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Comparison of Beinaglutide Versus Metformin for Weight Loss in Overweight and Obese Non-diabetic Patients

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ABSTRACT

Purpose We compared the efficacy and safety of beinaglutide, a glucagon-like peptide-1 (GLP-1) analogue with metformin in lowering the bodyweight of patients who were overweight/obese and non-diabetic.

Patients and Methods Seventy-eight non-diabetic patients were randomly selected and beinaglutide or metformin was administered for 12 weeks. The primary endpoints were changes in body weight and the proportions of patients who lost ≥ 5 and ≥ 10 % of their baseline body weights.

Results A total of 64 patients completed the study; patients in the beinaglutide group exhibited more bodyweight loss than those in the metformin group [(9.5 ± 0.8 %; 9.1 ± 0.9 kg) and (5.1 ± 0.9 %; 4.5 ± 0.8 kg), respectively, corresponding to a difference of approximately 4.5 kg (95 % confidence interval, 2.2–6.9 kg; $P < 0.01$)]. In the beinaglutide group, 90.6 and 40.6 % of the patients lost ≥ 5 and ≥ 10 % of their body weight, respectively, whereas, in the metformin group, these rates were 46.9 and 12.5 %, respectively ($P < 0.01$ and $P < 0.05$). Weight loss following beinaglutide treatment mainly resulted from the loss of fat mass. Compared to metformin, beinaglutide induced a greater decrease in the body mass index, weight circumference, percent body fat, and body fat mass (total, trunk, limb, android, and gynoid). Additionally, beinaglutide decreased serum insulin levels and ameliorated insulin resistance.

Conclusions Beinaglutide is more efficient than metformin at reducing weight and fat mass in patients who are overweight/obese and non-diabetic. Beinaglutide may be a useful therapeutic option for overweight/obesity control in the Chinese population.

* These authors equally contributed to this work.

Introduction

Obesity is currently a major public health issue worldwide. A weight loss of 5–10 % has been proven to prevent and alleviate obesity-related complications [1–4]. Obesity management depends mainly on lifestyle interventions, medications, and bariatric surgery according to recommendations based on the patient's body mass index (BMI) [5]. Although lifestyle intervention is considered the cornerstone for the treatment of overweight and obese individuals, it is difficult to maintain weight loss using this approach alone [6]. In China, orlistat is the only drug approved for treating obese patients who do not have type 2 diabetes mellitus (T2DM). In Western countries, liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is used for weight loss in non-diabetic obese patients [5, 7]. GLP-1RAs have been shown to reduce body weight in patients with T2DM and/or obese/overweight patients by suppressing appetite and delaying gastric emptying. These effects likely occur through the combined effect of the drug on the hypothalamus and the gastrointestinal tract [8–11].

The GLP-1RAs approved for the treatment of T2D in China, including beinaglutide and exenatide (short-acting GLP-1RAs), liraglutide and lixisenatide (daily-acting GLP-1RAs), and dulaglutide and loxenatide (weekly-acting GLP-1RAs) have different durations of action [12]. Different from other GLP-1RAs, beinaglutide is a recombinant GLP-1 that has 100 % homology to human GLP-1, and so can simulate the physiological mode of action of GLP-1, reduce food intake by suppressing appetite and delaying gastric emptying when injected before each meal [13]. The initial dose of beinaglutide used for the treatment of T2DM is 0.1 mg (50 µL), three times a day and after two weeks of treatment, the dose is increased to 0.2 mg (100 µL), three times a day [14]. According to one retrospective study, there is a mean reduction in body weight of 10.05 kg after three months of treatment with beinaglutide in patients with T2DM [15]. Metformin, a biguanide oral hypoglycaemic agent, which has been shown to exhibit favourable weight loss effects in patients with T2DM [16–18], is widely used in patients who are overweight/obese and insulin-resistant, although it has not been approved for the treatment of obesity in the absence of T2DM [19, 20]. It is unclear whether beinaglutide is beneficial for weight loss in patients who are overweight/obese but not diabetic and if the weight loss is different compared to that induced by metformin. Here, we assessed the effects and safety of beinaglutide in comparison with those of metformin at reducing the body weights of overweight/obese non-diabetic individuals.

Materials and Methods

Study design

This 12-week randomised, open, controlled, and a single-site clinical trial was conducted from May 2018 to December 2019 in the Department of Endocrinology, Drum Tower Hospital Affiliated with Nanjing University Medical School (ClinicalTrials.gov, number NCT03593668). Written informed consent was obtained from each participant prior to enrolment in the study. The trial received ethical approval from the Ethics Committee of Nanjing Drum Tower Hospital and was performed according to the Declaration of Helsinki.

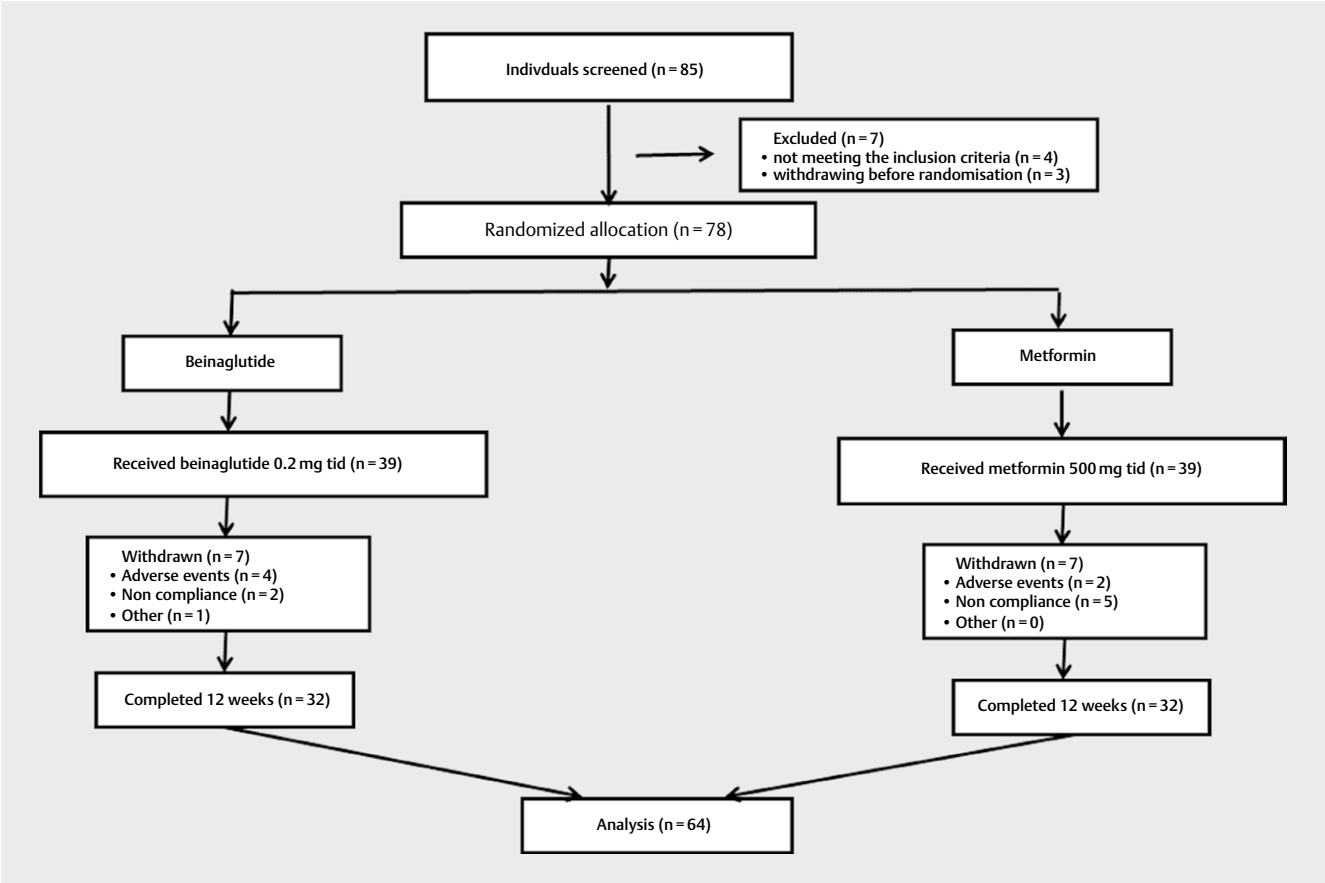
Enrolled participants met the guidelines for the diagnosis and treatment of obesity in China, namely a BMI of 28–37.5 kg/m^2 or at least 24 kg/m^2 accompanied by at least one obesity-related complication, such as dyslipidaemia, impaired glucose tolerance, impaired fasting glucose, non-alcoholic fatty liver (NAFLD), and hyperuricaemia [21]. Other inclusion criteria were age between 18–70 years and had achieved a < 5 % weight change after lifestyle intervention in the previous three months. Exclusion criteria included 1) not having diabetes mellitus, 2) use of weight-lowering medications or participation in other clinical studies three months prior to screening, 3) obesity induced by drug therapy, such as administration of systemic corticosteroids, 4) liver dysfunction [total bilirubin > 34.2 µmol/L or alanine transaminase (ALT) or aspartate transaminase (AST) levels more than three times the upper limit of the normal value], 5) renal dysfunction (serum creatinine ≥ 133 and ≥ 124 µmol/L for male and female patients, respectively), 6) known or suspected alcohol or narcotics abuse within the previous 6 months, 7) history of severe psychiatric disorders, 8) personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, or 9) breastfeeding mothers, pregnant women, or women unwilling to use appropriate contraception methods.

Study treatment

After a one-week screening period, a region random number table generated by Stata software was used to randomly assign the 78 participants (1:1) to receive 0.2 mg beinaglutide (Shanghai Benemae Pharmaceutical Corporation, Shanghai, China) subcutaneously or 0.5 g metformin orally, three times per day for 12 weeks (▶ **Fig. 1**). Beinaglutide was initiated at 0.1 mg before dinner, 0.1 mg before breakfast and dinner two days later, and then 0.1 mg before three meals two days later. The dose was then increased by 0.1 mg every two days until the final dose was reached (0.2 mg before three meals). The starting dose of metformin was 0.25 g before dinner, which was increased to 0.5 g three times daily in the same manner as for beinaglutide. The dose escalation schedules are mentioned in **Supplemental Table 1**.

Patients were evaluated at baseline and every four weeks. Bodyweight, waist circumference, BMI, vital signs, and adverse events were assessed at each visit. Baseline examination was performed in patients before the run-in phase. Body composition was evaluated by dual-energy X-ray (DXA) (Lunar iDXA, Encore 13.4; GE Healthcare, Little Chalfont, UK) and bioelectrical impedance analysis (BIA) (InBody770; InBody Co., Ltd. Cheonan-si, Chungcheongnan-do, Korea). Basal metabolic rate was measured by BIA. Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were assessed by transient elastography technology (FibroTouch, FT70000; Heskell Medical Technology Co., Ltd, Wuxi, Jiangsu, China). Finally, laboratory parameters, including glycated haemoglobin A1c, serum glucose, insulin levels at 0, 30, and 120 min during a 75-g glucose tolerance test, hepatic and renal function, and lipid profiles were monitored at baseline and the end of the study. The calculated values of fasting insulin × fasting blood glucose/22.5 were defined as insulin resistance (HOMA-IR).

Both groups were counselled on lifestyle modification. All participants were advised to consume a limited-energy balanced diet (women, 1000–1200 kcal per day; men, 1500–1800 kcal per day) and to engage in at least 150 min of physical activity per week throughout the trial.



▶ **Fig. 1** A flow chart of the enrolment of the study subjects.

Outcomes

The primary endpoints were a change in body weight from baseline and the proportion of people who lost ≥ 5 or ≥ 10 % of their initial weight. Secondary endpoints included changes in BMI, waist circumference, blood pressure, body composition, glucose and lipid metabolism, HOMA-IR, and serum uric acid as well as improvement of fatty liver and adverse events.

Adverse events during the trial period, with onset on or after the initiation of treatment and within 14 days after the end of the treatment, were reported. Serious adverse events were immediately reported to the Research Ethics Board of the Research Hospital and the Institutional Review Board of the Drug Clinical Trial Agency Office.

Statistical analysis

We predicted that beinaglutide would be superior to metformin in reducing body weight. Based on previous studies [10, 22], GLP-1RAs and metformin decreased body weight by around 3.4 ± 3.0 and 1.9 ± 2.9 kg, respectively. We conservatively estimated that beinaglutide would decrease body weight from baseline by 4 kg. Fifty participants (25 per arm) provided > 80 % power between arms with an alpha of 0.05. Considering a drop-out rate of 20 %, a total of 78 patients were recruited.

SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. For continuous variables, a paired Student's *t*-test or Wilcoxon matched-pairs signed-rank test was used for comparisons within groups. The differences between the treatment groups after adjusting for baseline values were compared by an independent sample *t*-test. The chi-squared test was used to evaluate the differences in categorical variables between groups. The data are expressed as means ± standard deviations (SD). $P < 0.05$ was defined as statistical significance.

Results

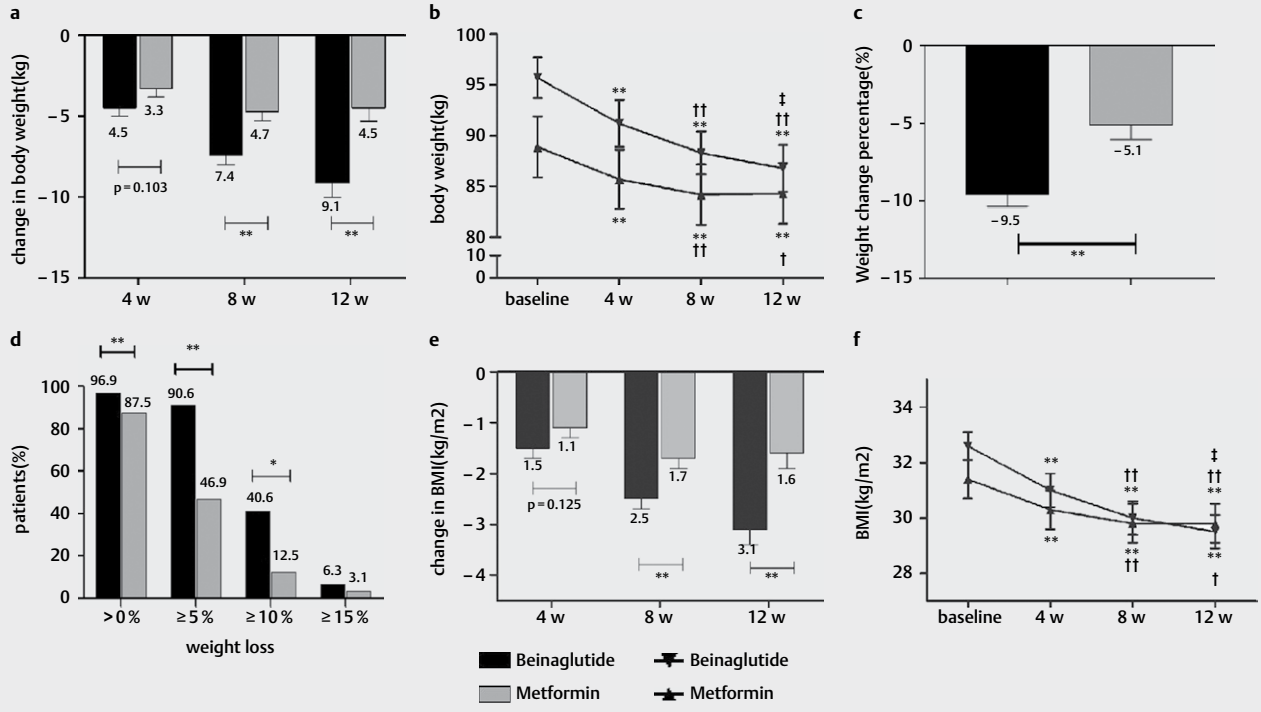
Clinical characteristics of the study participants

A total of 85 participants were screened, and 78 were randomly assigned to the two treatment groups. Seven patients in each group withdrew from the study (▶ **Fig. 1**). The baseline clinical characteristics were similar between the two groups (▶ **Table 1**). In total, 32 patients (16 males/16 females) aged 32.5 ± 1.6 years in the beinaglutide group and 32 patients (14 males/18 females) aged 32.3 ± 1.4 years in the metformin group completed the 12-week treatment. Similar proportions of obesity-related complications occurred in each group, including NAFLD, impaired glucose regulation, hyperuricaemia, and hypertension (▶ **Table 1**).

▶ **Table 1** Participant characteristics at baseline and after 12 weeks of treatment with beinaglutide or metformin.

	Beinaglutide		Metformin		*P* baseline	Estimated treatment difference, beinaglutide vs. metformin (mean, 95%CI)	*P* between the two groups
	Baseline	12 weeks	Baseline	12 weeks			
Number (n)	32	-	32	-			
Age (y)	32.5 ± 1 .6	-	32.3 ± 1.4	-	-	-	-
Sex (male/female)	16/16	-	14/18	-	-	-	-
Weight (kg)	94.0 ± 2.5	84.9 ± 2.2 * *	88.0 ± 2.5	83.4 ± 2.4 * *	0.090	−4.5 (−6.9 to −2.2)	<0.001
BMI (kg/m^2)	32.3 ± 0.4	29.2 ± 0.5 * *	31.2 ± 0.6	29.6 ± 0.6 * *	0.142	−1.5 (−2.2 to −0.7)	<0.001
WC (cm)	105.9 ± 1.5	95.7 ± 1.7 * *	102.0 ± 1.8	96.4 ± 1.8 * *	0.085	−4.7 (−8.0 to −1.5)	0.005
SBP (mmHg)	127.2 ± 2.6	124.0 ± 1.9	124.2 ± 2.5	122.3 ± 1.7	0.383	−1.3 (−7.6 to 4.9)	0.675
DBP (mmHg)	82.1 ± 2.0	77.8 ± 1.4	80.5 ± 1.8	80.1 ± 1.9	0.483	−3.8 (−9.6 to 2.9)	0.196
Number (n)	27	-	27	-	-	-	-
ALT (U/L)	52.8 ± 6.5	33.0 ± 6.3 *	41.8 ± 6.3	27.9 ± 4.6 *	0.253	−5.9 (−25.3 to 13.5)	0.545
AST (U/L)	31.7 ± 2.5	22.6 ± 2.2 *	26.5 ± 2.7	20.5 ± 1.5 *	0.176	−3.1 (−9.9 to 3.8)	0.375
UA (μmol/L)	450.0 ± 17.0	405.6 ± 16.7 * *	413.3 ± 23.8	419.0 ± 25.8	0.277	−50.1 (−87.8 to 12.4)	0.010
TG (mmol/L)	1.5 ± 0.1	1.3 ± 0.1	1.8 ± 0.2	1.7 ± 0.2	0.061	−0.1 (−0.5 to 0.3)	0.614
TC (mmol/L)	4.4 ± 0.1	4.3 ± 0.1	4.3 ± 0.2	4.6 ± 0.2	0.836	−0.3 (−0.7 to 0.1)	0.180
HDL-C (mmol/L)	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.2	1.1 ± 0.1	0.604	0.1 (−0.3 to 0.5)	0.501
LDL-C (mmol/L)	2.8 ± 0.1	2.7 ± 0.1	2.6 ± 0.2	2.8 ± 0.2	0.729	−0.2 (−0.5 to 0.1)	0.193
HbA1c (%)	5.4 ± 0.1	5.5 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	0.439	0.01 (−0.2 to 0.2)	0.922
FBG (mmol/L)	5.2 ± 0.1	5.1 ± 0.1	5.0 ± 0.1	4.9 ± 0.1	0.058	−0.03 (−0.3 to 0.2)	0.831
30 min glucose (mmol/L)	8.1 ± 0.3	7.6 ± 0.2	8.5 ± 0.2	8.1 ± 0.2	0.505	−0.1 (−0.9 to 0.7)	0.803
120 min glucose (mmol/L)	6.9 ± 0.3	6.2 ± 0.2	6.9 ± 0.4	6.9 ± 0.3	0.783	−0.6 (−1.4 to 0.3)	0.212
Fasting insulin (μIU/mL)	26.5 ± 5.2	14.9 ± 1.2 *	20.7 ± 1.8	17.6 ± 1.8	0.522	−8.4 (−18.6 to 1.8)	0.104
30 min insulin (μIU/mL)	125.1 ± 9.9	99.6 ± 10.5 *	140.6 ± 13.9	140.2 ± 18.6	0.221	−25.2 (−63.0 to 12.6)	0.186
120 min insulin (μIU/mL)	111.7 ± 14.0	68.8 ± 7.2 *	125.5 ± 14.4	102.2 ± 12.0	0.471	−19.6 (−61.6 to 22.4)	0.354
HOMA-IR	6.2 ± 1.3	3.4 ± 0.3 *	4.6 ± 0.4	3.8 ± 0.4	0.403	−2.0 (−4.5 to 0.4)	0.107
Hypertension (n/%)	5/32 (15.6)	-	3/32 (9.4)	-	0.708	-	-
Hyperuricaemia (n/%)	20/30 (66.7)	15/30 (50)	10/27 (37)	10/27 (37)	0.025	-	0.140
NAFLD (n/%)	31/32 (96.9)	25/32 (78.1)	27/29 (93.1)	24/29 (82.8)	0.600	-	0.481
IFG (n/%)	2/27(7.4)	0/27(0)	2/27(3.7)	0/27(0)	1.000	-	-
IGT (n/%)	5/27(18.5)	5/27(18.5)	8/27(29.6)	8/27(29.6)	0.526	-	-
Hyperlipidaemia (n/%)	3/30 (10)	2/30 (6.7)	6/27 (22.2)	4/27 (14.8)	0.283	-	1.000

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated haemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; TC, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference; . $P<0.05$ were considered indicative of significant differences between groups. * $P < 0.05$, * * $P < 0.01$, compared with baseline for each treatment.



▶ **Fig. 2** A comparison of changes in body weight (**a**), body weight (**b**), percentage weight loss (**c**), proportion of patients who lost at least 0, 5, 10, and 15 % of their initial body weight (**d**), changes in BMI (**e**), and BMI (**f**) during 12 weeks of treatment between beinaglutide or metformin groups (* P<0.05, * * P<0.01). a, c, d, and e * * P<0.001 * P<0.05; b and f * * P<0.001 * P<0.05 follow-up points vs. baseline. ††P<0.001 †P<0.05 follow-up points vs. 4 weeks. ‡ P<0.05 follow-up points vs. 8 weeks. BMI, body mass index. .

Primary endpoint

There was a downward trend in body weight during the 12 weeks follow-up period and more weight loss was observed at 8 weeks and 12 weeks in the beinaglutide group than in the metformin group (▶ **Fig 2a, b**). At the end of the study, participants in the beinaglutide group lost a mean of 9.5 ± 0.8 % (9.1 ± 0.9 kg) of their body weight, whereas those in the metformin group lost a mean of 5.1 ± 0.9 % (4.5 ± 0.8 kg) of their body weight (▶ **Fig. 2a, c**). Patients in the beinaglutide group showed a greater decrease in body weight (△ = − 4.5 kg; 95 % confidence interval (CI), − 6.9 to − 2.2 kg) than those in the metformin group at 12 weeks of treatment (P<0.01) (▶ **Table 1**). More patients lost ≥ 5 or ≥ 10 % of their body weight in the beinaglutide group than in the metformin group (90.6 vs. 40.6 % and 46.9 vs. 12.5 %, respectively; P<0.05). However, the proportion of patients who lost ≥ 15 % of their body weight did not significantly differ between the beinaglutide and metformin groups (6.3 and 3.1 %, respectively, P=0.556) (▶ **Fig. 2d**). Overall, approximately 96.9 % of participants in the beinaglutide group and around 87.5 % of those in the metformin group lost weight (▶ **Fig. 2d**).

BMI and waist circumference

BMI and waist circumference of the participants decreased significantly in the beinaglutide and metformin groups during the 12 weeks of treatment (all P<0.01 vs. baseline) (▶ **Fig. 2e, f**; ▶ **Table 1**). The beinaglutide group showed a greater decrease in BMI (3.1 ± 0.3 kg/m^2 vs. 1.6 ± 0.3 kg/m^2, △ = − 1.5 kg/m^2; 95 % CI, − 2.2 to − 0.7 kg/m^2) and waist circumference (△ = − 4.7 cm; 95 % CI, − 8.0 to − 1.5 cm) than did the metformin group (both P<0.01) (▶ **Table 1**, ▶ **Fig. 2e**).

Body composition, basal metabolic rate, and non-alcoholic fatty liver

A total of 27 of 28 participants in the beinaglutide group and 29 of 30 in the metformin group had their body composition evaluated along with liver steatosis and stiffness measures at baseline and 12 weeks later. A significant decrease in body fat mass was observed, including total, trunk, limb, android, and gynoid fat and the percent body fat following both treatments (P<0.01) (▶ **Table 2**). A greater decrease in total fat mass (△ = − 2.9 kg; 95 % CI, − 4.7 to − 1.0 kg; P<0.01), trunk fat mass (△ = − 2.0 kg; 95 % CI, − 3.2 to − 0.8 kg; P<0.01), limb fat mass (△ = − 0.9 kg; 95 % CI, − 1.6 to − 0.1 kg; P<0.05), android fat mass (△ = − 0.5 kg; 95 % CI, − 0.7 to − 0.2 kg; P<0.01), gynoid fat mass (△ = − 0.4 kg; 95 % CI, − 0.7 to − 0.2 kg; P<0.01), and percent body fat mass (△ = − 1.7 %; 95 % CI, − 3.1 to − 0.4 kg; P<0.05) in the beinaglutide group than in the metformin group (▶ **Table 2**). Beinaglutide significantly decreased the total, limb, android, and gynoid lean tissue masses (P<0.05), and metformin significantly decreased the limb and gynoid lean tissue masses (P<0.01); similar reductions in lean tissue mass were observed between the two groups (▶ **Table 2**).

Generally, the beinaglutide group experienced a greater loss of body fat mass, including total, trunk, limb, android, as well as gynoid mass, than of lean tissue mass in the same regions (P<0.05) (▶ **Fig. 3**). In the metformin group, the reductions in total, trunk,

▶ **Table 2** FibroTouch results and body composition at baseline and after 12 weeks of treatment with beinaglutide or metformin.

	Beinaglutide		Metformin		*P* baseline	Estimated treatment difference, beinaglutide vs. metformin (mean, 95 %CI)	*P* between the two groups
	Baseline	3 months	Baseline	3 months			
Number(n)	28	-	29	-	-	-	-
Fibro Touch	-	-	-	-	-	-	-
LSM (kPa)	8.5 ± 0.6	6.7 ± 0.4 *	8.3 ± 0.7	6.7 ± 0.3 *	0.994	−0.2 (−2.0 to 1.5)	0.794
CAP (dB/m)	306.1 ± 6.3	270.2 ± 5.5 * *	295.3 ± 6.5	276.4 ± 7.6 *	0.247	−17.1 (−35.1 to 0.9)	0.062
Number (n)	27	-	30	-	-	-	-
Body composition (BIA)	-	-	-	-	-	-	-
Visceral fat area (cm^2)	156.8 ± 6.3	127.2 ± 6.6 * *	158.6 ± 7.8	141.8 ± 6.9 *	0.542	−12.8 (−25.4 to −0.2)	0.046
Basal metabolic rate (kcal)	1634.4 ± 45.5	1601.3 ± 44.0 * *	1530.0 ± 45.0	1503.9 ± 42.9 *	0.124	−7.0 (−31.3 to 17.2)	0.564
Body composition (DXA)	-	-	-	-		-	
Percentage body fat (%)	38.4 ± 1.1	34.7 ± 1.2 * *	39.2 ± 0.8	37.2 ± 1.0 * *	0.210	−1.7 (−3.1 to −0.4)	0.012
Total Body fat mass (kg)	35.2 ± 1.0	29.1 ± 1.1 * *	33.8 ± 1.1	30.5 ± 1.2 * *	0.748	−2.9 (−4.7 to −1.0)	0.003
Trunk fat (kg)	20.5 ± 0.7	16.6 ± 0.8 * *	19.0 ± 0.8	17.1 ± 0.7 * *	0.199	−2.0 (−3.2 to −0.8)	0.002
Limb fat (kg)	13.6 ± 0.5	11.4 ± 0.4 * *	13.7 ± 0.6	12.4 ± 0.6 * *	0.919	−0.9 (−1.6 to −0.1)	0.021
Android fat (kg)	3.7 ± 0.2	2.8 ± 0.2 * *	3.2 ± 0.2	2.8 ± 0.2 * *	0.102	−0.5 (−0.7 to −0.2)	0.001
Gynoid fat (kg)	5.1 ± 0.2	4.2 ± 0.2 * *	4.9 ± 0.2	4.5 ± 0.2 * *	0.566	−0.4 (−0.7 to −0.2)	0.002
Total lean tissue mass (kg)	54.1 ± 2.0	52.6 ± 2.0 * *	50.0 ± 1.7	49.6 ± 1.6	0.103	−1.1 (−2.7 to 0.5)	0.182
Trunk lean tissue (kg)	24.5 ± 0.8	24.2 ± 0.9	22.7 ± 0.7	22.2 ± 0.8	0.082	0.2 (−0.6 to 0.9)	0.617
Limb lean tissue (kg)	25.9 ± 1.1	24.7 ± 1.0 * *	23.7 ± 0.9	22.8 ± 0.9 * *	0.114	−0.3 (−0.8 to 0.1)	0.141
Android lean tissue (kg)	3.8 ± 0.2	3.6 ± 0.2 *	3.5 ± 0.1	3.3 ± 0.1	0.067	−0.03 (−0.2 to 0.2)	0.770
Gynoid lean tissue (kg)	8.9 ± 0.4	8.6 ± 0.3 * *	8.1 ± 0.3	7.8 ± 0.3 * *	0.070	−0.1 (−0.3 to 0.1)	0.228

Abbreviations: BIA: bioelectrical impedance analysis; CAP: controlled attenuation parameter; DXA: dual-energy X-ray; LSM: liver stiffness measurement. Percent body fat was calculated by dividing total body fat mass by total body weight. $P < 0.05$ was considered to indicate significant difference. * $P < 0.05$, * * $P < 0.01$, compared with baseline for each treatment.

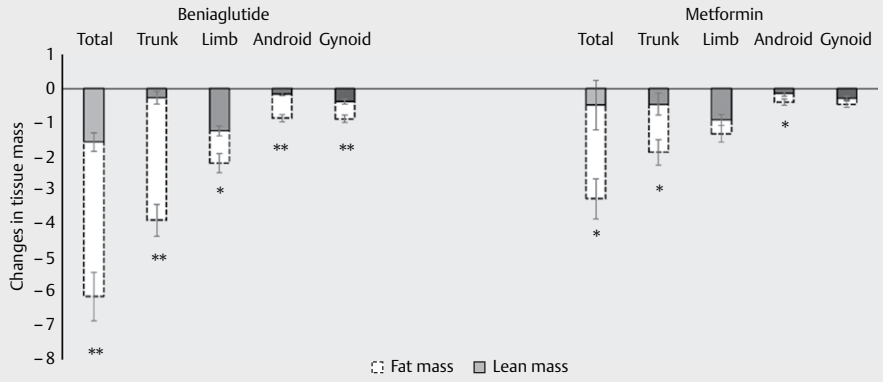
and android fat masses were greater than those of lean tissue masses in the same regions ($P < 0.05$) (▶ **Fig. 3**).

Visceral fat area and basal metabolic rate significantly decreased in the beinaglutide group (from 156.8 ± 6.3 cm^2 to 127.2 ± 6.6 cm^2, $P < 0.01$; from 1634.4 ± 45.5 kcal to 1601.3 ± 44.0 kcal, $P < 0.01$, respectively) and in the metformin group (from 158.6 ± 7.8 cm^2 to 141.8 ± 6.9 cm^2, $P < 0.05$; from 1530.0 ± 45.0 kcal to 1503.9 ± 42.9 kcal, $P < 0.05$, respectively) (▶ **Table 2**). Changes in visceral fat area and basal metabolic rate were similar in both groups (▶ **Table 2**).

Similarly, LSM and CAP decreased significantly in the beinaglutide group (from 8.5 ± 0.6 kPa to 6.7 ± 0.4 kPa, $P < 0.05$; from 306.1 ± 6.3 dB/m to 270.2 ± 5.5 dB/m, $P < 0.01$, respectively) and in the metformin group (from 8.3 ± 0.7 kPa to 6.7 ± 0.3 kPa, $P < 0.01$; from 295.3 ± 6.5 dB/m to 276.4 ± 7.6 dB/m, $P < 0.05$, respectively) (▶ **Table 2**). Similar changes in LSM and CAP were observed between the two groups (▶ **Table 2**). Beinaglutide and metformin treatments caused significant ($P < 0.05$) and similar reductions in serum ALT and AST levels (▶ **Table 1**).

Glucose and lipid levels and insulin resistance

There were no significant differences in serum glycated haemoglobin A1c and glucose levels at 0, 30, and 120 min during the 75 g



▶ **Fig. 3** Changes in fat mass and lean tissue mass in the same region after treatment with beinaglutide or metformin (* $P<0.05$, * * $P<0.01$).

▶ **Table 3** On-treatment (beinaglutide or metformin) adverse events.

	Beinaglutide	Metformin	*P*-value
	N (%)	N (%)	
Constipation	0	1 (2.6)	1.000
Diarrhoea	0	17 (43.6)	<0.001
Nausea	23 (59.0)	2 (5.1)	<0.001
Vomiting	8 (20.5)	0	0.005
Dizziness	13 (33.3)	2 (5.1)	0.002
Headache	0	0	-
Fatigue	2 (5.1)	1 (2.6)	1.000
Gastroenteritis	0	0	-
Nasopharyngitis	0	0	-
Injection site Swelling	0	-	-
Palpitation	1 (2.6)	0	1.000
Serious Adverse events	0	0	-
Hypoglycaemia	0	0	-

glucose tolerance test within or between the two groups, and the serum lipid profiles remained constant in both groups (▶ **Table 1**). Beinaglutide treatment resulted in a greater reduction in serum fasting, 30-min, and 120-min insulin levels and HOMA-IR levels (all $P<0.05$), whereas in the metformin group, serum fasting and 120-min insulin levels and HOMA-IR levels showed only a decreasing trend (▶ **Table 1**).

Serum uric acid and blood pressure

After 12 weeks of treatment, serum uric acid decreased significantly only in the beinaglutide group ($P<0.01$), and beinaglutide caused greater reductions in the serum uric acid than metformin ($P<0.05$). No noticeable change in blood pressure was observed in either group (▶ **Table 1**).

Adverse events

Gastrointestinal intolerance was the most common adverse event in the beinaglutide and metformin groups. In the beinaglutide group, 59.0 % of patients had nausea, and 20.5 % experienced vomiting, which was higher than that in the metformin group (5.1 and 0 %, respectively) ($P<0.01$), whereas 43.6 % of patients had diarrhoea during metformin treatment, which was higher than that in patients during beinaglutide treatment ($P<0.01$). Dizziness was also a common adverse event in the beinaglutide group, with 33.3 % of patients experiencing transient dizziness during the trial, which was higher than that in the metformin group ($P<0.01$). Most adverse events occurred in the first four weeks after enrolment, particularly in the first two weeks, and then gradually eased. Four patients in the beinaglutide group withdrew because of mild or moderate dizziness, and two patients in the metformin group withdrew because of diarrhoea. There were no serious adverse events and no hypoglycaemic events (▶ **Table 3**).

Discussion and Conclusions

Beinaglutide, at a thrice-daily dose of 0.2 mg, resulted in greater weight loss than metformin at a thrice-daily dose of 0.5 g in non-diabetic patients who were obese/overweight and who had been instructed to consume a limited-energy diet and engage in 150 min of physical activity weekly. Most patients (96.9 %) lost weight, and the mean change in body weight following beinaglutide treatment was −9.5 ± 0.8 % (−9.1 ± 0.9 kg). The reduction in body weight, BMI, and waist circumference, as well as the proportion of patients who lost not < 5 or 10 % of their body weight, was higher in the beinaglutide group.

Although the mean body weights at baseline in the beinaglutide group and the metformin group were 94.0 and 88.0 kg, respectively, and the mean basal metabolic rate was about 100 kcal lower in the metformin group, these differences in basal markers between the two groups were not significant. In addition, there was no significant difference in BMI at baseline between the two groups. Thus, this study examining the effect of these two medicines on inducing weight loss is valid.

Several other GLP-1RAs have been studied in a similar setting in the past. In 12-week studies, liraglutide (3.0 mg/d) resulted in a mean weight loss of 6.3 kg and 57.1 % of patients had a weight loss ≥ 5 %. Similarly, exenatide treatment (10 µg, twice daily) showed a mean weight loss of 4.29 kg with 47 % of patients achieving a weight loss ≥ 5 % [23, 24]. In a 52-week study, subcutaneous injection of semaglutide (0.4 mg/d) resulted in a mean weight loss

of 15.5 kg (13.8 %) with 91 %/74 % of patients achieving ≥ 5 %/ ≥ 10 % weight loss, respectively [25]. Among the current GLP-1RAs, only liraglutide (3.0 mg/d) is approved for weight loss treatment in patients with obesity among all hypoglycaemic drugs [26]. Our data are the first to show that in patients who are overweight/obese and non-diabetic, the short-acting GLP-1RA beinaglutide (0.6 mg/d) is able to produce a weight loss of 9.1 kg (9.5 %) with 90.6 %/46.9 % of patients achieving a weight loss of ≥ 5 %/ ≥ 10 %. This seems better than the weight loss achieved with liraglutide (3.0 mg/d) and exenatide (10 µg BID), but might be inferior to that achieved with semaglutide (0.4 mg/qd) [23–25]. However, the smaller number of patients, shorter observational time, and single ethnic background of the present study do not allow a fair comparison with the findings of these previous studies, and thus, a head-to-head multicentre and multi-ethnic study comparing these GLP-1RAs is necessary. In addition, the weight loss induced by beinaglutide in the present study is much the same as that observed in patients with T2DM who lost a mean of 10.5 kg (9.5 %) of their body weight after three months of treatment [15].

The benefits of treatment with GLP-1RAs include diminishing fat mass, particularly trunk and visceral fat in patients who are overweight/obese or have T2DM/prediabetes [27–29], which is likely to be related to delayed food absorption [30]. Other studies have shown the beneficial effects of metformin in reducing trunk and visceral fat mass in patients with T2DM [18, 27]. Consistent with these findings, we found a significant decrease in total, limb, trunk, android, gynoid, and percent body fat following treatment with both beinaglutide and metformin, with beinaglutide showing stronger effects. Similar to a previous study examining weight loss at a liraglutide dose of 1.2 mg/qd or 1.8 mg/qd in patients with T2DM [27, 29], we also observed that the weight loss induced by beinaglutide was due to a reduction in body fat content rather than a reduction in lean tissue mass.

The LSM and CAP levels, as well as the serum ALT and AST levels, decreased significantly in both the beinaglutide and metformin groups, suggesting an improvement in NAFLD in response to both medicines. Previous studies have shown that 24 weeks of treatment with liraglutide or metformin monotherapy effectively reduced intrahepatic fat content and improved liver function in patients with T2DM and NAFLD [31]. Additionally, one year of treatment with liraglutide improved pathological changes in patients with non-alcoholic steatohepatitis [32]. Likewise, three years of treatment with exenatide also decreased serum ALT and AST levels in patients with T2DM [9]. A reduction in body weight and fat mass have been found to be closely related to a decrease in ALT and AST [9, 27]. In the present study, the observed reduction in trunk fat content, particularly in the android region, in response to beinaglutide and metformin may help alleviate NAFLD.

GLP-1RAs have been shown to regulate postprandial glucagon release and insulin secretion in a glucose-dependent manner [30, 33]. The patients in the present study showed no changes in glucose levels after 12 weeks of beinaglutide treatment. Importantly, no patient experienced hypoglycaemia, suggesting that the glucose-dependent mode of action of beinaglutide is safe in non-diabetic patients who are overweight/obese. This observation supports that reported by previous studies, in which there was no occurrence of hypoglycaemia associated with metformin use in non-diabetic patients who are overweight/obese [17, 18].

The amount of adipose tissue is closely related to uric acid secretion, and that patients who are overweight/obese often exhibit hyperuricaemia, whereas fat loss, particularly visceral fat loss, significantly reduces uric acid secretion [34]. In the current study, the significantly reduced serum uric acid levels observed following beinaglutide treatment may be related to the greater weight loss and fat loss that occurred with the use of this drug. A low basal metabolic rate is a risk factor for increased body weight and fat mass [35]. In the present study, the basal metabolic rates of patients at baseline were lower than normal, and although the decrease in lean tissue mass was less than that of fat mass, a small degree of lean tissue loss was still observed following both treatments. A decreased basal metabolic rate is not conducive to maintaining weight loss. Although all participants were advised to maintain a limited-energy balanced diet and engage in physical activity, more targeted muscle-building exercises and dietary adjustments may help prevent loss of muscle mass [35, 36].

The safety profile of beinaglutide was similar to previous findings regarding other GLP-1RAs [7, 25]. Nausea and dizziness were the most common adverse events observed in our study. As previously observed for metformin [17], the main side effect in this study was diarrhoea. Overall, the total adverse reactions were similar between the two groups, and no serious adverse events occurred.

The limitations of our study include that it is a non-multicentre, non-double-blind, study with a short follow-up time, a relatively small sample size, and the lack of follow-up after discontinuation of the therapy. As a result, the time for which the weight loss was maintained and the rate of any subsequent weight gain were not assessed. This study is the first to examine the effect of beinaglutide on weight in non-diabetic subjects, with a prominent weight loss effect (nearly 10 kg) after its use. However, a subsequent multicentre, double-blind, and extended follow-up study is needed, which can clarify whether beinaglutide is suitable for the long-term weight loss treatment in non-diabetics who are overweight/obese. The lack of a control treatment with orlistat, the usage of which is currently approved in China for weight loss, is another limitation of this study, as it would be helpful to clarify how beinaglutide compares to orlistat for weight reduction in patients who are overweight/obese.

In summary, treatment of non-diabetic patients who were overweight/obese with beinaglutide for 12 weeks achieved a greater degree of weight loss and fat mass reduction than with metformin treatment. The weight loss achieved with beinaglutide treatment mainly resulted from a reduction in fat mass rather than in lean tissue mass, thus ameliorating metabolic disorders. Beinaglutide may therefore be an option for Chinese patients who are overweight/obese. This study strengthens the clinical data supporting the use of GLP-1RAs in non-diabetic patients who are overweight/obese.

Author Contributions

W.H.F. and Y.B. designed the study, supervised the research, and reviewed the manuscript. D.L.Z. reviewed the manuscript. L.J.G., H.H., and L.Z. collected data, performed the statistical analyses,

and wrote the manuscript. N.J.Z. and Y.Z.F collected data. All authors read and approved the final manuscript.

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Conflict of Interest

All authors have no conflicts of interest, financial ties, or grant support to disclose.

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