

ORIGINAL ARTICLE

Clinical Trials and Investigations

Effect of Calorie Restricted Diet Versus Liraglutide on Intrapancreatic Fat Deposition in People With Obesity: A Pilot Study

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Correspondence: Wenjun Wu (wuwenjung@163.com)**Received:** 26 July 2025 | **Revised:** 3 December 2025 | **Accepted:** 13 January 2026**ABSTRACT**

Objective: This pilot study compared the effects of a calorie restricted diet (CRD) versus liraglutide on intrapancreatic fat deposition (IPFD) in people with obesity and explored associations between changes in adiposity-related metrics and glycemic-related parameters.

Methods: In this 24-week prospective nonrandomized study, participants with obesity received CRD or liraglutide. Primary endpoint was the change in pancreatic fat fraction (PFF). Secondary endpoints included changes in body weight, liver fat fraction (LFF), visceral fat area (VFA), and glycemic-related parameters.

Results: Both CRD ($n=23$) and liraglutide ($n=23$) demonstrated significant and comparable reductions in PFF (time effect: $p<0.001$; interaction effect: $p=0.560$). Significant and similar improvements were also observed in body weight, LFF, VFA, HbA1c, HOMA2-IR, and ISIM (all time effects: $p<0.001$; all interaction effects: $p>0.05$). Regression analysis indicated that Δ HOMA2-IR was positively associated with Δ weight and Δ LFF but negatively with Δ PFF, while Δ ISIM was negatively associated with Δ VFA and positively with Δ PFF.

Conclusions: Both CRD and liraglutide significantly and similarly reduce pancreatic, liver, and visceral fat, while improving glycemic-related parameters in people with obesity. Preliminary findings suggest liver and visceral fat loss primarily drive improved insulin resistance, whereas pancreatic fat reduction may relate to subtler insulin dynamics changes, warranting further investigation.

Trial Registration: This study is a sub-study of the registered trial ChiCTR1900022948

1 | Introduction

The prevalence of obesity has surged dramatically, leading to a global epidemic which imposes significant health and economic burdens [1]. The primary concern associated with obesity arises

from excessive ectopic fat accumulation in vital organs such as the pancreas and liver, which increases the risk of metabolic disorders, particularly type 2 diabetes mellitus (T2DM) [2, 3]. Excessive intrapancreatic fat deposition (IPFD) plays a pivotal role in the transition from obesity to T2DM, and ample evidence suggests

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that this condition is potentially reversible [4–8]. The Diabetes Remission Clinical Trial (DiRECT) has demonstrated that the reduction of IPFD associated with weight loss closely correlates with the remission of T2DM [9, 10]. Therefore, targeting the reduction of IPFD offers promising avenues for preventing or reversing glucose metabolism disorders in individuals with obesity.

Weight loss is widely regarded as the key to reducing IPFD [4]. Substantial evidence, including prospective studies, has confirmed that interventions such as bariatric surgery [11–14] and specific dietary regimens—including very low-energy (600 kcal/day) [15] and Mediterranean/low-carbohydrate diets [16]—can significantly decrease IPFD in individuals with obesity or metabolic abnormalities. Among dietary strategies, calorie restricted diet (CRD), which limits daily energy intake while meeting essential nutritional requirements and adhering to balanced macronutrient ratios, is regarded as one of the most sustainable, safe, and stable dietary interventions for weight management [17]. Despite this, the impact of CRD on IPFD remains unexplored. Moreover, while GLP-1 receptor agonists (GLP-1Ra) are considered one of the most promising pharmacotherapies for weight loss [18], their effects on IPFD in people with obesity are still unclear [19].

In this prospective, nonrandomized pilot study, we conducted a real-world investigation to evaluate the comparative effects of a 24-week treatment with CRD or liraglutide on IPFD in people with obesity, while exploring the relationships between reductions in adiposity-related metrics and improvements in glycemic-related parameters. The results aim to provide preliminary clinical evidence, thereby informing the design of larger, definitive trials to guide weight management strategies for people with obesity at high risk of glucose metabolism disorders.

2 | Methods

2.1 | Study Design

This pilot study was a 24-week, prospective, nonrandomized, real-world investigation conducted from June 2019 to January 2023 at the Affiliated Wuxi People's Hospital of Nanjing Medical University. The study (a substudy of the registered trial ChiCTR1900022948) conformed to the Declaration of Helsinki and was approved by the independent ethics committee. All participants provided written informed consent.

2.2 | Participants

Eligible participants were aged 18–65 years with obesity defined as body mass index (BMI) ≥ 28 kg/m² according to the reference standard established by The Work Group on Obesity in China [20], including those without diabetes or with newly diagnosed T2DM. Key exclusion criteria included: (1) a self-reported weight fluctuation $\geq 5\%$ within 90 days prior to screening; (2) secondary obesity (e.g., Cushing's syndrome, hypothyroidism) or obesity induced by long-term medication use; (3) medically treated diabetes; (4) any history of liver disease or daily alcohol intake > 20 g for women or > 30 g for men; (5) any diseases requiring special dietary or limited physical activity; (6) history or presence of pancreatitis, personal or first-degree relative(s) history

of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma, or calcitonin ≥ 100 ng/L; (7) contraindications for magnetic resonance imaging (MRI); (8) severe hepatic, renal, or cardiac insufficiency or history of malignancies or psychiatric disorders; (9) female who was pregnant, breastfeeding, intending to conceive, or of childbearing potential not using effective contraception during the study.

2.3 | Procedures

This study was conducted by a multidisciplinary team (MDT) in weight management composed of two endocrine physicians, a registered nutritionist, a nutrition technician, two rehabilitation physicians, and two radiologists. The study flow comprised screening, enrollment, a 24-week intervention, and follow-up. Potentially eligible individuals were screened against the inclusion and exclusion criteria. Within 2 weeks after screening, eligible participants, after consultation with the MDT and based on their personal preference, were enrolled to receive either CRD or liraglutide intervention for 24 weeks. During the intervention, participants attended follow-up visits every 4 weeks until week 24. Participants who discontinued or were lost to follow-up were excluded from the final analysis. A detailed participant flow diagram is provided in Figure 1.

Participants in the CRD group underwent a dietary regimen strictly established by the nutritionist. The total daily caloric intake of CRD was calculated by multiplying the basal metabolic rate obtained from the bioelectrical impedance analysis by the activity factor (Table S1) and then subtracting 500 kcal. The macronutrient proportions for calorie contributions were 40% from carbohydrates, 25% from protein, and 35% from fat. Participants in the liraglutide group underwent subcutaneous liraglutide daily. The dosage was initiated at 0.6 mg/day and increased by 0.6 mg each week to achieve 1.8 mg/day or the maximum tolerated dose (at least 1.2 mg/day).

Meanwhile, all participants received a standardized, individualized exercise regimen under the guidance of rehabilitation physicians, including aerobic and resistance training, alongside a lifestyle modification program, the full details of which are described in the online [Supporting Information](#).

A WeChat group was created to maintain close contact with participants, providing communication and guidance. Participants reported their diet type, food quantity, exercise condition, weight data, and any discomfort daily through pictures and text messages in the group. Throughout the study implementation, the MDT monitored the WeChat group daily. In case of issues, the MDT would address them, decide on solutions, and keep records. Outpatient visits were conducted every 4 weeks until week 24.

2.4 | Assessments

At screening, all participants underwent the anthropometric and biochemical measurements. Body weight and height were measured by a calibrated scale (HNH-318, Omron). Waist circumference, hip circumference, and blood pressure were

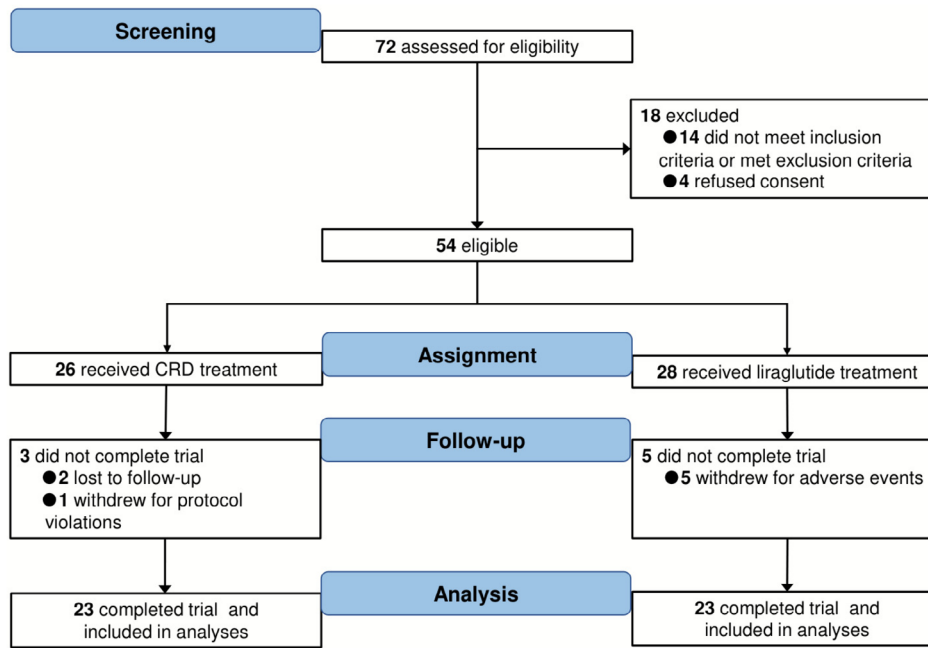


FIGURE 1 | Participant flow diagram of the pilot study.

measured by a qualified nurse. BMI was calculated as body weight in kilograms divided by height in meters squared. The body compositions including body fat percent and visceral fat area (VFA) were determined using bioelectrical impedance analysis by an InBody S10 device (Biospace). HbA1c, fasting plasma glucose (FPG), fasting insulin (FINS), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), liver enzymes, and renal function were analyzed using fasting blood samples in a central laboratory. Blood samples were collected after an oral glucose tolerance test (OGTT) to detect 2-h postprandial plasma glucose (PPG) and postprandial insulin (PINS) levels. Insulin resistance and β -cell function were estimated by updated homeostasis model assessment model of insulin resistance (HOMA2-IR) and updated homeostasis model assessment model of beta-cell function (HOMA2-% β), respectively, using the HOMA2 Calculator (HOMA2 v2.2.3; Diabetes Trials Unit, University of Oxford, <https://www.dtu.ox.ac.uk/homacalculator/>). Insulin sensitivity was assessed by Matsuda insulin sensitivity index (ISIM), which was calculated as follows: $10,000 / (FPG \times FINS \times \text{mean glucose} \times \text{mean insulin during OGTT})^{1/2}$.

At baseline (2 weeks after screening), eligible participants underwent abdominal MRI to assess intrapancreatic and intrahepatic fat deposition by quantifying the proton density fat fraction (PDFF) using the chemical shift-based six-point Dixon MRI technique, as detailed in our previous study [21].

In addition to screening (week 2) and baseline (week 0) visits, participants visited the study center every 4 weeks. At these visits, anthropometric measurements were conducted, and adverse events were documented. At week 24, all participants completing the study were reevaluated, including the anthropometric and biochemical measurements as at the screening and abdominal MRI as at baseline.

2.5 | Endpoints

The primary endpoint was the change in pancreatic fat fraction (PFF) from baseline to week 24 (the end of the treatment). Secondary endpoints comprised changes in: (1) adiposity-related metrics, including body weight, BMI, waist circumference, hip circumference, body fat percent, VFA, and liver fat fraction (LFF); (2) glycemic-related parameters, including HbA1c, FPG, PPG, HOMA2-IR, ISIM, and HOMA2-% β .

2.6 | Statistical Analyses

Data analysis was performed using SPSS version 20.0 (SPSS Software), and graphical creation was conducted using GraphPad Prism version 8.0. Statistical significance was defined as a two-tailed p value < 0.05 . Continuous and categorical data are presented as mean \pm SD and n , %, respectively.

Baseline continuous and categorical variables were compared using independent-samples t -tests and chi-square tests, respectively. Efficacy analyses for all endpoints were performed using repeated-measures ANOVA (RM-ANOVA) to examine the main effects of time and group and their interaction. The primary endpoint (change in PFF) was tested at $p < 0.05$. A hierarchical Bonferroni correction was applied to secondary endpoints within prespecified domains: (1) adiposity-related metrics (seven tests) and (2) glycemic-related parameters (six tests). Additional metabolic parameters were analyzed with RM-ANOVA and a separate Bonferroni correction (nine tests).

To explore the associations among changes in adiposity-related metrics, changes in glycemic-related parameters, and treatment assignment, we first performed Pearson correlation analysis on the change values of all significantly improved endpoints and the treatment assignment. Subsequently, stepwise multivariable

linear regression was used to identify independent predictors for improvements in glycemic-related parameters. Two models were constructed: Model 1 included changes in adiposity-related metrics as unadjusted covariates, while Model 2 was further adjusted for age, sex, and treatment assignment. Multicollinearity was assessed using variance inflation factors (VIF), with a value > 10 indicating its presence.

3 | Results

3.1 | Study Flow and Participants

Of the 72 individuals screened between June 2019 and January 2023, 54 were enrolled and assigned to two treatment groups (CRD, $n = 26$; liraglutide, $n = 28$). Three in the CRD group withdrew from the study (two lost to follow-up, one for protocol violations), and five in the liraglutide group withdrew for adverse events (unbearable nausea and vomiting). Ultimately, 46 participants (CRD, $n = 23$; liraglutide, $n = 23$) completed the study and were included in the final analysis (Figure 1).

The baseline characteristics of the two groups were balanced. As shown in Table 1, there were no significant differences in demographic parameters, the primary endpoint (PFF), or secondary endpoints including adiposity-related metrics and glycemic-related parameters (all $p > 0.05$). Additional baseline metabolic parameters, including blood pressure, lipid profile, and liver enzymes, were also comparable between groups (Table S2).

3.2 | Primary Endpoint: Change in PFF

Both the CRD and liraglutide interventions resulted in a significant reduction of the primary endpoint, PFF, over the 24-week treatment period (CRD, $14.1\% \pm 7.2\%$ to $10.5\% \pm 6.2\%$; liraglutide, $13.5\% \pm 6.6\%$ to $9.2\% \pm 3.6\%$; main effect of time: $p < 0.001$, Table 2). As visually summarized in Figure 2, the distribution of PFF shifted markedly downward from baseline to posttreatment in both groups, with individual data points and connecting lines illustrating consistent within-subject reductions. However, RM-ANOVA indicated that the magnitude of this reduction was not significantly different between the two groups (group \times time interaction effect: $p = 0.560$, Table 2).

3.3 | Secondary Endpoints: Changes in Adiposity-Related Metrics and Glycemic-Related Parameters

Significant improvements were observed across most key secondary endpoints following the 24-week intervention. Both CRD and liraglutide led to substantial reductions in body weight, BMI, waist circumference, hip circumference, body fat percentage, VFA, and LFF (main effects of time: $p < 0.001$; Table 2). Glycemic-related parameters, including HbA1c, FPG, PPG, HOMA2-IR, and ISIM, also showed significant improvement over time (main effects of time: $p < 0.001$; Table 2). In contrast, no significant change was observed in HOMA2-% β (main effect of time: $p = 0.267$; Table 2). Nevertheless, for all

TABLE 1 | Baseline characteristics of trial population.

	CRD ($n = 23$)	Liraglutide ($n = 23$)	<i>p</i>
Demographics			
Male, <i>n</i> , %	10, 43.5%	6, 26.1%	0.216
Age (years)	31.9 \pm 8.1	29.7 \pm 6.3	0.315
Smoking habits, <i>n</i> , %	5, 21.7%	1, 4.3%	0.080
Alcohol habits, <i>n</i> , %	4, 17.4%	3, 13.0%	0.681
Newly diagnosed diabetes, <i>n</i> , %	10, 43.5%	5, 21.7%	0.116
Primary endpoint			
PFF (%)	15.2 \pm 6.9	18.3 \pm 7.9	0.164
Secondary endpoints			
Adiposity-related metrics			
Weight (kg)	94.9 \pm 17.8	99.1 \pm 17.5	0.424
BMI (kg/m ²)	34.0 \pm 4.9	35.4 \pm 3.6	0.259
Waist circumference (cm)	107.1 \pm 11.8	108.6 \pm 10.0	0.638
Hip circumference (cm)	112.0 \pm 10.3	113.8 \pm 8.0	0.506
Body fat percent (%)	40.3 \pm 5.7	42.9 \pm 4.2	0.078
VFA (cm ²)	167.7 \pm 36.7	187.5 \pm 31.7	0.056
LFF (%)	14.1 \pm 7.2	13.5 \pm 6.6	0.753
Glycemia			
HbA1c (%)	6.9 \pm 2.5	6.1 \pm 1.0	0.144
FPG (mmol/L)	7.2 \pm 3.4	6.0 \pm 1.8	0.139
PPG (mmol/L)	11.7 \pm 6.7	8.6 \pm 3.4	0.054
Insulin resistance/sensitivity			
HOMA2-IR	3.2 \pm 1.6	3.8 \pm 2.1	0.235
ISIM	2.2 \pm 1.2	2.0 \pm 1.4	0.677
Insulin secretion			
HOMA2-% β	137.0 \pm 77.4	184.3 \pm 90.0	0.062

Note: Data are mean \pm SD or *n*, %. Comparison between groups was analyzed by independent *t*-tests (continuous variables) or chi-square tests (categorical variables).

Abbreviations: CRD, calorie restricted diet; FPG, fasting glucose; HbA1c, hemoglobin A1c; HOMA2-IR, updated homeostasis model assessment of insulin resistance; HOMA2-% β , updated homeostasis model assessment beta-cell function; ISIM, Matsuda insulin sensitivity index; LFF, liver fat fraction; PFF, pancreatic fat fraction; PPG, postprandial glucose; VFA, visceral fat area.

these endpoints, no significant group \times time interaction effects were detected (all $p > 0.05$; Table 2). This finding was consistent after applying a hierarchical Bonferroni correction for multiple comparisons.

TABLE 2 | Changes in primary and secondary endpoints after a 24-week treatment with CRD or liraglutide.

Variable	CRD (n = 23)			Liraglutide (n = 23)			p	
	Baseline	Posttreatment	Baseline	Posttreatment	Time	Group	Interaction (unadjusted)	Interaction (adjusted)
Primary endpoint								
PFF (%)	14.1 ± 7.2	10.5 ± 6.2	13.5 ± 6.6	9.2 ± 3.6	< 0.001***	0.557	0.560	—
Secondary endpoints								
Adiposity-related metrics								
Weight (kg)	94.9 ± 17.8	82.5 ± 17.6	99.1 ± 17.5	84.2 ± 18.7	< 0.001***	0.573	0.316	1.000
BMI (kg/m ²)	34.0 ± 4.9	29.5 ± 4.8	35.4 ± 3.6	30.0 ± 4.5	< 0.001***	0.423	0.341	1.000
Waist circumference (cm)	107.1 ± 11.8	94.1 ± 12.3	108.6 ± 10.0	94.2 ± 13.2	< 0.001***	0.808	0.536	1.000
Hip circumference (cm)	112.0 ± 10.3	104.2 ± 10.2	113.8 ± 8.0	104.6 ± 8.0	< 0.001***	0.670	0.444	1.000
Body fat percent (%)	40.3 ± 5.7	32.6 ± 7.4	42.9 ± 4.2	35.4 ± 5.0	< 0.001***	0.080	0.929	1.000
VFA (cm ²)	167.7 ± 36.7	115.2 ± 44.3	187.5 ± 31.7	131.6 ± 34.6	< 0.001***	0.078	0.691	1.000
LFF (%)	15.2 ± 6.9	7.1 ± 4.4	18.3 ± 7.9	8.0 ± 5.2	< 0.001***	0.206	0.270	1.000
Glycemia								
HbA1c (%)	6.9 ± 2.5	5.3 ± 0.3	6.1 ± 1.0	5.2 ± 0.2	< 0.001***	0.111	0.200	1.000
FPG (mmol/L)	7.2 ± 3.4	5.2 ± 0.6	6.0 ± 1.8	5.0 ± 0.6	< 0.001***	0.114	0.196	1.000
PPG (mmol/L)	11.7 ± 6.7	7.0 ± 1.6	8.6 ± 3.4	6.3 ± 1.4	< 0.001***	0.051	0.151	0.906
Insulin resistance/sensitivity								
HOMA2-IR	3.2 ± 1.6	2.0 ± 1.1	3.8 ± 2.1	2.2 ± 1.4	< 0.001***	0.316	0.302	1.000
ISIM	2.2 ± 1.2	4.2 ± 2.9	2.0 ± 1.4	4.3 ± 2.4	< 0.001***	0.716	0.896	1.000
Insulin secretion								
HOMA2-%β	137.0 ± 77.4	141.6 ± 47.5	184.3 ± 90.0	156.7 ± 53.8	0.267	0.073	0.157	0.942

Note: Data are presented as mean ± SD. Between-group differences in the changes from baseline were assessed using repeated-measures ANOVA. *p* values for the time effect (overall change within groups), group effect (overall difference between groups), and interaction effect (difference in changes between groups over time) are reported. The primary endpoint was tested at a significance level of *p* < 0.05. For the secondary endpoints, a hierarchical Bonferroni correction was applied within two prespecified domains: (1) adiposity-related metrics (seven tests) and (2) glycemic-related parameters (six tests). Adjusted *p* values for the interaction effects are reported in the table. Significance levels are indicated as follows: ****p* < 0.001. Abbreviations: CRD, calorie restricted diet; FPG, fasting glucose; HbA1c, hemoglobin A1c; HOMA2-IR, updated homeostasis model assessment of insulin resistance; HOMA2-%β, updated homeostasis model assessment beta-cell function; ISIM, Matsuda insulin sensitivity index; LFF, liver fat fraction; PFF, pancreatic fat fraction; PPG, postprandial glucose; VFA, visceral fat area.

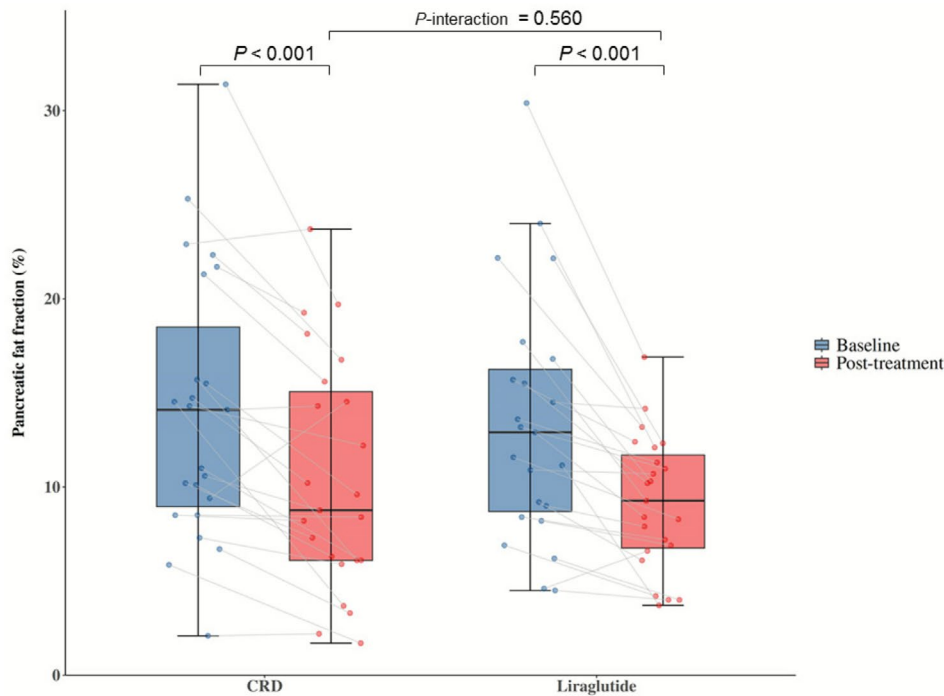


FIGURE 2 | Changes in pancreatic fat fraction after a 24-week treatment with CRD or liraglutide. Box plots show the distribution of pancreatic fat fraction at baseline (blue) and after 24-week treatment (red) with CRD or liraglutide. Boxes represent the median and interquartile range; whiskers extend to 1.5×IQR, with individual data points overlaid and connected by lines. *p* values are from repeated-measures ANOVA (time effect: $p < 0.001$; interaction effect: $p = 0.560$). CRD, calorie restricted diet.

3.4 | Changes in Additional Metabolic Parameters

Changes in additional metabolic parameters are detailed in Table S3. Both interventions led to significant improvements over time in SBP, DBP, TG, HDL-C, ALT, and AST (all main effect of time: $p < 0.001$). Meanwhile, no significant group×time interaction effects were observed for any of these parameters (all $p > 0.05$), either before or after correction for multiple comparisons. TC and γ GT remained stable throughout the study period in both groups. Although an unadjusted analysis suggested a potential differential effect on LDL-C (unadjusted group×time interaction: $p = 0.045$), this finding did not persist after rigorous multiple comparison correction ($p = 0.405$).

3.5 | Exploratory Analyses: Associations Between Reductions in Adiposity-Related Metrics and Improvements in Glycemic-Related Parameters

Initial pairwise Pearson correlations revealed interrelationships among reduced adiposity-related metrics, improved glycemic-related parameters, and treatment assignment (Figure S1). Subsequently, to identify independent predictors of improvements in glycemic-related parameters, we performed stepwise multivariable linear regression, adjusting for potential confounders. Only statistically significant associations from this regression are reported in Table 3.

For Δ HbA1c, Δ PFF was a significant positive predictor in the unadjusted model (Model 1: $B = 0.143$, 95% CI [0.010, 0.275], $p = 0.036$), but this association was not significant after

adjustment for age, sex, and treatment assignment in Model 2. In contrast, distinct and robust associations were observed for parameters of insulin resistance and sensitivity. For Δ HOMA2-IR, significant independent positive associations were found with Δ weight and Δ LFF ($B = 0.081$, 95% CI [0.028, 0.135], $p = 0.004$; $B = 0.110$, 95% CI [0.044, 0.177], $p = 0.002$, respectively) in both Model 1 and Model 2, while a significant independent negative association with Δ PFF was also robust to adjustment ($B = -0.114$, 95% CI [-0.217, -0.010], $p = 0.033$). Similarly, for Δ ISIM, a significant independent positive association with Δ PFF and a significant independent negative association with Δ VFA persisted ($B = 0.233$, 95% CI [0.049, 0.417], $p = 0.014$; and $B = -0.063$, 95% CI [-0.087, -0.040], $p < 0.001$, respectively) in both Model 1 and Model 2.

4 | Discussion

This prospective, nonrandomized, real-world pilot study compared the therapeutic effects of two common weight management approaches—CRD and liraglutide—on IPFD in people with obesity. Our preliminary findings indicated that both interventions significantly and comparably reduced PFF after 24 weeks, alongside significant and similar reductions in body weight and other ectopic fat deposits, including LFF and VFA. Glycemic-related parameters such as HbA1c, FPG, PPG, HOMA2-IR, and ISIM also showed comparable improvements in both groups, though no significant change was observed in HOMA2-% β . Further regression analysis revealed that improved insulin resistance (Δ HOMA2-IR) was associated with reductions in body weight and liver fat, but negatively with

TABLE 3 | Multivariable linear regression analysis of associations between changes in adiposity-related metrics and glycemic-related parameters.

Dependent variable	Model	Significant predictors	B	95% CI	p
ΔHbA1c	Model 1	ΔPFF	0.143	0.010, 0.275	0.036*
	Model 2	<i>No variables selected</i>	—	—	—
ΔHOMA-IR	Model 1	ΔPFF	-0.114	-0.217, -0.010	0.033*
		ΔLFF	0.110	0.044, 0.177	0.002**
		ΔWeight	0.081	0.028, 0.135	0.004**
	Model 2	ΔPFF	-0.114	-0.217, -0.010	0.033*
		ΔLFF	0.110	0.044, 0.177	0.002**
		ΔWeight	0.081	0.028, 0.135	0.004**
ΔISIM	Model 1	ΔPFF	0.233	0.049, 0.417	0.014*
		ΔVFA	-0.063	-0.087, -0.040	<0.001***
	Model 2	ΔPFF	0.233	0.049, 0.417	0.014*
		ΔVFA	-0.063	-0.087, -0.040	<0.001***

Note: Data are unstandardized regression coefficients (B) with 95% confidence intervals (CI) from stepwise multivariable linear regression. Model 1: unadjusted. Model 2: adjusted for age, sex, and treatment group. Only predictors retained in the final model of the stepwise selection ($p < 0.05$ for entry) are shown. Significance levels are indicated as follows: *** $p < 0.001$.

Abbreviations: HbA1c, hemoglobin A1c; HOMA2-IR, updated homeostasis model assessment of insulin resistance; ISIM, Matsuda insulin sensitivity index; LFF, liver fat fraction; PFF, pancreatic fat fraction; VFA, visceral fat area.

ΔPFF. Meanwhile, improved insulin sensitivity (ΔISIM) correlated negatively with visceral fat loss yet positively with ΔPFF.

Sufficient evidence supported the reversibility of IPFD, with weight loss identified as the effective strategy for its reversal [4, 22]. Several prospective studies reported that bariatric surgeries significantly reduced IPFD by 18% to 67% in individuals with obesity with or without diabetes at 6 months after surgery, as compared to presurgery levels [11–14, 23]. An 8-week very low-energy diet (600 kcal/day) also resulted in a significant decline in IPFD from elevated baseline levels in patients with T2DM [15]. Another randomized controlled trial found that an 18-month Mediterranean/low-carbohydrate diet intervention led to significantly lower IPFD levels in people with abdominal obesity or dyslipidemia with or without diabetes, as compared to a low-fat diet group [16]. These studies reinforced the effectiveness of both bariatric surgeries and dietary interventions in improving IPFD. However, few studies have evaluated the impact of CRD, one of the most sustainable and stable dietary interventions for weight management, on IPFD. Meanwhile, no prospective studies have been conducted on the effect of GLP-1Ra, the most promising pharmacotherapy for weight loss currently, on IPFD in people with obesity [19]. Our study not only confirmed the efficacy of CRD and liraglutide in reducing IPFD in people with obesity, but also demonstrated their comparable efficacy through a head-to-head comparison.

In addition to the notable improvements in IPFD, our study also confirmed significant and comparable reductions in body weight and other ectopic fat deposits, including LFF and VFA, at 24 weeks of treatment with either CRD or liraglutide. Previous randomized controlled trials have validated the effectiveness of CRD and GLP-1Ra in reducing weight, LFF, and VFA; however, the results have been inconsistent when comparing the efficacy

of both interventions [24–27]. In comparison to the aforementioned trials, our real-world study considered people's personal preferences in selecting weight loss treatments, as these preferences may significantly impact weight loss outcomes—an aspect that randomized controlled trials cannot fully capture. Consequently, our real-world study provides a more accurate reflection of people's responsiveness to these two weight management strategies in practice.

Weight loss positively enhances insulin sensitivity in people with obesity and may even restore pancreatic β -cell function, potentially reversing T2DM in individuals with obesity and T2DM [9, 15, 28]. Our study found that after a 24-week intervention with either CRD or liraglutide, there were significant and comparable improvements in glycemic-related parameters encompassing HbA1c, FPG, PPG, FINS, PINS, HOMA2-IR, and ISIM. However, HOMA2-% β showed no significant change at pre- and posttreatment. Further analysis indicated that the observed improvements in glycemic-related parameters were not related to treatment assignment but were closely associated with reductions in PFF, body weight, waist circumference, hip circumference, body fat percent, VFA, and LFF. This suggested that the ameliorations of glycemic-related parameters in people with obesity may not depend on the weight management approaches but rather on the reductions in body weight and ectopic fat deposits in the pancreas and liver, as well as other visceral areas.

Beyond the primary and secondary endpoints, both interventions led to significant and comparable improvements in additional metabolic parameters, including blood pressure, lipid profile (specifically reductions in TG and increases in HDL-C), and liver enzymes (ALT and AST). The absence of significant group \times time interaction effects for these parameters suggested that the observed benefits are likely a consequence of weight loss

itself, rather than a unique effect of either dietary or pharmacological strategy. These findings reinforce the broad metabolic benefits achievable through effective weight reduction, irrespective of the specific modality employed in this population.

To evaluate the relationships between improvements in glycemic-related parameters and reductions in adiposity-related metrics, we performed multivariable regression analysis. Although pancreatic fat reduction (Δ PFF) was initially associated with improved HbA1c, this association disappeared after adjustment for confounders, suggesting that its apparent benefit might be attributed to the treatment, which triggered broader metabolic benefits including reductions in pancreatic fat, body weight, and other ectopic fat depots. However, a more complex picture emerged regarding measures of insulin dynamics. Improved insulin resistance (Δ HOMA2-IR) was independently associated with reductions in body weight and liver fat but showed a negative correlation with Δ PFF. Meanwhile, improved insulin sensitivity (Δ ISIM) was negatively correlated with visceral fat loss yet positively correlated with Δ PFF. These findings can be interpreted within the framework of the dual circulation hypothesis, which posits that ectopic fat in the pancreas and liver is central to T2DM pathogenesis [29, 30]—a process potentially reversible through weight loss [30, 31]. This is strongly supported by the Counterpoint study, in which an 8-week very low-energy diet normalized both β -cell function and hepatic insulin sensitivity in tandem with reductions in pancreatic and liver fat in T2DM patients [15]. Our previous cross-sectional findings also align, having identified a negative correlation between PFF and HOMA2- β and a positive correlation between LFF and HOMA2-IR [21]. Consistent with this established background, our intervention confirmed that liver fat loss improved insulin resistance and visceral fat reduction enhanced insulin sensitivity. However, a key difference from the Counterpoint study emerged: unlike those findings, a significant reduction in PFF in both of our groups did not yield a significant improvement in HOMA2- β . A plausible explanation for this discrepancy may be attributed to the difference in study populations. Unlike the Counterpoint study, which included patients with established T2DM, our cohort comprised individuals without diabetes or with newly diagnosed T2DM, in whom β -cell function was not severely impaired. This limited scope for further enhancement, as there was “little room for improvement,” likely explains the absence of significant changes in HOMA2- β following either intervention. More interestingly, we even found Δ PFF was negatively correlated with Δ HOMA2-IR and positively with Δ ISIM, which appears to contradict the established theoretical framework. We speculated that the reduction in IPFD might facilitate subtle, compensatory increases in insulin secretion. A rise in insulin would mathematically elevate the HOMA2-IR value and lower the ISIM value, thus providing a coherent explanation for the observed associations. In summary, our pilot findings point to the divergent contributions of ectopic fat depots: liver and visceral fat loss are the primary drivers of improved insulin resistance, whereas pancreatic fat reduction may be potentially linked to subtler changes in insulin secretion, warranting further investigation.

This study has three major strengths. First, it presents the first head-to-head comparison of CRD and liraglutide on IPFD in obesity, while exploring the relationships between reductions

in adiposity-related metrics and improvements in glycemic-related parameters. Second, the real-world, pragmatic design enhances the ecological validity and clinical applicability of the findings by reflecting actual clinical decision-making. Third, the quantification of IPFD was performed using chemical shift MRI, a highly suitable noninvasive modality that minimizes the influence of visceral fat and has been validated against histologic analysis [4, 32, 33]. However, several limitations must be acknowledged. The primary limitation stems from the nonrandomized design, which may introduce selection bias. Although no statistically significant differences were found in baseline characteristics, trending imbalances were observed in several parameters, suggesting that the interpretation of comparable efficacy between interventions should be made cautiously. Furthermore, the modest sample size, inherent to this pilot study, limits statistical power for between-group comparisons and precludes stratified analysis by glucose metabolism status. Nevertheless, the study provides valuable preliminary data and robust effect-size estimates for designing future fully powered trials. Larger-scale, randomized studies are warranted to confirm these findings and explore efficacy across different subpopulations.

In conclusion, this pilot study provides preliminary evidence that a 24-week intervention with either CRD or liraglutide leads to comparable reductions in IPFD and other ectopic fat deposits, such as liver and visceral fat, alongside improvements in glycemic-related parameters in adults with obesity. Regression analysis further indicates that reductions in liver and visceral fat are primary contributors to improved insulin resistance, whereas pancreatic fat reduction may play a more nuanced role in modulating insulin secretory dynamics. As an exploratory investigation, this work provides the preliminary mechanistic insights and effect-size estimates to inform the design of larger, definitive trials aimed at developing targeted weight management strategies for individuals with obesity at high risk of glucose metabolism disorders.

Author Contributions

W.W. designed the study and oversaw all clinical aspects of study conduct and manuscript preparation. H.C. contributed to data collection and statistical analyses and wrote the manuscript. X.J. and X.Z. (Xiaowei Zhu) designed the protocol and reviewed the manuscript. X.Z. (Xiaowen Zhu) and C.L. contributed to data collection. M.C. contributed to MRI data collection and analysis. Q.Z. and S.D. contributed to data collection and follow-up. W.W. is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** oby70153-sup-0001-Supinfo1.docx.