestyles that have become common in modern society [1]. Obesity, in particular 'android obesity', characterized by abdominal-visceral fat accumulation [2], is associated with increased insulin resistance [3] and is a major risk factor for the development of type 2 diabetes (T2D) [4]. Unfortunately, most antidiabetes therapies are associated with further weight gain as glucose metabolism changes [5–7]. In addition, in patients with T2D, diabetes medication is the most common cause of hypoglycaemia [8] and patients may accordingly exhibit defensive snacking, which may exacerbate weight gain [7].

Weight gain is an undesirable characteristic, as it further increases cardiovascular (CV) risk [9]. Visceral fat in particular increases the risk, with a recent metaregression analysis reporting a 2% increase in the relative risk of a CV disease event for a 1-cm increase in waist circumference [10]. Furthermore, weight gain and hypoglycaemia are barriers to effective disease management and to reaching glycated haemoglobin A1c (HbA1c) goals, as they increase physicians' reluctance to intensify treatment and decrease patient adherence [11]. Therefore, therapies that minimize weight gain while improving glycaemic control are highly desirable, especially if the risk of iatrogenic hypoglycaemia is low. Reductions in visceral and abdominal subcutaneous adipose tissue are associated with improvements in fasting glucose levels, glucose tolerance and lipid profiles [12] and would be especially valuable.

Glucagon-like peptide-1 (GLP-1) is a naturally occurring incretin hormone with a potent blood-glucose lowering action only during hyperglycaemia because it induces insulin secretion and reduces glucagon secretion in a glucose-dependent manner [13,14]. In addition, GLP-1 slows gastric emptying and induces satiety [15], leading to decreased energy intake [16] and weight loss [17]. Therefore, GLP-1 has great potential as a T2D therapy. Unfortunately, its half-life is very short ($t_{1/2} = 1–2$ min), as it is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) [13]. Liraglutide is a GLP-1 analogue with 97% amino acid sequence identity to native human GLP-1 and an acyl side-chain attachment, which makes it bind to albumin. These small structural differences prolong the half-life of the analogue to 13 h, making it suitable for once-daily administration [18]. Large phase 3 clinical studies have consistently shown that liraglutide is well tolerated, improves glycaemic control with a low risk of hypoglycaemia, improves indices of beta-cell function, improves systolic blood pressure and is associated with weight loss [19–24]. The Liraglutide Effect and Action in Diabetes-3 (LEAD-3) trial showed that monotherapy with once-daily liraglutide 1.8 mg reduced mean HbA1c levels by 1.1% with a concomitant sustained mean weight loss of 2.5 kg over 52 weeks [21]. The previous drug-naïve subgroup in this trial experienced an improvement in HbA1c from a baseline of 8.6% to below 7.0% and this improvement was sustained for the trial duration of 52 weeks. Similarly, the LEAD-2 trial showed that once-daily liraglutide 1.8 mg in combination with metformin reduced HbA1c levels by 1.0% with a concomitant mean weight loss of 2.8 kg over 26 weeks [20]. Here, as part of large preplanned substudies within the LEAD-3 and LEAD-2 trials, we examined the effect of liraglutide-induced weight loss on body composition.

Methods

Study Design and Treatment

Detailed methods for the main LEAD-2 and LEAD-3 studies have been published elsewhere [20,21]. Briefly, these studies were multicentre, randomized, double-blind, double-dummy, parallel-group trials of 26 weeks (LEAD-2) or 52 weeks (LEAD-3) involving patients with T2D. Patients in the LEAD-2 study were randomized to one of five different treatment arms consisting of 0.6, 1.2 or 1.8 mg/day liraglutide, 4 mg/day glimepiride or placebo, all in combination with 1.5–2.0 g/day metformin. Patients in the LEAD-3 trial were randomized to one of three different treatment arms consisting of 1.2 or 1.8 mg/day liraglutide or 8 mg/day glimepiride. As part of these trials, substudies assessing the effect of treatment on body composition were performed at selected sites in Australia, Belgium, Ireland, New Zealand, Spain, Sweden and the UK (LEAD-2), and Mexico and the USA (LEAD-3). Body composition was measured at randomization and at the end of the study via low-radiation dual-energy X-ray absorptiometry (DXA) in the LEAD-2 and LEAD-3 trials and single-slice abdominal computerized tomography (CT) in the LEAD-2 trial. To ensure standardization, the same procedural instructions were provided to all participating centres and all DXA and CT scans were analysed centrally by fully blinded specialists at SYNARC Paris (France), SYNARC A/S (Denmark) and SYNARC Hamburg (Germany). Both trials were conducted in accordance with the Declaration of Helsinki.

Patients

Participation in the DXA and CT substudies was optional. Inclusion criteria for the substudies were identical to those for the LEAD-2 and LEAD-3 trials. Namely, individuals diagnosed with T2D and treated with diet and exercise (LEAD-3 trial only), oral hypoglycaemic agents (OHAs) as monotherapy (LEAD-2 and LEAD-3 trials), or in combination therapy (LEAD-2 trial only). Patients were aged 18–80 years, had a BMI $\leq$40 kg/m^2 (LEAD-2) or $\leq$45 kg/m^2 (LEAD-3), and HbA1c of 7.0–10.0% (if treated with OHA combination therapy in the LEAD-2 trial or OHA monotherapy in the LEAD-3 trial), or 7.0–11.0% (if treated with OHA monotherapy in the LEAD-2 trial or diet and exercise in the LEAD-3 trial).

Efficacy Assessments

To assess glycaemic control, HbA1c was measured using a National Glycohemoglobin Standardization Program certified assay. Total body weight was also monitored.

The main endpoint was change in body composition. Endpoints measured via DXA scans (LEAD-2 and LEAD-3 substudies) were total fat tissue mass, percentage of body fat and total lean tissue mass; efficacy endpoints measured via CT images (LEAD-2 only) were visceral and abdominal subcutaneous adipose tissue area, and liver-to-spleen attenuation ratio. Visceral and abdominal subcutaneous tissue areas measured by single-slice CT have been shown to have a strong direct linear correlation with visceral and abdominal subcutaneous tissue mass respectively [25], allowing for changes in these two tissue types to be compared. In healthy individuals, the mean CT radiodensity for the liver is consistently higher than that for the spleen [26]. As the fatty liver has lower mean CT radiodensity than the spleen, the liver-to-spleen attenuation ratio is used as an index of liver fat (i.e. hepatic steatosis), with increases in the ratio indicating reduced hepatic steatosis [26]. In addition, changes in serum concentrations of alanine aminotransferase (ALT) and asapartate aminotransferase (AST) were analysed in the full study populations of the LEAD-2 and LEAD-3 trials.

Statistical Analysis

For all efficacy endpoints, data from a premature termination visit were carried forward for patients not completing the full study period. All efficacy endpoints were analysed using an analysis of covariance (ANCOVA) model with trial treatment, country and previous antidiabetic treatment as fixed effects and baseline value as a covariate. In the LEAD-2 study, DXA equipment was also included as a fixed effect in the ANCOVA model. Simultaneous pairwise comparisons on a 5% significance level were also carried out between different treatment arms using Dunnett's method. Data are reported as mean $\pm$ SE.

Results

A total of 160 patients (14.7% of the main study population) participated in the DXA substudy and 154 patients (14.1% of the main study population) participated in the CT substudy within the LEAD-2 trial. A smaller cohort of 61 patients (approximately 8.2% of the main study population) participated in the DXA substudy within the LEAD-3 trial. Baseline characteristics were similar for the entire trial population and the substudies' cohorts (table 1).

The number of patients completing the DXA substudies was 136 (85%) in the LEAD-2 trial and 46 (75%) in the LEAD-3 trial. A total of 131 (85%) patients completed the CT substudy within the LEAD-2 trial.

HbA1c and Body Weight Assessment

Mean HbA1c was reduced from baseline in all liraglutide treatment arms in a dose-dependent manner. In the LEAD-2 substudy, HbA1c was reduced by 0.6, 0.9 and 1.0% with liraglutide 0.6, 1.2 and 1.8 mg (all in combination with metformin) respectively. These reductions were significantly different to the 0.4% HbA1c increase observed with placebo (in combination with metformin; $p < 0.0001$ for all liraglutide arms), but did not differ significantly from the 0.7% decrease observed with glimepiride (also in combination with metformin). In the LEAD-3 substudy, HbA1c reductions of 0.5 and 0.9% were observed with liraglutide 1.2 and 1.8 mg monotherapy respectively, compared with a reduction of 0.2% with glimepiride monotherapy. The differences in HbA1c change from baseline across treatment arms were not significant.

In the substudies, mean body weight was reduced from baseline in all liraglutide treatment arms. In the LEAD-2 substudy, mean body weight decreases of 0.9, 2.0 and 3.2 kg were observed with liraglutide 0.6, 1.2 and 1.8 mg (all in combination with metformin) respectively. These changes in body weight from baseline were significantly different to the increase from baseline observed with glimepiride/metformin treatment (1.7 kg; $p = 0.0006$ for liraglutide 0.6 mg, $p < 0.0001$ for liraglutide 1.2 mg and liraglutide 1.8 mg) but did not differ significantly from the decrease from baseline (1.3 kg) observed in the

Table 1 Baseline demographic and disease characteristics of patients from the Liraglutide Effect and Action in Diabetes (LEAD)-2 and LEAD-3 trials and the dual-energy X-ray absorptiometry (DXA) and computerized tomography (CT) substudies within these trials

	LEAD-2					LEAD-3		
	Liraglutide 1.8 mg + metformin (1.5–2 g) All/substudy only (n = 242/37)	Liraglutide 1.2 mg + metformin (1.5–2 g) All/substudy only (n = 241/31)	Liraglutide 0.6 mg + metformin (1.5–2 g) All/substudy only (n = 242/35)	Placebo + metformin (1.5–2 g) All/substudy only (n = 122/20)	Glimepiride 4 mg + metformin (1.5–2 g) All/substudy only (n = 244/37)	Liraglutide 1.8 mg All/substudy only (n = 247/20)	Liraglutide 1.2 mg All/substudy only (n = 251/23)	Glimepiride 8 mg All/substudy only (n = 248/18)
Sex, men	142 (59)/19 (51)	129 (54)/17 (55)	151 (62)/27 (77)	73 (60)/15 (75)	140 (57)/26 (70)	121 (49)/10 (50)	117 (47)/12 (52)	133 (54)/6 (33)
Age, years	57 (9)/58 (9)	57 (9)/59 (8)	56 (11)/58 (10)	56 (9)/56 (10)	57 (9)/56 (9)	52 (11)/54 (9)	54 (11)/55 (11)	53 (11)/54 (13)
Weight, kg	88 (16)/91 (15)	88 (19)/86 (15)	88 (17)/93 (12)	91 (17)/94 (16)	89 (17)/97 (12)	93 (21)/94 (14)	93 (19)/94 (15)	93 (19)/88 (14)
Previous treatment: OHA monotherapy, n	83 (34)/14 (38)	91 (38)/10 (32)	81 (34)/12 (34)	41 (34)/7 (35)	89 (37)/15 (41)	87 (35)/9 (45)	91 (36)/11 (48)	94 (38)/8 (44)
OHA combination, n	159 (66)/23 (62)	150 (62)/21 (68)	161 (67)/23 (66)	81 (66)/13 (65)	156 (64)/22 (60)	160 (65)/11 (55)	160 (64)/12 (52)	154 (62)/10 (56)

Data are mean (s.d.) or n (%). OHA, oral hypoglycaemic agents

placebo/metformin treatment arm. In the LEAD-3 substudy, treatment with liraglutide 1.2 mg and liraglutide 1.8 mg (both in monotherapy) resulted in decrease in body weight from baseline of 2.4 and 2.3 kg. These body weight changes from baseline were significantly different to the increase from baseline observed with glimepiride treatment (2.0 kg; $p = 0.0043$ for liraglutide 1.2 mg, $p = 0.0068$ for liraglutide 1.8 mg) (figure 1).

DXA Assessments

Absolute and Relative Changes in Total Body Fat Mass and Lean Tissue Mass

Generally, liraglutide treatment reduced fat mass more than lean tissue mass while glimepiride increased the mass of one or both tissue types.

Absolute total fat tissue mass was reduced in all liraglutide treatment arms. In the LEAD-2 substudy, mean dose-dependent reductions from baseline of 0.7, 1.6 and 2.4 kg were observed with liraglutide 0.6, 1.2 and 1.8 mg (all in combination with metformin). These reductions were significantly different to the mean increase from baseline (1.1 kg) observed with glimepiride (also in combination with metformin; $p = 0.0138$ for liraglutide 0.6 mg; $p = 0.0001$ for liraglutide 1.2 mg; $p < 0.0001$ for liraglutide 1.8 mg), but not significantly different to the mean decrease from baseline (1.1 kg) observed with placebo (in combination with metformin; $p = 0.9542$ for liraglutide 0.6 mg, $p = 0.8942$ for liraglutide 1.2 mg, $p = 0.2905$ for liraglutide 1.8 mg). In the LEAD-3 substudy, mean reductions from baseline (2.0 and 1.0 kg) with liraglutide 1.2 and 1.8 mg (monotherapy) were significantly different to the mean increase from baseline (2.4 kg) observed with glimepiride ($p = 0.0007$ for liraglutide 1.2 mg; $p = 0.0067$ for liraglutide 1.8 mg) (figure 1).

The relative total body fat (percentage of total body weight) was also reduced in all liraglutide treatment arms. In the LEAD-2 substudy, mean dose-dependent reductions from baseline (0.5, 1.1 and 1.2%) were observed with liraglutide 0.6, 1.2 and 1.8 mg (all in combination with metformin). For liraglutide 1.2 and 1.8 mg these reductions were significantly different to the mean increase from baseline (0.4%) observed with glimepiride (also in combination with metformin; $p = 0.0496$ for liraglutide 1.2 mg; $p = 0.0373$ for liraglutide 1.8 mg), but not significantly different to the mean decrease from baseline (0.2%) observed with placebo (in combination with metformin; $p = 0.9694$ for liraglutide 0.6 mg, $p = 0.4889$ for liraglutide 1.2 mg, $p = 0.3871$ for liraglutide 1.8 mg). A weak but statistically significant direct linear correlation was found between change in per cent fat in

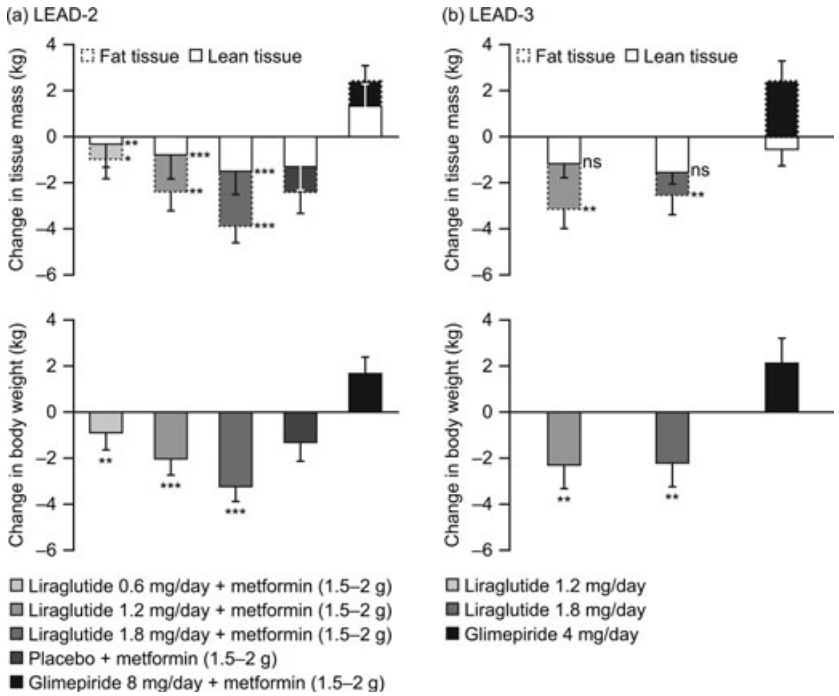

Fig. 1 Change in body weight composition and total body weight (mean ± SE) from dual-energy X-ray absorptiometry (DXA) substudies in (a) Liraglutide Effect and Action in Diabetes (LEAD)-2 at week 26 and (b) LEAD-3 at week 52. p-values are for changes from baseline for: liraglutide vs. glimepiride (both in combination with metformin) in the LEAD-2 population and liraglutide vs. glimepiride in the LEAD-3 population. ***$p < 0.0001$, **$p < 0.01$, *$p < 0.05$, ns = not significant.

total body and change in HbA1c ($r = 0.23$; $p = 0.0085$). In the LEAD-3 substudy, mean reductions from baseline of 0.9 and 0.3% observed with liraglutide 1.2 and 1.8 mg (monotherapy) respectively, were significantly different to the mean increase from baseline (2.6%) observed with glimepiride ($p = 0.0001$ for liraglutide 1.2 mg; $p = 0.0009$ for liraglutide 1.8 mg). A weak but statistically significant direct linear correlation was also found between change in per cent fat in total body and change in HbA1c ($r = 0.33$; $p = 0.0267$) in this substudy.

Absolute total lean body tissue mass was also reduced in all liraglutide treatment arms in a dose-dependent manner. In the LEAD-2 substudy, mean reductions from baseline (0.3, 0.8 and 1.5 kg) with liraglutide 0.6, 1.2 and 1.8 mg (all in combination with metformin) were significantly different to the mean increase from baseline (1.3 kg) with glimepiride (also in combination with metformin; $p = 0.0023$ for liraglutide 0.6 mg; $p < 0.0001$ for liraglutide 1.2 and 1.8 mg). However, these reductions were not significantly different to the mean decrease from baseline (1.3 kg) observed with placebo (in combination with metformin; $p = 0.1535$ for liraglutide 0.6 mg, $p = 0.7487$ for liraglutide 1.2 mg, $p = 0.9833$ for liraglutide 1.8 mg). In the LEAD-3 substudy, mean reductions from baseline (1.1 and 1.5 kg) with liraglutide 1.2 and 1.8 mg (monotherapy) were greater than the mean reduction from baseline (0.6 kg) with glimepiride, although differences between treatment groups were not significant (figure 1). Changes in limb lean tissue mass, a surrogate for skeletal muscle mass [27], were also assessed in the LEAD-3 DXA substudy, with no significant differences found between treatment arms.

CT Assessments (LEAD-2 Substudy Only)

Visceral and Abdominal Subcutaneous Adipose Tissue Area

The mean reductions in tissue area from baseline to 26 weeks in the metformin combination (LEAD-2) study were greater for visceral adipose tissue than abdominal subcutaneous adipose tissue. Visceral adipose tissue area was reduced from baseline in all treatment arms: reductions of 20.4 cm^2 (13%), 30.6 cm^2 (17%) and 30.4 cm^2 (16%) were achieved in the liraglutide 0.6 mg, liraglutide 1.2 mg and liraglutide 1.8 mg groups respectively; a 5.3 cm^2 (5%) reduction was observed in the glimepiride group, and an 11.3 cm^2 (8%) reduction in the placebo group (all in combination with metformin).

Differences between treatment groups for the changes from baseline were significant for the liraglutide 1.2 and 1.8 mg groups compared with glimepiride ($p = 0.0193$ and $p = 0.0206$ respectively). Subcutaneous adipose tissue area was reduced in the liraglutide 0.6, 1.2 and 1.8 mg groups by 16.5 cm^2 (5%), 23.6 cm^2 (8%) and 26.3 cm^2 (9%) respectively, and in the placebo group by 18.8 cm^2 (4%). Subcutaneous adipose tissue area increased by 6.7 cm^2 (3%) in the glimepiride group. Differences between treatment groups for the changes from baseline were significant for all liraglutide groups compared with glimepiride ($p = 0.0057$ for liraglutide 0.6 mg, $p = 0.0003$ for liraglutide 1.2 mg and $p < 0.0001$ for liraglutide 1.8 mg) (figure 2). Therefore, when comparing relative reductions in visceral and subcutaneous adipose tissue area with liraglutide by CT scan, there was a slightly larger reduction in visceral adipose tissue compared with subcutaneous adipose tissue. Weak but statistically significant direct linear correlations were found between change in percentage fat in trunk and change in HbA1c ($r = 0.22$; $p = 0.0088$) and change in visceral adipose tissue area and change in HbA1c ($r = 0.25$; $p = 0.0047$). However, there was no significant correlation between change in abdominal subcutaneous adipose tissue area and change in HbA1c ($r = 0.02$; $p = 0.8226$).

Changes from baseline in the ratio of visceral adipose tissue to abdominal subcutaneous adipose tissue were similar among all treatment groups. Decreases of 0.03, 0.04 and 0.05 in the ratios were observed with liraglutide 0.6 mg, 1.2 mg and 1.8 mg respectively, compared with a decrease of 0.04 in the glimepiride group and no change in the placebo group. Differences between treatment groups were not significant.

Liver-to-Spleen Attenuation Ratio and Effects on Liver Transaminases

The liver-to-spleen attenuation ratio was assessed by CT in the metformin combination (LEAD-2) study. The ratio increased from baseline (0.10) with liraglutide 1.8 mg, possibly indicating reduced hepatic steatosis. This increased ratio was significantly different to the

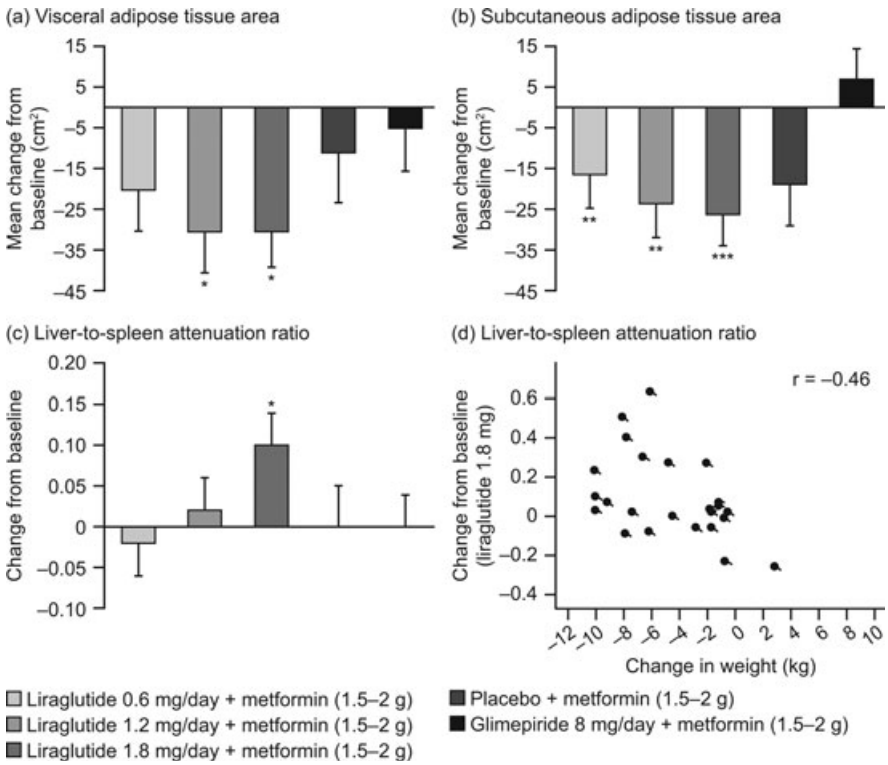

Fig. 2 Data from the computerized tomography (CT) substudy in the Liraglutide Effect and Action in Diabetes-2 trial; (a) and (b) changes from baseline in visceral adipose tissue area and subcutaneous adipose tissue area respectively (mean ± SE); (c) change from baseline in liver-to-spleen attenuation ratio at week 26 (mean ± SE); (d) correlation between change in the liver-to-spleen attenuation ratio and weight loss. p-values are for changes from baseline for liraglutide vs. glimepiride (all in combination with metformin). ***$p < 0.0001$, **$p < 0.01$, *$p < 0.05$.

unchanged ratio in the glimepiride group ($p = 0.0451$). The ratio did not change in either the liraglutide 1.2 mg, the glimepiride or the placebo groups and decreased slightly (0.02) with liraglutide 0.6 mg. Differences between these treatment groups were not significant (figure 2). A tendency towards a correlation between change in liver-to-spleen attenuation ratio and change in body weight from baseline was observed in the liraglutide 0.6 mg ($r = -0.56$) and liraglutide 1.8 mg ($r = -0.46$) treatment arms (figure 2).

In the full study populations of the LEAD-2 and LEAD-3 trials differences between treatment groups for the changes in AST levels from baseline were not significant. In the LEAD-2 study, ALT levels were reduced in the liraglutide 0.6, 1.2 and 1.8 mg groups by 1.0, 2.3 and 3.5 U/L respectively, and in the metformin and glimepiride combination group by 0.1 U/L. ALT levels increased by 1.9 U/L in the metformin group. Differences between treatment groups for the changes from baseline were significant for liraglutide 1.8 mg compared with metformin ($p = 0.0008$) and with glimepiride and metformin combination ($p = 0.0167$) and for liraglutide 1.2 mg compared with metformin ($p = 0.0133$). In the LEAD-3 study ALT levels were reduced from baseline in all treatment arms by 2.9 and 3.6 U/L with liraglutide 1.2 mg and liraglutide 1.8 mg respectively, and by 0.5 U/L with glimepiride. Differences between treatment groups for the changes from baseline were significant for liraglutide 1.8 mg compared with glimepiride ($p = 0.0318$).

Discussion

The LEAD-2 and LEAD-3 studies have shown that liraglutide (as monotherapy or in combination with metformin) produced sustained improvements in glycaemic control with concomitant and sustained weight loss and with very low risk of hypoglycaemia [20,21]. The DXA and CT assessments reported here show that reductions in body weight with liraglutide primarily come from reductions in fat mass rather than lean tissue mass. In addition, these substudies show that, although both visceral and abdominal subcutaneous adipose tissue areas are reduced, decreases in visceral adipose tissue area seem greater, and that treatment with liraglutide 1.8 mg increases the liver-to-spleen attenuation ratio, possibly indicating reduced hepatic steatosis.

Treatment with once-daily liraglutide 1.8 mg resulted in greater reductions in fat tissue mass (1.0–2.4 kg) than in lean tissue mass (1.5 kg), confirming the results of a shorter study in which fat mass decreased (1.0 kg) and lean tissue mass increased (0.7 kg) after 8 weeks of treatment with liraglutide 0.6 mg once-daily [28]. In addition, the CT assessment from within the LEAD-2 study showed that both abdominal subcutaneous and visceral adipose tissue areas were reduced. However, reductions in visceral adipose tissue area were larger. These are all desirable traits because elevated fat mass levels are associated with decreased insulin sensitivity and increased morbidity and mortality [29]. Furthermore, although abdominal subcutaneous fat has been independently associated with increased glucose and lipid levels, this association is stronger for visceral fat and has been causally associated with insulin resistance [30].

The fact that liraglutide treatment reduced visceral and abdominal subcutaneous fat in patients with T2D is an important advantage of this treatment because other antihyperglycaemic agents do not generally have such effects on body composition. Total body weight and total body fat have been shown to increase with the thiazolidinediones rosiglitazone and pioglitazone [31–33]. For example, increases in body weight and total body fat of 3.9 and 3.5 kg respectively, were observed over 24 weeks with pioglitazone treatment [32]. However, the amount of visceral fat did not change [31,32] or tended to decrease [33]. In patients with increased risk factors for T2D, metformin treatment significantly reduced fat mass and increased lean mass, although body weight and BMI remained unchanged [34]. In animal models, the exendin-based GLP-1 therapies exendin (1–30) and exendin-4 (exenatide) significantly reduce fat tissue [35,36], whereas the DPP-4 inhibitor, vildagliptin, has been shown not to have a significant effect on body composition [37,38]. The effect of the DPP-4 inhibitor, sitagliptin, on body composition has not been reported.

Excess adiposity results in increased levels of free fatty acids, leading to fat storage in non-adipose tissues, such as muscle, liver and pancreas [3]. Excess fat in the liver causes non-alcoholic fatty liver disease (NAFLD), an asymptomatic liver condition seen in 50–55% of patients with T2D that can progress to cirrhosis and hepatocellular carcinoma. Data from five different studies following NAFLD patients for an average of 3.5–11 years suggest that progressive liver damage is observed in approximately 28% of patients [39]. Reductions in adiposity are likely to have a positive effect on NAFLD, possibly explaining why hepatic steatosis was reduced in the group treated with liraglutide (1.8 mg) and metformin combination therapy but unchanged in the group treated with glimepiride monotherapy.

Reductions in fat tissue observed in this study may result in improvements in cardiometabolic parameters,

such as blood pressure and lipids. Thus, compared with glimepiride, systolic blood pressure was significantly reduced by 2.7 mmHg ($p = 0.0467$) and 3.6 mmHg ($p < 0.0118$) with liraglutide 1.8 mg in the LEAD-2 and LEAD-3 trials respectively. There was no significant difference in diastolic blood pressure [20,21]. Levels of total cholesterol, low density lipoprotein cholesterol, free fatty acids and triglycerides also decreased significantly from baseline after 26 weeks of treatment with liraglutide 1.8 mg as demonstrated in a metaanalysis of the LEAD 1–6 trials [40]. In addition, the observed reductions in hepatic steatosis may lead to improvements in biomarkers of liver function such as ALT and AST. In this study we have shown that ALT levels decreased with liraglutide treatment in the full study populations of the LEAD-2 and LEAD-3 trials. Exenatide also reduces hepatic steatosis in an obese mouse model [41]. While clinical trials with exenatide treatment have not directly investigated its effect on hepatic steatosis, results from an open-ended, open-label uncontrolled clinical trial showed that levels of ALT and AST significantly decreased in patients with elevated baseline ALT after 3 years of treatment with exenatide [42].

Body weight, absolute and relative total body fat, and absolute lean body tissue mass were also reduced in the placebo and metformin arm within the LEAD-2 substudy. This finding can be explained by the fact that a proportion of patients in the placebo group discontinued sulphonylurea treatment at randomization, which may be the reason why changes from baseline in these parameters were not significantly different between the placebo arm and liraglutide arm (both in combination with metformin).

The percentage of withdrawals observed within the DXA and CT substudies (15% for the substudy within LEAD-2 and 25% for the substudy within LEAD-3) were similar to those observed in the main studies [20,21].

These studies are limited by the small size of their populations. However, studies investigating the effect of thiazolidinediones, metformin or DPP-4 inhibitors on body composition were comparable in size [31–34,37,38]. Another limitation is that results from these studies cannot be extrapolated to the very young and the very old, as these subpopulations were excluded. Further studies in these groups are needed. Nevertheless, the results of this study, showing for the first time the beneficial effects of liraglutide treatment on body composition in patients with T2D, are very promising.

In summary, reductions in body weight in patients with T2D treated with liraglutide are primarily as a result of reductions in fat mass rather than lean tissue mass. Moreover, visceral fat, which is strongly associated with increased glucose and lipid levels, appears to be reduced to a greater extent than subcutaneous abdominal fat. These reductions in adiposity, in particular, visceral adiposity, may have a positive impact on long-term CV risk, as well as a role in reducing hepatic steatosis.

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Supporting Information

The following supporting information is available for this article:

Appendix S1.

Additional Supporting Information may be found in the online version of this article.

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Conflicts of Interest

J. J. has nothing to declare.

M. A. N. has served on advisory boards for Novo Nordisk, Copenhagen, Denmark; has received honoraria/consulting fees from Novo Nordisk, Copenhagen, Denmark.

D. R. M. has received lecture and advisory fees from Novo Nordisk. Oxford Centre for Diabetes, Endocrinology and Metabolism has a Partnership for the Foundation of OCDEM, with Novo Nordisk.

A. F. has nothing to declare.

K. H. has served on advisory boards for Novo Nordisk.

M. D. and M. Z. D. are employed by Novo Nordisk A/S, Copenhagen, Denmark.

B. J. S. has nothing to declare.

A. J. G. has served on advisory boards for Novo Nordisk; has attended Speakers' Bureaux for Novo Nordisk.

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