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CLINICAL TRIAL

Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: A randomized trial

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ABSTRACT

Aims/Introduction: To compare the effects of gliclazide, liraglutide and metformin on body composition in patients with type 2 diabetes mellitus with non-alcoholic fatty liver disease.

Materials and Methods: A total of 85 patients were randomly allocated to receive gliclazide (n = 27), liraglutide (n = 29) or metformin (n = 29) monotherapy for 24 weeks. Body composition was measured using dual-energy X-ray absorptiometry.

Results: Liraglutide and metformin reduced total, trunk, limb, android and gynoid fat mass; this also led to weight reduction. However, gliclazide treatment produced no significant changes in weight or fat mass, likely because reductions in fat mass were concomitant with increases in lean tissue mass. Blood glucose concentrations and glycated hemoglobin levels improved in all treatment arms; levels of the latter were lower in patients treated with liraglutide and metformin. Serum alanine aminotransferase concentrations decreased in all treatment arms, whereas serum aspartate aminotransferase concentrations were reduced only by liraglutide and metformin. In all patients, weight loss and total, trunk, limb, and android fat mass reductions were positively correlated with decreases in serum alanine aminotransferase and aspartate aminotransferase levels, whereas reductions in waist circumference were positively correlated with lower serum alanine aminotransferase levels.

Conclusions: Compared with gliclazide, liraglutide and metformin monotherapies result in greater weight loss, reductions in body fat mass, and better blood glucose control among type 2 diabetes mellitus patients with non-alcoholic fatty liver disease. Reductions in weight, fat mass and waist circumference favorably affect hepatic function.

INTRODUCTION

Type 2 diabetes mellitus is closely associated with non-alcoholic fatty liver disease (NAFLD), as both are outcomes of long-term obesity[1–3]. Weight loss of 5–10% has been shown to effectively prevent type 2 diabetes mellitus and NAFLD progression in patients at risk[4,5]. Established antidiabetic agents are used to improve glycemic control, thereby decreasing the risk of diabetic complications. However, weight gain caused by some antihyperglycemic therapies – especially increased body fat and central obesity – results in long-term deterioration in glycemic control, with worsening hypertension, NAFLD and hyperlipidemia; this could ultimately lead to cardiovascular diseases[6–9]. Metformin[6,7] (a biguanide) and liraglutide[6,10–15] (a glucagon-like peptide-1 analog) decrease blood glucose concentrations and produce weight loss in patients with type 2 diabetes mellitus; the latter is used when the response to the former is poor. Such weight loss is mainly due to reductions in fat (specifically abdominal visceral fat) rather than in lean tissue mass, as

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shown by dual-energy X-ray densitometry (DXA) and computed tomography (CT)[10–14]. Therefore, liraglutide might be the preferred agent for treating type 2 diabetes mellitus in patients with central obesity, as they have high risks of cardiovascular disease[15–19]. Similarly, metformin was also found to reduce total, visceral and subcutaneous fat mass, as assessed by CT, in overweight/obese women with polycystic ovary syndrome. Furthermore, visceral fat mass decreased more than subcutaneous fat mass with continuous treatment[20,21]. DXA assessment also showed that metformin reduces fat mass in obese insulin-resistant children and in individuals with youth-onset type 2 diabetes mellitus[22,23].

Sulphonylureas used to treat type 2 diabetes mellitus often cause weight gain owing to overeating caused by inappropriate insulin secretion, even under conditions of hypoglycemia[6,7]. In patients with type 2 diabetes mellitus receiving metformin monotherapy, DXA and CT assessments showed that adding the sulphonylurea glimepiride led to weight gain by increasing both lean body mass and fat mass (visceral fat decreased, while subcutaneous fat increased), whereas glimepiride monotherapy led to weight gain because the increased fat mass outweighed the reduction in lean mass[12]. Although many recent antidiabetic agents are associated with lower weight gain, sulphonylureas remain important antidiabetic agents[6,7].

Previous studies have compared the effects of glucagon-like peptide-1 analogs and glimepiride on fat and lean tissue mass, as well as on the visceral and subcutaneous fat of patients with type 2 diabetes mellitus[12,24,25]. Compared with glimepiride, gliclazide is associated with fewer hypoglycemic events, and with less overeating and weight gain[26]. To date, it is unclear whether glucagon-like peptide-1 analogs, metformin and gliclazide have different effects on fat mass in patients with type 2 diabetes mellitus and concomitant NAFLD. Our primary aim was to assess the effects of gliclazide monotherapy on body composition and fat mass compared with the effects of liraglutide and metformin monotherapies.

METHODS

Patients

Eligibility criteria for the present study were patients with type 2 diabetes mellitus aged 18–70 years, no hypoglycemic drug use during the preceding 3 months, glycated hemoglobin (HbA1c) levels of 7.0–14%, body mass index (BMI) of 20–38 kg/m^2, diagnosed with NAFLD (defined as fatty liver on ultrasonography with alcoholic intake <140 and <210 g per week for women and men, respectively, not treated with medications affecting hepatic steatosis and no history of autoimmune liver disease or viral hepatitis) and weight fluctuations of <10% within the past 3 months. Exclusion criteria were a history of allergy to any of the investigational drugs, pancreatic or severe gastrointestinal disease(s), abnormal liver function (serum aspartate aminotransferase [AST] ≥2.5-fold the upper limit of normal), moderate-to-severe renal function impairment (estimated glomerular filtration rate <60 mL/min/1.73 m^2, calculated using the modification of diet in renal disease equation), congestive heart failure (New York Heart Association grade III or IV), proliferative retinopathy confirmed by an ophthalmologist, other severe concomitant disease(s), medullary thyroid carcinoma, multiple endocrine neoplasia, pregnancy, or planning pregnancy.

All patients provided written informed consent before their enrollment. The study protocol was approved by the hospital's Research Ethics Board (Protocol: AF/SQ-2014-026-02), and conforms to the provisions of the Declaration of Helsinki.

Study design

This was a single-center, open-label, prospective, randomized trial (protocol: clinicaltrials.gov: NCT03068065). Patients with type 2 diabetes mellitus were recruited from Drum Tower Hospital, which is affiliated with the Nanjing University Medical School, Nanjing, China. Data from the same trial were used in a previous study[27] to investigate the effects of liraglutide, metformin and gliclazide on intrahepatic fat content.

Using computer-generated random numbering, the participants were randomly divided into three groups in 1:1:1 ratios to receive 24 weeks of treatment with metformin (Glucophage; Bristol-Myers Squibb, Shanghai, China), liraglutide (Victoza; Novo Nordisk, Beijing, China) or gliclazide (Diamicron; Servier, Tianjin, China). Participants were provided diet and exercise guidance aiming for at least 150 min per week of moderate intensity aerobic activity, and were required to record a 3-day diet and exercise diary before each follow-up visit; information from the diaries was used to provide appropriate advice. The subcutaneous dose of liraglutide was 0.6 mg q.d. during the first week, 1.2 mg q.d. during the second week and 1.8 mg q.d. from the third week to the end of the study. The oral dose of metformin was 250 mg t.i.d. during the first week, 500 mg t.i.d. during the second week and 1,000 mg b.i.d. from the third week to the end of the study. The initial oral dose of gliclazide was 30 mg before breakfast; this was gradually increased a maximum of 120 mg/day in order to reach the target for a fasting capillary plasma glucose concentration of <7.0 mmol/L.

Study outcomes

The primary end-points of the present study were the change in weight, BMI and body composition during a 24-week follow-up period. Secondary end-points included changes in the following factors at 24 weeks: blood glucose, HbA1c, waist circumference, liver function and lipid profile.

Standard meal tolerance test, glucose, insulin, blood biochemistry and HbA1c

All participants underwent a standard (85-g carbohydrate-equivalent) meal tolerance test at baseline and after 24 weeks of treatment. Serum glucose concentrations were measured 0, 30, 60 and 120 min after ingesting a standard meal. Participants returned to the Clinical Research Center at the end of weeks 2 and 4, and then every 4 weeks thereafter for a total of seven

follow-up visits to measure fasting and postprandial blood glucose concentrations. HbA1c was measured at baseline, and at the end of 12 and 24 weeks. Fasting serum lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides), and serum alanine aminotransferase (ALT), AST, uric acid and creatinine concentrations were measured at baseline, and at the end of weeks 4, 12 and 24.

Body composition and distribution of body fat and lean mass

Bodyweight, BMI, waist circumference and blood pressure were measured at every visit. The total, trunk, limb, android and gynoid fat mass, as well as the lean tissue mass, were evaluated using DXA (Lunar iDXA, Encore 13.4; GE Healthcare, Madison, Wisconsin, USA) at baseline and at the end of week 24. The total fat mass percentage (total lean tissue mass percentage) was calculated by dividing the weight of the total fat mass (total lean tissue mass) by bodyweight. Analogous calculations were carried out to determine the percentages of the fat and lean masses for the same body sites.

Safety and evaluation of adverse events

All adverse events observed during the study were recorded, and serious adverse events were reported immediately to the institutional review board of the Drug Clinical Trial Agency Office and the Research Ethics Board of Drum Tower Hospital.

Sample size

The study cohort was determined based on bodyweight as the primary end-point. With an α of 0.05, 29 participants per arm provided >90% power to detect a 2-kg difference between arms. Secondary outcome measures included body fat and lean tissue mass, fasting serum concentrations of triglycerides, HbA1c, ALT, AST, and serum glucose concentrations, which were each measured 0, 30, 60 and 120 min after ingesting the carbohydrate-equivalent meal. To allow for dropouts, we planned to recruit at least 92 participants.

Statistical analysis

All statistical analyses were carried out using SPSS software version 17.0 (SPSS Inc., Chicago, Illinois, USA). The primary analysis included participants who completed the intervention. Normally distributed quantitative variables are presented as the mean ± standard error. One-way analysis of variance with the least significant difference was used to test the arm baseline means. Analysis of covariance (ANCOVA) was used to compare differences among the intervention arms after adjusting for the baseline values. Categorical data were analyzed using the χ^2-test. Differences between pre- and post-intervention values within each arm were evaluated using paired Student's *t*-tests. Correlation analyses of the variables' associations with changes in ALT and AST were assessed. A *P*-value <0.05 was considered significant.

RESULTS

Baseline values

A total of 93 participants (mean age 47.2 ± 1.2 years, BMI 27.6 ± 0.3 kg/m^2 and HbA1c 9.16 ± 0.17%) were successfully screened for participation in the present study; 30 were randomly allocated to the liraglutide arm, 31 to the metformin arm and 32 to the gliclazide arm. A total of 29 participants in the liraglutide arm, 29 in the metformin arm and 27 in the gliclazide arm completed the 24-week drug intervention (Figure 1). At baseline, the three arms were similar in terms of age; sex; duration of diabetes; body composition variables; serum lipid profiles, HbA1c, ALT and AST levels; and glucose concentrations during the standard meal tolerance test (Tables 1–2).

Weight loss, body composition, and body fat and lean mass distributions

Bodyweight decreased significantly only in the liraglutide (from 81.1 ± 2.3 kg to 75.5 ± 2.0 kg, $P < 0.01$) and metformin (from 74.8 ± 2.5 kg to 71.2 ± 2.6 kg, $P < 0.01$) arms (Table 1). Weight reduction was more marked in the liraglutide and metformin arms than in the gliclazide arm (both $P < 0.01$; Table 1).

Likewise, BMI and waist circumference decreased significantly in the liraglutide and metformin arms (all $P < 0.01$ vs baseline), but not in the gliclazide arm (Table 1). A greater decrease in BMI was observed in the liraglutide and metformin arms than in the gliclazide arms (both $P < 0.01$ vs gliclazide; Table 1).

We evaluated changes in body composition values from baseline to 24 completed weeks of the intervention within each treatment arm (Table 1). In the liraglutide arm, there was a significant decrease in total ($\Delta = -3.6 \pm 0.6$ kg), trunk ($\Delta = -2.6 \pm 0.4$ kg), limb ($\Delta = -0.9 \pm 0.2$ kg), android ($\Delta = -0.6 \pm 0.1$ kg) and gynoid ($\Delta = -0.4 \pm 0.1$ kg) fat mass (all $P < 0.01$ vs respective baseline values). In the metformin arm, total ($\Delta = -2.8 \pm 0.8$ kg), trunk ($\Delta = -2.1 \pm 0.6$ kg), limb ($\Delta = -0.7 \pm 0.3$ kg), android ($\Delta = -0.4 \pm 0.1$ kg) and gynoid ($\Delta = -0.3 \pm 0.1$ kg) fat mass decreased significantly ($P < 0.01$–0.05 vs respective baseline values). No significant changes in fat mass occurred in the gliclazide arm. The decreases in total, trunk, limb and android fat mass were greater in the liraglutide than in the gliclazide arm (all $P < 0.01$; Table 1). Furthermore, the decreases in total, trunk and android fat mass were significantly greater in the metformin arm than in the gliclazide arm ($P < 0.01$–0.05; Table 1).

Liraglutide significantly decreased the android ($\Delta = -0.11 \pm 0.04$ kg, $P < 0.05$) and gynoid ($\Delta = -0.19 \pm 0.07$ kg, $P < 0.05$) lean tissue masses. Gynoid lean tissue was significantly reduced in the metformin arms ($\Delta = -0.12 \pm 0.05$ kg, $P < 0.05$), but was significantly increased in the gliclazide arms ($\Delta = -0.11 \pm 0.05$ kg, $P < 0.05$).

Generally, the liraglutide arm was characterized by a greater loss of total, trunk, limb and android fat than of lean tissue

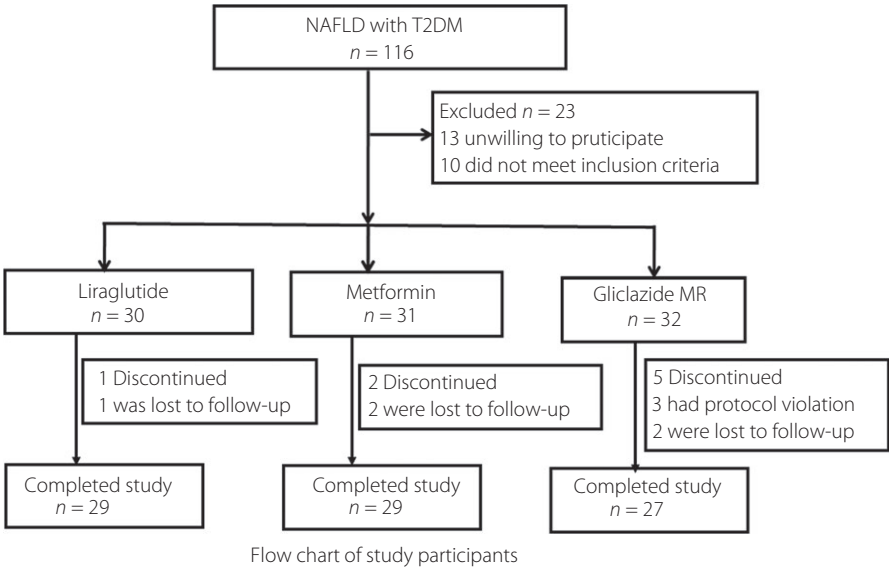

Figure 1 | Flowchart of study participants. Of the 93 randomized participants who met the inclusion criteria, eight participants did not complete the study, as they either discontinued follow-up visits (n = 5) or had protocol violations (n = 3). MR, modified release; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

Table 1 | Bodyweight and body composition at baseline and post-intervention

	Liraglutide		Metformin		Gliclazide		*P*-value for intergroup comparisons	
	Baseline	24 months	Baseline	24 months	Baseline	24 months	Baseline	24 months
n	29	–	29	–	27	–	–	–
Sex (male/female)	21/8	–	19/10	–	19/8	–	0.847	–
Age (years)	46.8 ± 1.8	–	46.3 ± 2.3	–	48.2 ± 2.5	–	0.789	–
Disease course (months)	2–39	–	1–12	–	1–24	–	0.093	–
Bodyweight	81.1 ± 2.3	75.5 ± 2.0**,††	74.8 ± 2.5	71.2 ± 2.55**,††	78.13 ± 2.43	77.54 ± 2.57	0.175	<0.001
BMI (kg/m^2)	28.1 ± 0.6	26.2 ± 0.5**,††	26.8 ± 0.7	25.5 ± 0.7**,††	27.5 ± 0.5	27.3 ± 0.5	0.292	<0.001
WC (cm)	95.6 ± 1.4	90.8 ± 1.4**	92.6 ± 1.6	89.6 ± 2.2**	95.6 ± 1.5	93.8 ± 1.6	0.274	0.099
Total fat mass (kg)	25.2 ± 6.1	21.6 ± 5.5**††	23.3 ± 5.8	20.6 ± 6.9**†	24.6 ± 5.7	24.0 ± 6.3	0.485	0.006
Trunk fat (kg)	15.9 ± 4.3	13.3 ± 3.7**,††	14.2 ± 3.9	12.1 ± 4.7**,††	15.1 ± 3.8	14.7 ± 4.2	0.282	0.005
Limb fat (kg)	8.2 ± 2.0	7.2 ± 1.8**,††	8.1 ± 2.3	7.5 ± 2.6**	8.4 ± 2.2	8.3 ± 2.2	0.884	0.024
Android fat (kg)	2.8 ± 0.9	2.2 ± 0.7**,††	2.4 ± 0.9	2.0 ± 1.0**,†	2.6 ± 0.8	2.5 ± 0.9	0.277	0.002
Gynoid fat (kg)	3.1 ± 0.9	2.8 ± 0.8**	2.9 ± 0.9	2.7 ± 1.0*	3.1 ± 0.8	3.0 ± 0.8	0.790	0.060
Total lean tissue (kg)	52.0 ± 8.7	51.8 ± 8.9	47.6 ± 9.6	47.7 ± 9.9	50.3 ± 9.4	49.5 ± 12.9	0.203	0.140
Trunk lean tissue (kg)	24.4 ± 3.9	24.4 ± 4.1	22.4 ± 4.2	22.8 ± 4.3	23.7 ± 4.2	24.0 ± 4.1	0.193	0.384
Limb lean tissue (kg)	24.0 ± 4.7	23.8 ± 4.7	21.7 ± 5.2	21.5 ± 5.4	23.0 ± 5.2	23.3 ± 5.2	0.228	0.111
Android lean tissue (kg)	3.7 ± 0.7	3.6 ± 0.7*	3.4 ± 0.8	3.4 ± 0.8	3.6 ± 0.7	3.6 ± 0.7	0.244	0.062
Gynoid lean tissue (kg)	8.2 ± 1.6	8.0 ± 1.6*††	7.4 ± 1.7	7.2 ± 1.7*††	7.9 ± 1.7	8.0 ± 1.8*	0.147	0.002

Data are mean ± standard error. *P < 0.05, **P < 0.01 compared with baseline for each treatment, †P < 0.05, ††P < 0.01 compared with gliclazide post-intervention. BMI, body mass index; WC, waist circumference.

mass (all P < 0.01; Figure 2). In the metformin arm, the reductions in limb (P < 0.05) and android (P < 0.01) fat mass were greater than that of lean tissue mass. There were slight increases in trunk (P < 0.01) and total (P < 0.05) lean tissue masses in the metformin arm, but these increases were smaller than the corresponding reductions in fat mass; hence, the overall weight was reduced in the metformin arm over the study period (Figure 2). In the gliclazide arm, the corresponding fat and lean tissue masses decreased and increased, respectively (Figure 2).

Table 2 | Participant characteristics at baseline and post-intervention

	Liraglutide		Metformin		Gliclazide		*P*-value for inter-group comparisons	
	Baseline	24 months	Baseline	24 months	Baseline	24 months	Baseline	24 months
n	29	–	29	–	27	–	1	–
SBP (mmHg)	120 ± 3	107 ± 2**	127 ± 4	112 ± 3**	122 ± 3	113 ± 3*	0.343	0.260
RBP (mmHg)	78.8 ± 2	75 ± 1*	79 ± 2	76 ± 2	76 ± 2	74 ± 2	0.549	0.846
ALT (U/L)	49.73 ± 5.79	27.42 ± 2.39**	51.01 ± 5.87	28.44 ± 3.24**	42.12 ± 4.98	31.84 ± 3.85*	0.487	0.350
AST (U/L)	31.22 ± 2.56	24.02 ± 1.09**	34.09 ± 3.13	22.64 ± 1.64**	26.83 ± 2.04	23.09 ± 1.55	0.157	0.509
TG (mmol/L)	2.73 ± 0.25	1.83 ± 0.18**	2.45 ± 0.25	2.30 ± 0.32	2.86 ± 0.33	1.92 ± 0.24	0.576	0.161
CH (mmol/L)	4.86 ± 0.18	4.35 ± 0.15*	5.18 ± 0.17	4.58 ± 0.19**	5.37 ± 0.22	4.57 ± 0.19	0.157	0.888
HDL-C (mmol/L)	0.99 ± 0.04	1.02 ± 0.04	1.16 ± 0.06	1.18 ± 0.06	1.11 ± 0.05	1.12 ± 0.06	0.049	0.650
LDL-C (mmol/L)	2.50 ± 0.14	2.27 ± 0.10	2.81 ± 0.14	2.25 ± 0.13**	2.93 ± 0.18	2.40 ± 0.17**	0.125	0.757
FBG (mmol/L)	8.80 ± 0.44	5.76 ± 0.26**	7.96 ± 0.35	6.04 ± 0.24**	8.97 ± 0.31	6.48 ± 0.25**	0.134	0.095
30-min BG (mmol/L)	11.60 ± 0.60	7.30 ± 0.35**	10.71 ± 0.50	9.06 ± 0.41**,††	11.61 ± 0.50	9.16 ± 0.36**,††	0.398	<0.001
60-min BG (mmol/L)	14.76 ± 0.70	9.12 ± 0.51**	13.83 ± 0.54	10.78 ± 0.39**,††	14.68 ± 0.54	11.64 ± 0.52**,††	0.481	<0.001
120-min BG (mmol/L)	14.70 ± 0.79	7.36 ± 0.36**	14.06 ± 0.72	8.69 ± 0.47**,†	15.54 ± 0.55	10.49 ± 0.59**,††,‡	0.334	<0.001
HbA1c (%)	8.91 ± 0.32	5.90 ± 0.11**	9.36 ± 0.33	6.03 ± 0.09**	9.07 ± 0.23	6.47 ± 0.17*,††,‡	0.563	0.003

Data are mean ± standard error. *$P < 0.05$, **$P < 0.01$ compared with pretreatment for each agent; †$P < 0.05$, ††$P < 0.01$ compared with liraglutide post-intervention; ‡$P < 0.05$ compared with metformin post-intervention. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BG, blood glucose; CH, total cholesterol; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

Glucose concentrations and HbA1c

The standard meal tolerance test was repeated after 24 weeks; the blood glucose concentrations measured at 0, 30, 60 and 120 min were decreased in all three arms ($P < 0.001$ for all arms; Table 2). At 30, 60 and 120 min, blood glucose concentrations were lower in the liraglutide arm than in the gliclazide and metformin arms ($P < 0.01$–0.05). At 120 min, blood glucose concentrations were lower in the metformin arms than in the gliclazide arm ($P < 0.05$; Table 2).

Although the three treatment arms had similar HbA1c values at baseline, these values decreased significantly in all three arms at weeks 12 and 24 (all $P < 0.001$ vs their respective baselines; Figure 3, Table 2). At week 12, the HbA1c value was higher in the gliclazide arm than in the liraglutide arm ($P = 0.002$), and was higher in the gliclazide arm than in the liraglutide and metformin arms at week 24 ($P = 0.001$ and $P = 0.014$, respectively; Figure 3, Table 2).

Liver function

Serum ALT concentrations decreased significantly in all three treatment arms ($P < 0.01$–0.05), whereas serum AST concentrations decreased significantly only in the liraglutide and metformin arms ($P < 0.01$ for both; Table 2).

Correlation analysis

For all participants, weight loss was positively correlated with ΔALT and ΔAST ($0 < r < 1$, $P < 0.01$), whereas reductions in waist circumferences were positively correlated with ΔALT ($0 < r < 1$, $P < 0.05$; Table S1). Reductions in total, trunk, limb and android fat mass were strongly correlated with ΔALT and ΔAST ($0 < r < 1$, $P < 0.01$–0.05; Table S1).

Adverse events

The major adverse events in the liraglutide and metformin arms were gastrointestinal-related. In the liraglutide arm, 22 patients had appetite suppression, three had nausea, four had diarrhea, three had abdominal distension and one had a temporary rash at the injection site. In the metformin arm, six patients had appetite suppression, four had nausea, ten had diarrhea, five had abdominal distension and two had a mild hypoglycemic reaction. Two patients in the gliclazide arm had a mild hypoglycemic reaction as a result of dosage escalation. None of the patients dropped out of the study because of adverse events.

DISCUSSION

The present study compared the distribution of body mass after 24 weeks of monotherapy with liraglutide, metformin or gliclazide in type 2 diabetes mellitus patients with NAFLD (i.e., in patients with high cardiovascular risk). Importantly, the results showed that bodyweight, and total body, trunk, limb, android and gynoid fat mass decreased significantly after liraglutide and metformin monotherapies, whereas no changes in weight or fat mass were found with gliclazide monotherapy. The weight losses observed in the liraglutide and metformin arms were mainly related to reductions in fat mass rather than in lean mass. The weight stability observed in the gliclazide arm resulted from decreases in fat mass concomitant with increases

in lean tissue mass. Liraglutide was superior to gliclazide in reducing total body, trunk, limb and android fat mass; furthermore, metformin was superior to gliclazide in reducing total body, trunk and android fat mass. Lower HbA1c levels were achieved with liraglutide and metformin monotherapies than with gliclazide monotherapy. Moreover, reductions in weight, fat mass and waist circumference appeared to have a favorable effect on hepatic function.

The present study used accurate body fat measurements based on DXA to evaluate body composition. Previous studies showed that liraglutide achieved continuous improvements in glycemic control accompanied by sustained weight loss[11,12,22,28,29]. For patients with type 2 diabetes mellitus who are poorly controlled with metformin, adding liraglutide over 24 weeks decreased BMI; total, android and trunk fat mass; and waist circumference[29]. In another study, bodyweight, total

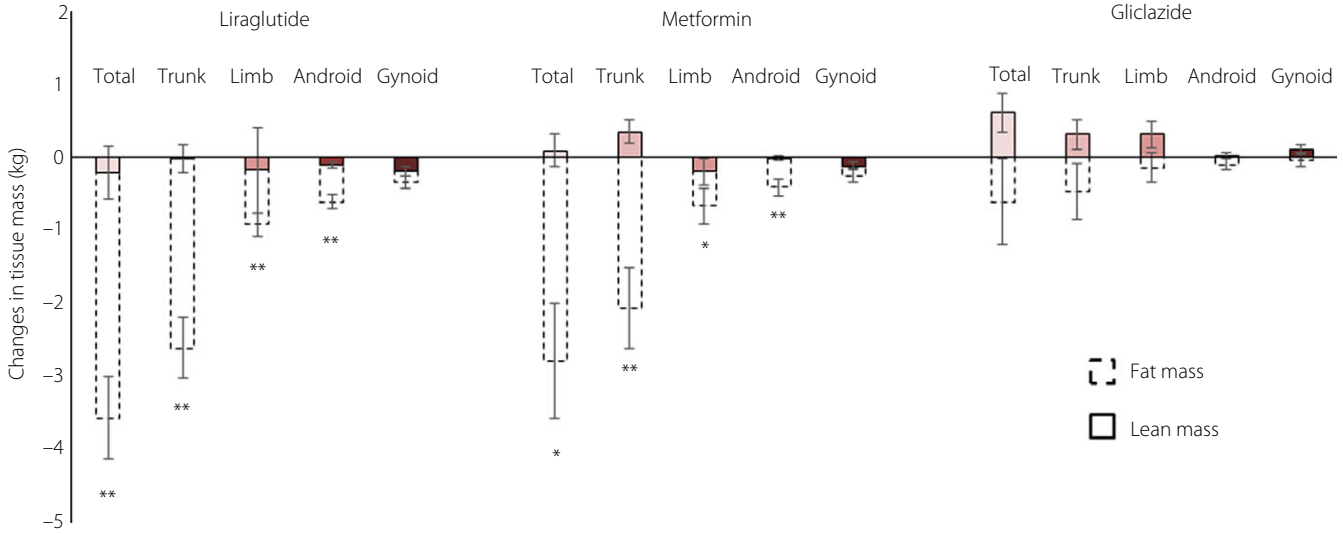

Figure 2 | Changes in fat mass vs changes in lean tissue in the same region with the use of liraglutide, metformin and gliclazide (**P* < 0.05, ***P* < 0.01). Data are shown as the mean ± standard error of the mean.

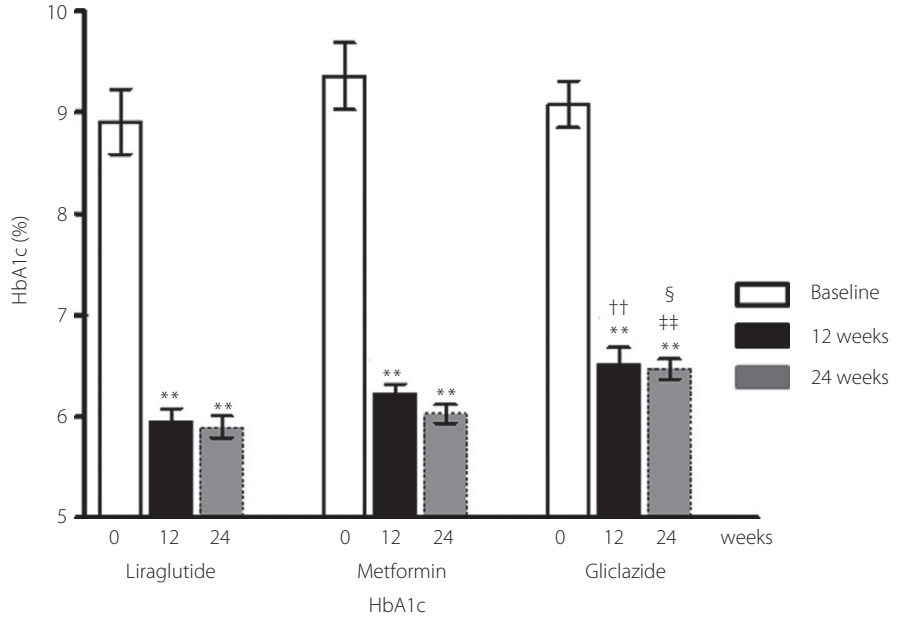

Figure 3 | Glycated hemoglobin (HbA1c) at baseline, and after 12 and 24 weeks of treatment. ***P* < 0.01, HbA1c compared with respective baseline values for liraglutide, metformin and gliclazide. $^{††}P$ < 0.01, HbA1c in the gliclazide arm compared with the liraglutide arm after 12 weeks of treatment. $^{‡‡}P$ < 0.01, HbA1c in the gliclazide arm compared with liraglutide after 24 weeks of treatment. $^{§}P$ < 0.05, HbA1c in the gliclazide arm compared with metformin after 24 weeks of treatment. Data are shown as the mean ± standard error of the mean.

fat mass, lean mass, fat percentage, and visceral and subcutaneous fat significantly decreased after 12 weeks of liraglutide treatment, as measured by DXA or CT[11].

Weight loss associated with liraglutide has been attributed to decreases in fat mass rather than in lean tissue mass[12]; consistent with this, we observed greater reductions in fat mass than in lean tissue mass in the trunk, android, gynoid and limb regions (in the liraglutide arm), as confirmed by DXA. Trunk fat content, especially in the android region (which is associated with NAFLD), is closely associated with cardiovascular disease risk[15–19]. Hence, liraglutide appears to be effective in patients with both type 2 diabetes mellitus and NAFLD.

Using DXA or CT, the Liraglutide Effect and Action in Diabetes-2 (LEAD-2) trial found that adding 0.6, 1.2 or 1.8 mg of liraglutide to metformin monotherapy decreased total fat mass and lean tissue mass over 26 weeks; these reductions were in stark contrast to the increased total fat and lean tissue masses observed by adding glimepiride. In the liraglutide 1.2 or 1.8 mg arms, the decreases in abdominal visceral fat were greater than the reductions in subcutaneous fat[12]. The LEAD-3 trial confirmed that monotherapy with 1.2 and 1.8 mg liraglutide over 52 weeks reduced total fat mass; again, this was in significant contrast to the increased value observed with glimepiride monotherapy[12]. Unlike these studies, we compared changes in the body composition of patients with type 2 diabetes mellitus who were administered liraglutide and sulphonylurea gliclazide, which is associated with fewer hypoglycemic events and less weight gain than other sulphonylureas, such as glimepiride[26]. Compared with gliclazide, we found that liraglutide produced greater reductions in total body, trunk, limb, android and gynoid fat mass. Notably, the stable weights of the participants in the gliclazide arm resulted from a balance between reduced fat mass and increased lean tissue mass; although gliclazide is a type of sulphonylurea, it did not cause weight gain and might therefore offer some benefit in terms of fat mass reduction.

In a previous study comparing body composition after 6 months of gliclazide, metformin or acarbose treatment, patients in the metformin arm achieved significant decreases in their body fat and body fat mass percentages, but none of these three agents changed abdominal fat distributions[30]. In the present study, we found that metformin reduced bodyweight, and total, trunk and android fat mass to a greater extent than gliclazide. The most important results of the present study were that metformin monotherapy reduced fat mass while increasing the total lean tissue mass, and that fat mass reduction with metformin was primarily achieved in the trunk. As metformin monotherapy leads to weight loss in the trunk and android regions, this agent might be suitable for treating abdominal obesity in type 2 diabetes mellitus patients with NAFLD.

We found that the reductions in bodyweight and fat mass were strongly correlated with ΔALT and ΔAST, suggesting that weight loss and reductions in body fat are associated with better liver function in patients with NAFLD. Elevated AST indicates more severe hepatocyte damage owing to NAFLD[31]. Serum ALT concentrations decreased significantly in all three treatment arms of the present study, whereas serum AST concentrations decreased significantly only in the liraglutide and metformin arms, indicating that the latter two agents are more effective against NAFLD. In a previous study, weight reduction was found to be correlated with decreases in intrahepatic fat, which reaffirms the importance of weight loss in alleviating NAFLD[27]; as such, the greater benefits of liraglutide and metformin in patients with NAFLD might be related to their promotion of weight loss and reduction in fat mass.

Glycemic control is typically improved by weight loss, especially by adipose tissue reduction[28,32]. Blood glucose and HbA1c levels improved in all three arms after 24 weeks of intervention, particularly in the liraglutide and metformin arms. Body weight and android fat mass decreased in the liraglutide and metformin arms, but were unchanged in the gliclazide arm. As weight loss is beneficial for maintaining sustained glycemic control, the greater bodyweight reductions associated with liraglutide and metformin might help to ensure satisfactory long-term glycemic control. Compared with participants in other studies who experienced shorter durations of hypoglycemic drug withdrawal[33–35], the present participants' characteristics, including no hypoglycemic drugs use in the 3 months preceding enrollment, the receipt of (non-stringent) diet and exercise guidance, and maintaining a 3-day diet and exercise diary before each follow-up visit, might have helped to elicit weight loss and a more appreciable decrease in HbA1c in our study.

The limitations of the present study included the small number of patients, as well as the 24-week follow-up period, which might be insufficient to assess the benefits of weight loss and decreased fat mass.

Overall, the present results showed that liraglutide and metformin are superior to gliclazide in terms of reducing bodyweight, BMI and body fat mass, and improving HbA1c levels. Furthermore, liraglutide and metformin reduced fat mass rather than lean tissue mass, which is helpful for improving bodyweight and glycemic control in type 2 diabetes mellitus patients with NAFLD. The stable weight associated with gliclazide resulted from concomitant reductions in fat mass and increases in lean tissue mass. Reductions in weight, fat mass and waist circumference help improve hepatic function.

One important future endeavor would be to identify the effects of newly launched antihyperglycemic drugs, such as sodium-dependent glucose transporter 2 on body composition. To date, it has been observed that 26 weeks of treatment with 100 or 300 mg of canagliflozin, a sodium-dependent glucose transporter 2, results in weight loss by reducing both fat and lean masses[36]. Future research should focus on identifying combinations of antihyperglycemic agents that decrease fat mass, rather than lean tissue mass.

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DISCLOSURE

The authors declare no conflict of interest.

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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 | Correlations between body composition measurements and alanine aminotransferase and aspartate aminotransferase levels.