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CLINICAL TRIAL REPORT

# Progressive Weight Loss-Induced Remission of Insulin Resistance/Hyperinsulinemia and Improvements in Cardiovascular Risk Factors

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**Background:** Hyperinsulinemia (HI) is a common endocrine metabolic disorder in obesity and is closely associated with cardiovascular disease.

**Aim:** This study aims to investigate the effects of progressive weight reduction on HI and cardiovascular risk factors.

**Methods:** We enrolled 68 patients with overweight or obesity. Body composition assessments, clinical indicator sampling and a 75g-oral glucose tolerance test were conducted at baseline and after 12-month weight loss to assess HI and insulin sensitivity. And the people were divided into four groups based on the percent of weight loss (<10%, ~20%, ~30%, >30%) to study the remission of HI and changes in body composition and cardiovascular risk factors.

**Results:** A total of 66 participants were studied at the end. Progressive weight loss significantly reduced plasma glucose and insulin ($P<0.001$, $P_{for\ trend}<0.001$) and did not progressively reduce cardiovascular risk factors ($P_{for\ trend}<0.001$). The greater the percentage of weight loss, the greater the remission rate of insulin resistance and hyperinsulinemia ($P_{for\ trend}<0.001$), which reaches 100% when weight loss exceeds 30%. After adjusting for factors such as age, gender, and medication usage, remission of HI was still associated with progressive weight loss.

**Conclusion:** With progressive weight loss, people with overweight or obesity experienced further improvements in glycemic outcomes, body compositions, HI and insulin resistance.

**Keywords:** hyperinsulinemia, obesity, Insulin resistance, weight loss, body composition

## Introduction

Obesity is characterized by the abnormal accumulation of adipose tissue, surpassing the threshold of physiological normality, and posing a negative impact on health.[1] During the past 40 years, overweight and obesity have significantly risen in China, regardless of gender, age categories, and geographic areas, leading to significant national healthcare spending on the management of non-communicable diseases.[2,3] Considerable research has shown that obesity is associated with numerous metabolic abnormalities and diseases, including atherogenic dyslipidemia, metabolic associated steatosis liver disease (MASLD), obstructive sleep apnea syndrome, cardiovascular disease, and type 2 diabetes (T2D).[4–6]

As common metabolic disorders associated with obesity, insulin resistance (IR) and hyperinsulinemia (HI) have garnered significant attention. Recent studies have implicated HI in various pathological conditions, including cardiovascular disease,[7] inflammation, aging, obesity, and cancer.[8] Evidence continues to mount that HI is a consequence of excessive insulin secretion in relation to the level of IR, and can be dissociated with IR,[9] even more prevalent than IR.[10] Excessive insulin production is like a chronic fuel surplus, which causes β-cell failure and T2D by promoting further IR, weight gain and/or inflammation. A confirmed positive correlation exists between the state of obesity and insulin levels,

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which has been proven in both animal models and humans.[6] Furthermore, the recent emergence of the concept of selective insulin resistance, in which tissues resist insulin's influence on glucose transport while maintaining sensitivity in adipose tissue[11,12] caused a resurgence of interest in the relationship between obesity and HI.

As a primary treatment for T2D,[13] weight loss has conclusively and repeatedly demonstrated its effectiveness in preventing or delaying the onset of T2D in individuals with obesity,[14,15] and reduce multiple cardiovascular risk factors, such as blood sugar, blood lipids, and blood pressure. HI can be reduced with pharmaceutical, dietary, and physical interventions.[16] Inhibition of circulating insulin offered either temporary or permanent defense against the development of obesity.[16] Although the causal relationship between obesity and HI is inconclusive, these findings are still important to help us understand the reversibility of this form of islet β-cell dysfunction. Most treatment guidelines emphasize the importance of a team-based approach to obesity management and typically advocate for a moderate reduction in body weight, specifically, a 5% to 10% decrease over a period of 6 to 12 months to enhance metabolic function and health results.[17] A moderate decrease in body weight of 5% has improved glycemic control, and more substantial (10–25%) weight loss can achieve progressive improvement, including remission of T2DM.[5,13] However, the relationship between progressive weight loss and sustained alterations in insulin levels remains uncertain. We have not seen any studies that indicate the level of weight loss at which IR and HI can be completely remitted.

We hypothesize that progressive weight loss induced by both conventional medication and lifestyle guidance leads to progressive decreases in body fat, blood pressure, lipid profile and insulin levels. The aim of the current research was to conduct a prospective study in patients with obesity who accepted the combination of intensive lifestyle intervention and personalized medicine treatment, to explore the impact of moderate and progressive weight loss on body composition and remission of IR and HI and further explore appropriate weight-loss goals and potential pathophysiological mechanisms that might contribute to the prevention of HI and obesity-related disease progression.

# Methods

## Study Design and Participants

This prospective, non-randomized study was conducted between April 2021 and 2023 and included people (age 18 to 60, BMI≥24kg/m$^2$) who came to our outpatient clinic. Individuals were excluded if they 1) smoked, 2) consumed excessive alcohol (weekly alcohol intake >140 – 350 g/week for men and >210 – 420 g/week for women), 3) had a history of bariatric surgery, 4) were using medications that might disrupt insulin function, 5) had experienced significant weight loss (−3 kg) in the last 3 months, 6) suffered from bulimia or anorexia nervosa, 7) patient self-reported hyperthyroidism, type 1 or 2 diabetes. All participants recruited in this study underwent a comprehensive medical assessment at baseline, which included review of clinical history, physical examination, measurements of body composition, blood tests, and a 75-gram oral glucose tolerance test (OGTT). These evaluations were repeated for each participant after 12-month weight loss. Participants were divided into four groups based on weight loss percentage: group 1 with weight loss<10%, group 2 with weight loss 10~20%, group 3 with weight loss 20~30%, group 4 with weight loss>30%. Before their involvement, all subjects were required to sign a written informed consent document. The study protocol received approval from the Ethics Committee of Tianjin Union Medical Center (No. 2021C06), and the study was officially registered on www.chictr.org.cn with the registration number ChiCTR2100044305. The study complies with the Declaration of Helsinki. Before their involvement, all subjects were required to sign a written informed consent document.

## Interventions

All participants were entered into a 12-month intensive lifestyle therapy that included a high-protein diet and a moderate-intensity exercise lifestyle. The diet was designed individually with around 500 kcal of calories deducted from their total daily energy requirements assessed by InBody 770 and consisted of 50% carbohydrate, 25% protein, and 25% fat.[18] A 3-day diet records were collected to calculate energy and macronutrient intakes to assess subjects' implementation of the dietary intervention. The exercise intervention was designed to adhere to the FITT-VP (frequency, intensity, time, type of exercise, volume, and progression) principle recommended by the World Health Organization,[19] including at least 150 minutes per week of moderate-intensity aerobic physical activity (with a target heart rate monitored by an exercise

bracelet gradually increasing to 60% to 70% of the maximum heart rate). Meanwhile, resistance exercise should be performed for 20 minutes at a time, 2–3 times per week, to avoid extra muscle mass loss as weight loss.

A specialized endocrinologist has tailored a medication treatment plan for patients aimed at weight reduction. 20 participants received subcutaneous injections of 0.5 milligrams (mg) of semaglutide once a week, 45 participants took 1.5 grams of metformin daily, 22 participants took empagliflozin (10 mg) daily, and 3 participants took pioglitazone (15 mg) daily. During the initial assessment, 23 patients were diagnosed with newly developed type 2 diabetes, and their treatment was managed according to the Chinese Guidelines for the Prevention and Treatment of T2D.[20] Consequently, Therefore, they may have received a combination of the above two or three medications during intervention. Furthermore, none of the patients among them utilized insulin to manage their blood glucose levels. Participants were regularly contacted by phone to promote adherence, and they met with the study dietitian monthly for body weight measurement and to receive dietary and exercise counseling. All participants attended at least 10 individual consultations to ensure individualized weight loss.

## Sociodemographic and Clinical Information Collection

Baseline data collection encompassed gender, age, and medical history details, including blood pressure. A digital automatic blood pressure monitor was employed to measure blood pressure after a 10-minute period of rest.

## Anthropometric and Body Composition Assessments

Subjects arrived at the clinic before 8 AM after an overnight fast and underwent anthropometrical evaluations, including height and weight. Body mass index (BMI) was calculated as weight dividing height squared ($kg/m^2$). The subjects stood on the body composition analyzer (Inbody 770, Bio-space Inc., South Korea) with hands and feet aligned to the four electrodes to measure weight, body fat mass (BFM), fat free mass (FFM), skeletal muscle mass (SMM), percent of body fat (PBF), percent of fat free mass (PBF), visceral fat area (VFA), fat mass index (FMI) and skeletal mass index (SMI).

## Blood Sampling and Measurements

Blood tests were conducted at baseline and in the last week of 1-year intervention. Before obtaining blood samples, participants fasted overnight. Serum lipids were measured using an automatic biochemical analyzer (TBA-120FR, Toshiba, Tokyo). Glycated hemoglobin (HbA1c) was determined using a high-performance chromatography. The OGTT was performed before 8:00 AM after an overnight fast. At time 0, participants ingested a 75-g glucose load. Blood sampling was performed at 0, 60 and 120 min after glucose load to determine plasma glucose and insulin concentrations.

## Estimation of IR and β-Cell Function

The glucose and insulin levels during the OGTT are the most direct indicators for assessing insulin resistance and pancreatic function, including fasting plasma glucose (FPG), 1-hour postprandial glucose (1hPG), and 2-hour postprandial glucose (2hPG), along with fasting insulin (FINS), 1-hour postprandial insulin (1hINS), and 2-hour postprandial insulin (2hINS). To assess the stimulating effect of blood glucose and insulin secretion, the area under the curve (AUC) for both glucose and insulin, as well as the incremental area under the curve (iAUC) were calculated. Two indices were calculated to measure insulin sensitivity. The formula of the homoeostasis model assessment of insulin resistance (HOMA-IR) was (FPG×FINS)/22.5,[21] and the Matsuda insulin sensitivity index ($ISI_{Matsuda}$) was calculated as 10,000/square root ([FPG (mg/dL)×FINS] [mean glucose (mg/dL)×mean insulin]). The triglyceride-glucose index (TyG) index was calculated as ln[TG (mg/dL)× glucose (mg/dL)/2].[22] Insulinogenic Index at 60 minutes ($IGI_{60}$) was calculated as [Δinsulin (60–0 minutes)/Δglucose (60–0 minutes) (mg/dL)]. The disposition index (DI) was calculated by multiplying $IGI_{60}$ multiplied by $ISI_{Matsuda}$ reflecting β-cell function by assessing the insulin secretion ability to reflect the IR state of each participant. Except for special annotations, included values of glucose and insulin were in units of mmol/L and mU/L, respectively.

## Definition of HI and HI Remission

HI is defined as FINS > 15 mU/L or 2hINS > 80 mU/L. Remission HI is defined as FINS < 15 mU/L and 2hINS < 80 mU/L.[10] We define fasting HI (FHI) as FINS > 15 mU/L and 2hINS < 80 mU/L, postprandial HI (PHI) is defined as 2hINS > 80 mU/L and FINS < 15 mU/L.

## Statistical Analysis

Continuous data were expressed as mean ± standard deviation or median (interquartile range), depending on whether its distribution is normal. The normality of the distribution was assessed using the Shapiro–Wilk test. Paired student's *t* test and Wilcoxon signed-rank test were used to compare the differences in continuous values of patients at baseline and after intervention. The homogeneity of variance was assessed using the Levene test. A One-Way ANOVA was performed for trend analysis. Kruskal–Wallis tests and ANOVA were used for subgroup analyses. Furthermore, Spearman correlation analysis was performed to evaluate the relationship between changes of body composition and AUC-INS after intensive lifestyle intervention. Differences in categorical variables were assessed using Fisher's exact test or the chi-square test. Ordinal multivariate multifactor logistic regression was used to analyze the relationship between weight reduction and the alleviation of hyperinsulinemia. The delta variation was calculated according to the formula, Δ= post − pre, Δ% = Δ× 100/pre. *P* value < 0.05 was considered to indicate statistical significance. Analyses were conducted using SPSS 26.0 software.

# Results

## Trial Population

In this study, a total of 68 participants were enrolled, with 66 completing all visits. One subject withdrew from the study due to challenges in adhering to the lifestyle intervention, and one subject was excluded because of a high glucose level caused by self-discontinuation of the medicine. These people were excluded before the examination following the intervention and thus were not included in the analyses. Characteristics of the participants before and after the 12-month intensive intervention are shown in Table 1. Changes in body composition and metabolic indices for each group are shown in Table 2.

**Table 1** Clinical Characteristics of Study Population Before and After Intervention

| | Before | After | Difference (95% CI) | P |
|---|---|---|---|---|
| Demographics | | | | |
| Male/Female | 27/39 | – | – | – |
| Age (years) | 31.97 ± 11.74 | – | – | – |
| Body composition | | | | |
| Height (cm) | 167.71 ± 8.89 | 167.80 ± 8.83 | 0.67 (0.46, 0.79) | 0.248 |
| Weight (kg) | 102.65 ± 19.96 | 84.68 ± 16.26 | −17.97 (−20.89, −15.05) | <0.0001 |
| Body mass index (kg/m$^2$) | 36.23 ± 5.33 | 29.97 ± 4.79 | −6.26 (−7.22, −5.30) | <0.0001 |
| Body fat mass (kg) | 45.30 ± 12.12 | 31.36 ± 10.49 | −13.93 (−16.32, −11.55) | <0.0001 |
| Fat free mass (kg) | 57.35 ± 10.79 | 53.32 ± 9.68 | −4.03 (−4.84, −3.22) | <0.0001 |
| Skeletal muscle mass (kg) | 32.07 ± 6.49 | 29.41 ± 5.79 | −2.65 (−3.16, −2.15) | <0.0001 |
| Percent body fat (%) | 43.78 ± 5.90 | 36.54 ± 7.28 | −7.24 (−8.54, −5.94) | <0.0001 |
| Percent fat free mass (%) | 56.23 ± 5.90 | 63.46 ± 7.29 | 7.23 (5.93, 8.54) | <0.0001 |
| Visceral fat area (cm$^2$) | 207.85 ± 45.10 | 148.44 ± 49.87 | −59.41 (−69.78, −49.04) | <0.0001 |
| Fat mass index | 16.05 ± 3.97 | 11.18 ± 3.72 | −4.87 (−5.67, −4.07) | <0.0001 |
| Skeletal muscle index | 8.58 ± 1.09 | 7.88 ± 1.03 | −0.71 (−0.82, −0.60) | <0.0001 |
| Glycemic factors | | | | |
| HbA1c (%) | 6.24 ± 1.36 | 5.35 ± 0.33 | −0.89 (−1.21, −0.57) | <0.0001 |
| Fasting plasma glucose (mmol/L) | 5.11 (4.69, 6.18) | 4.44 (4.10, 4.73) | −1.49 (−2.06, −0.91) | <0.0001 |
| 1 hour plasma glucose (mmol/L) | 10.68 (8.85, 13.59) | 7.87 (6.82, 9.60) | −3.07 (−3.94, −2.21) | <0.0001 |
| 2 hour plasma glucose (mmol/L) | 8.68 (7.71, 12.07) | 6.19 (5.49, 7.38) | −3.90 (−4.92, −2.87) | <0.0001 |
| Fasting insulin (μU/mL) | 23.25 (15.78, 39.20) | 12.38 (8.78, 15.65) | −16.93 (−22.36, −11.49) | <0.0001 |
| 1 hour plasma insulin (μU/mL) | 176.45 (86.89, 200.00) | 95.29 (58.27, 178.03) | −36.56 (−52.51, −20.61) | <0.0001 |
| 2 hour plasma insulin (μU/mL) | 151.35 (100.55, 200.00) | 72.28 (41.79, 115.58) | −65.97 (−80.92, −51.01) | <0.0001 |
| AUC-GLU (mmol × h/l) | 17.69 (14.85, 22.42) | 13.57 (11.80, 15.27) | −5.77 (−7.34, −4.20) | <0.0001 |
| AUC-INS (μU/mL× h/l) | 262.39 (173.13, 312.08) | 141.24 (89.25, 246.39) | −78.01 (−100.56, −55.45) | <0.0001 |
| HOMA-IR | 5.46 (3.96, 10.17) | 2.49 (1.64, 3.03) | −5.84 (−8.03, −3.65) | <0.0001 |

(*Continued*)

**Table 1** (Continued).

| | Before | After | Difference (95% CI) | P |
|---|---|---|---|---|
| Insulinogenic index at 60 min | 1.31 (0.66, 1.91) | 1.49 (0.86, 2.33) | 0.45 (0.01, 0.91) | 0.112 |
| Matsuda insulin sensitivity index | 1.70 (1.20, 2.17) | 4.05 (2.67, 5.75) | 2.53 (1.85, 3.21) | <0.0001 |
| Disposition index | 1.93 (0.99, 3.65) | 5.20 (2.96, 8.04) | 6.79 (2.01, 11.58) | <0.0001 |
| The Triglyceride-glucose index | 9.09 (8.87, 9.34) | 8.71 (8.56, 8.97) | −0.38 (−0.48, −0.27) | <0.0001 |
| Cardiovascular risk factors | | | | |
| Systolic Blood Pressure (mmHg) | 138.00 (125.25, 153.00) | 129.50 (120.00, 135.00) | −11.92 (−14.78, −9.07) | <0.0001 |
| Diastolic Blood Pressure (mmHg) | 82.50 (75.25, 90.00) | 78.00 (71.75, 82.00) | −5.74 (−7.37, −4.12) | <0.0001 |
| Triglycerides (mmol/L) | 1.59 (1.24, 2.03) | 1.02 (0.79, 1.43) | −0.84 (−1.38, −0.31) | <0.0001 |
| Total Cholesterol (mmol/L) | 4.91 (4.37, 5.68) | 4.46 (3.76, 4.95) | −0.61 (−0.87, −0.36) | <0.0001 |
| LDL Cholesterol (mmol/L) | 3.06 (2.56, 3.66) | 2.77 (2.30, 3.27) | −0.39 (−0.59, −0.18) | <0.0001 |
| HDL Cholesterol (mmol/L) | 1.13 (1.07, 1.30) | 1.21 (1.08, 1.43) | 0.07 (0.01, 0.13) | 0.014 |

**Notes**: Continuous variables are expressed as mean ± standard deviation or median with interquartile range. Differences from baseline are expressed as mean and 95% confidence interval. The p values were calculated using Paired *t*-test or Wilcoxon signed-rank test according to the type of variables.
**Abbreviations**: HbA1c glycosylated hemoglobin; INS, insulin; GLU, glucose; AUC, area under the curve; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence intervals.

**Table 2** Clinical Characteristics Changes of the Study Population After Intervention According to Weight Loss Groups

| Variables | Group 1 (n=15) | Group 2 (n=31) | Group 3 (n=11) | Group 4 (n=9) | *P* | $P_{for\ trend}$ |
|---|---|---|---|---|---|---|
| Body composition | | | | | | |
| Weight loss | −6.46 ± 3.20 | −13.92 ± 3.47 | −26.58 ± 6.43 | −40.59 ± 6.74 | <0.0001 | <0.0001 |
| Weight loss% | −6.76 ± 2.78 | −14.09 ± 2.42 | −24.39 ± 3.11 | −34.11 ± 3.03 | <0.0001 | <0.0001 |
| Excess weight loss% | −22.22 ± 14.21 | −38.72 ± 9.58 | −70.55 ± 20.50 | −81.43 ± 14.73 | <0.0001 | <0.0001 |
| Body mass index ($kg/m^2$) | −2.36 ± 1.09* | −5.02 ± 1.01* | −8.85 ± 1.67* | −13.83 ± 2.57* | <0.0001 | <0.0001 |
| Body fat mass (kg) | −4.69 ± 2.31* | −11.08 ± 3.46* | −19.18 ± 5.07* | −32.74 ± 7.17* | <0.0001 | <0.0001 |
| Fat free mass (kg) | −1.77 ± 1.80* | −1.83 ± 2.25* | −7.75 ± 2.78* | −7.84 ± 2.31* | <0.0001 | <0.0001 |
| Skeletal muscle mass (kg) | −1.15 ± 1.04* | −1.90 ± 1.30* | −4.73 ± 1.74* | −5.21 ± 1.41* | <0.0001 | <0.0001 |
| Percent body fat (%) | −2.37 ± 1.80* | −5.79 ± 2.50* | −9.69 ± 2.90* | −17.37 ± 3.51* | <0.0001 | <0.0001 |
| Percent fat free (%) | 2.37 ± 1.80* | 5.79 ± 2.50* | 9.69 ± 2.90* | 17.37 ± 3.51* | <0.0001 | <0.0001 |
| Visceral fat area ($cm^2$) | −20.79 ± 11.60* | −46.67 ± 18.29* | −81.38 ± 28.43* | −140.81 ± 20.42* | <0.0001 | <0.0001 |
| Fat mass index | −1.71 ± 0.84* | −4.00 ± 1.10* | −6.43 ± 1.57* | −11.19 ± 2.68* | <0.0001 | <0.0001 |
| Skeletal muscle index | −0.29 ± 0.22* | −0.60 ± 0.25* | −1.11 ± 0.27* | −1.29 ± 0.39* | <0.0001 | <0.0001 |
| Glycemic factors | | | | | | |
| HbA1c (%) | −0.51 ± 0.92* | −0.76 ± 1.33* | −0.99 ± 1.06* | −1.84 ± 1.71* | 0.092 | 0.014 |
| FPG (mmol/L) | −0.67 ± 0.94* | −1.04 ± 1.47* | −1.50 ± 1.79* | −4.51 ± 4.48* | <0.0001 | <0.0001 |
| 1hPG (mmol/L) | −1.57 ± 2.43* | −2.31 ± 2.14* | −3.30 ± 2.30* | −7.92 ± 5.82* | <0.0001 | <0.0001 |
| 2hPG (mmol/L) | −2.47 ± 3.16* | −3.31 ± 3.80* | −4.53 ± 3.44* | −7.39 ± 5.87* | 0.025 | 0.002 |
| FINS (μU/mL) | −14.01 ± 19.37* | −9.81 ± 12.03* | −30.73 ± 32.62* | −29.44 ± 28.17* | 0.011 | 0.016 |
| 1hINS (μU/mL) | −22.85 ± 63.74 | −24.82 ± 60.20* | −53.57 ± 72.33 | −79.03 ± 60.54* | 0.095 | 0.02 |
| 2hINS (μU/mL) | −55.70 ± 53.40* | −52.48 ± 55.74* | −95.21 ± 71.39* | −93.80 ± 63.96* | 0.091 | 0.047 |
| AUC-GLU (mmol × h/L) | −3.14 ± 4.05* | −4.49 ± 4.27* | −6.31 ± 4.69* | −13.87 ± 10.62* | <0.0001 | <0.0001 |
| AUC-INS (μU/mL× h/L) | −57.70 ± 88.45* | −55.96 ± 82.15* | −116.55 ± 100.68* | −140.65 ± 87.19* | 0.030 | 0.009 |
| HOMA-IR | −3.81 ± 5.65* | −3.12 ± 3.83* | −9.13 ± 9.43* | −15.08 ± 17.88* | 0.002 | 0.001 |
| $IGI_{60}$ | 0.09 ± 0.89* | 0.45 ± 1.73* | 0.39 ± 1.31* | 1.13 ± 3.54* | 0.627 | 0.217 |
| $ISI_{Matsuda}$ | 1.49 ± 1.29* | 1.77 ± 1.70* | 2.77 ± 3.63* | 6.58 ± 1.92* | <0.0001 | <0.0001 |
| Disposition index | 2.77 ± 3.63* | 3.75 ± 6.62* | 4.76 ± 3.19* | 26.45 ± 48.69* | 0.011 | 0.04 |
| TyG | −0.33 ± 0.37* | −0.31 ± 0.43* | −0.36 ± 0.37* | −0.69 ± 0.47* | 0.128 | 0.045 |

(*Continued*)


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**Table 2** (Continued).

| Variables | Group 1 (n=15) | Group 2 (n=31) | Group 3 (n=11) | Group 4 (n=9) | *P* | $P_{for\ trend}$ |
|---|---|---|---|---|---|---|
| Cardiovascular risk factors | | | | | | |
| SBP (mmHg) | −10.47 ± 9.75* | −12.42 ± 12.10* | −12.00 ± 9.95* | −12.56 ± 15.78* | 0.958 | 0.708 |
| DBP (mmHg) | −4.27 ± 4.42* | −5.42 ± 6.77* | −5.73 ± 4.00* | −9.33 ± 10.51* | 0.330 | 0.078 |
| Triglycerides (mmol/L) | −0.13 ± 0.71 | −0.62 ± 0.71* | −2.38 ± 4.93* | −0.91 ± 0.70* | 0.053 | 0.139 |
| Total Cholesterol (mmol/L) | −0.42 ± 0.85 | −0.52 ± 1.01* | −0.88 ± 1.41 | −0.95 ± 0.96* | 0.487 | 0.156 |
| LDL Cholesterol (mmol/L) | −0.12 ± 0.58 | −0.37 ± 0.81* | −0.47 ± 1.10 | −0.82 ± 0.84* | 0.249 | 0.045 |
| HDL Cholesterol (mmol/L) | −0.05 ± 0.22 | 0.05 ± 0.20 | 0.25 ± 0.27* | −0.08 ± 0.27 | 0.014 | 0.056 |

**Notes**: Four groups of weight loss: G1, <10%; G2,10% ~ 2°%; G3,20% ~ 30.%; G4, >30%. Continuous variables are expressed as median ± standard deviation or interquartile range. P values are provided for comparisons with baseline. *P < 0.05 vs baseline in each group. $P_{for\ trend}$ indicated the change trend of the clinical indices among the four groups and was calculated by analysis of variance and Mann–Whitney *U*-test. $P_{for\ trend}$ <0.05 was considered statistically significant.
**Abbreviations**: HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose;1hPG, 1 hour plasma glucose; 2hPG, 2 hour plasma glucose; FINS, fasting plasma insulin; 1hINS, 1 hour plasma insulin; 2hINS, 2 hour plasma insulin, INS, insulin; GLU, glucose; AUC, area under the curve; HOMA-IR, homeostasis model assessment of insulin resistance; $IGI_{60}$, insulinogenic index at 60 min; $ISI_{Matsuda}$, Matsuda insulin sensitivity index; DI, disposition index. TyG, the triglyceride-glucose index; SBP, systolic blood Pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

## Weight Loss and Body Composition After Intervention

After 12-month intensive intervention, the body weight of participants reduced by an average of 18.0 kg, which was equivalent to an average decrease in body weight of 16.9%. And the people were divided into four groups to study according to the percent of weight loss% (1~10%, ~20%, ~30%, >30%). Overall, EWL, BMI, BFM, FFM, SMM, PBF, VFA, FMI and SMI decreased significantly ($P$<0.0001) after 12-month intervention. From first group to last group, the reduction in the above physical parameters continued with increase of weight loss ($P_{for\ trend}$<0.0001). Although FFM reduced after weight loss, PFF increased with progressive weight reduction. Changes in body composition in the overall population and in each group after weight loss are shown in Table 1 and Table 2, respectively.

## Glycemic Factors (Insulin Sensitivity and β-Cell Function)

Overall, glycemic control and insulin response improved after 12-month weight loss. HbA1c, glucose, insulin, AUC-GLU, AUC-INS and iAUC-INS were all reduced after the 12-month intervention (Table 1). As the percentage of weight loss increases, the metabolic benefits gradually improve ($P$<0.0001, $P_{for\ trend}$<0.0001). Although moderate weight loss (<10% weight loss) significantly decreased FINS and 2hINS (Figure 1A), blood glucose is better controlled (Table 2). Regardless of the weight loss effects, FINS, 2hINS, and iAUC decreased after weight loss in all groups (Table 2 and Figure 1A–D). AUC-INS significantly reduced after initial weight loss, and the change approximately doubled following a 30% loss in weight (Table 2 and Figure 1D). After 12 months of intervention, insulin sensitivity improved compared to baseline in each group, while IGI60 remained unchanged (Table 2). HOMA-IR and TyG continued to decrease with progressive weight loss ($P$<0.05, $P_{for\ trend}$<0.05), $ISI_{Matsuda}$ increased gradually between the four groups (Table 2). DI as an indicator of insulin secretion capacity taking into account IR,[21] is regarded as a more informative and applicable measure of β-cell functionality. In participants with overweight and obesity, DI increased compared with baseline, and the rise after 30% weight loss was approximately tenfold after moderate weight loss (Table 2).

## Cardiovascular Factors

All cardiovascular risk factors involved improved after weight loss. There was no difference in the decrease of SBP and DBP among the four weight loss groups. TC and LDL-C also decreased in group 2 and 4, HDL-C only increased in group 3. Numerically, TG in groups 2, 3, and 4 shows a progressive decrease, but there is no statistical trend. The results are demonstrated in Table 1 and Table 2.

## Improvement Rates of HI, IR and Delayed Insulin Secretion

At inclusion, most of the subjects were in an imbalance of insulin secretion and utilization, 92.4% of participants had HI, 90.9% had IR (HOMA-IR≥2.69), and 68.18% had delayed insulin secretion. After 0~10% weight loss, only 2 of 13 patients (15.38%)

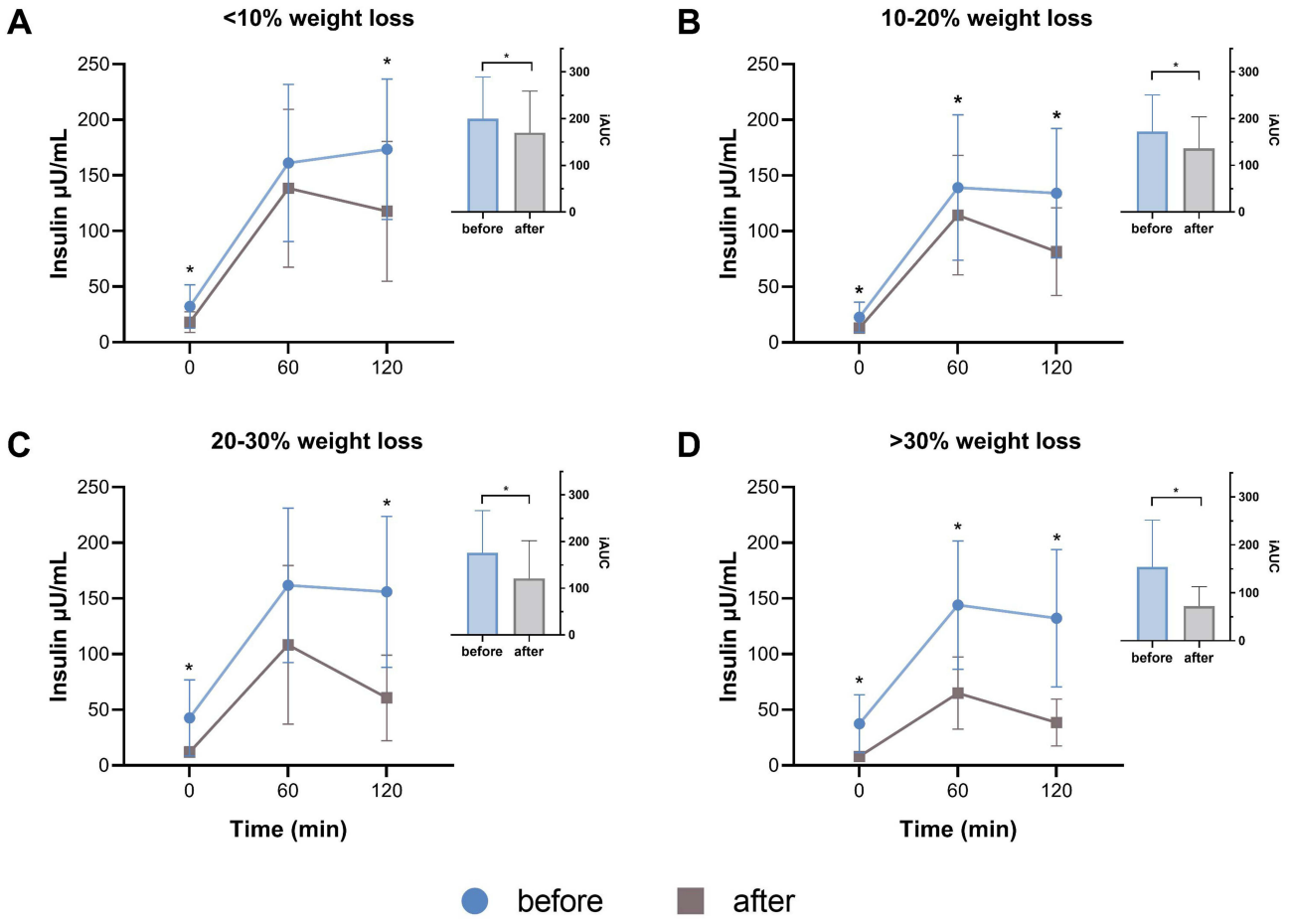


**Figure 1** Insulin responses during the oral glucose challenge in four weight loss group. (**A**) Effect of <10% weight loss on insulin response. (**B**) Effect of 10–20% weight loss on insulin response. (**C**) Effect of 20–30% weight loss on insulin response. (**D**) Effect of >30% weight loss on insulin response.*p<0.05 was considered statistically significant.
**Abbreviation**: iAUC, Incremental Area Under the Curve.

achieved relief from HI, 3 of 14 participants (21.43%) achieved relief from IR, and 6 of 13 patients (46.15%) returned to the normal peak time of insulin. The results indicated that with the increase in weight loss, the improvement rates of HI, FHI, PHI and IR considerably improved ($P<0.05$, $P_{for\ trend}<0.01$), and all of the previously mentioned abnormalities in insulin secretion and utilization got 100% alleviation when the weight loss percentage reached 30%. Figure 2 depicts the results.

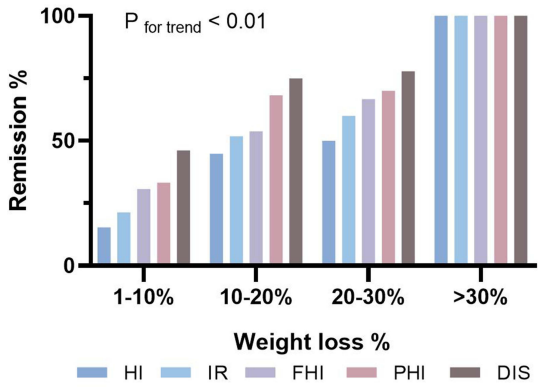


**Figure 2** Remission rate of early metabolic abnormalities in four weight loss groups.Trend test was conducted by One-Way ANOVA. P for trend <0.05 was considered statistically significant.
**Abbreviations**: HI, hyperinsulinemia; IR, insulin resistance; FHI, fasting hyperinsulinemia; PHI, postprandial hyperinsulinemia; DIS, delayed insulin secretion.


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## Association Between Weight Loss and HI After Intervention

In order to evaluate the relationships between weight loss and ΔAUC-INS, we separately analyzed the association between the reduction of AUC-INS and weight loss percentage, VFA, BFM and SMM. Spearman correlation analysis showed that the change of weight loss ($r$=0.35, $p$<0.001, Figure 3A), VFA ($r$=0.37, $p$<0.001, Figure 3B), BFM ($r$=0.36, $p$<0.001, Figure 3C) and SMM ($r$=0.27 $p$<0.001, Figure 3D) had a moderate strength correlation to ΔAUC-INS. Results were demonstrated in Figure 3. Taking into account the impact of medication on weight reduction, we analyzed the differences in the types and number of medications used among four groups (Table 3). The results show that there were no differences in the types and quantities of medications used among the four groups. Multivariate multifactor logistic regression analysis confirmed that HI relief can promote weight loss (odds ratio (OR): 13.56 (95% confidence intervals (CI) 12.35, 14.77), $p$<0.001). Neither gender, nor medications, nor family history of T2D, nor conventional antidiabetic drug use, influenced its effectiveness (Table 4).

# Discussion

The results from this prospective study demonstrate that weight loss induced by lifestyle and medicine treatment decreases fat mass, blood pressure and blood lipids, improves glucose and insulin responses. Only IR, HI, insulin, glucose control and body composition progressively improved with stepwise weight loss. Moreover, remission in HI is significantly associated with better weight loss.

During 12-month supervise intervention, about 94% of participants achieved the goal of 5–10% weight loss, more than 13.7% of participants successfully lost more than 30% of their weight, individuals included lost an average of 7.24% of PBF. This finding is superior to the results of a randomized trial combining Liraglutide with exercise for 52 week.[23]

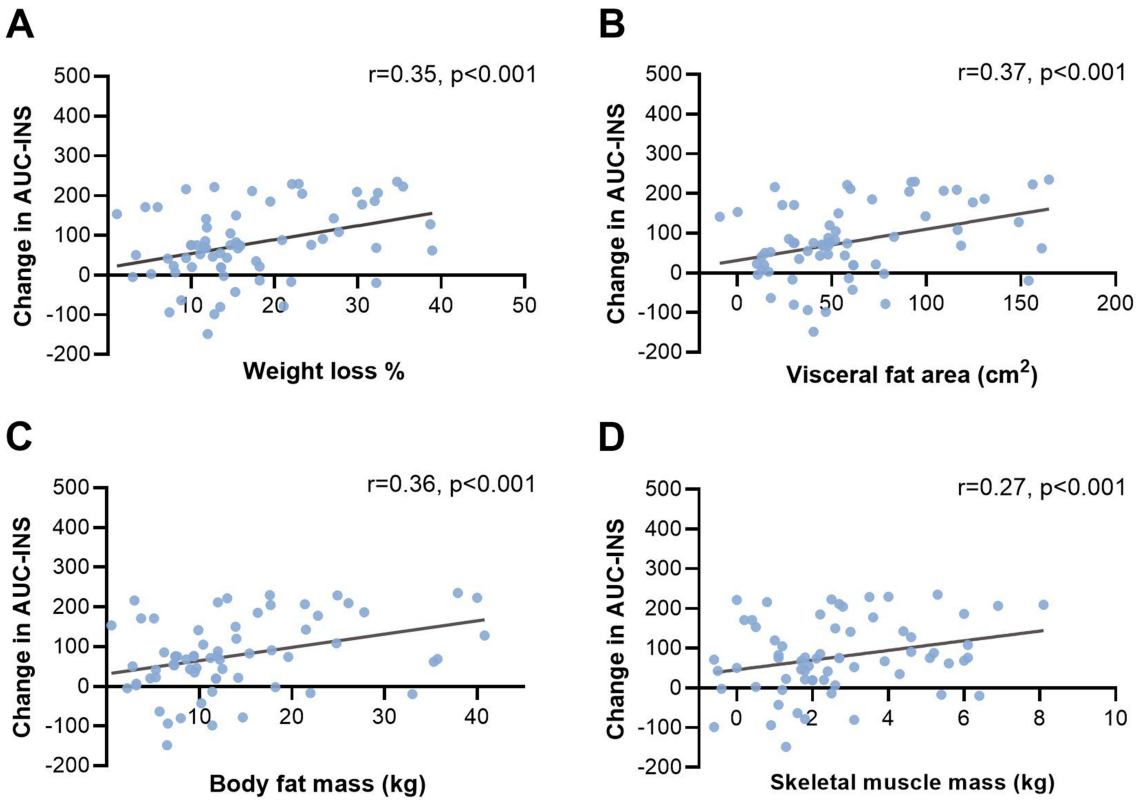


**Figure 3** Correlation between changes in body composition and AUC-INS decrease. (**A**) Correlation between change in AUC-INS and weight loss%. (**B**) Correlation between change in AUC-INS and visceral fat area. (**C**) Correlation between change in AUC-INS and body fat mass. (**D**) Correlation between change in AUC-INS and skeletal muscle mass.p<0.05 was considered statistically significant. Spearman correlation analysis was performed to evaluate the relationship between changes of body composition and AUC-INS.

**Abbreviations**: INS, insulin; AUC, area under the curve.

**Table 3** The Usage of Antidiabetic Medications Among Different Weight Loss Groups

| Variables | Group 1 (n=15) | Group 2 (n=31) | Group 3 (n=11) | Group 4 (n=9) | $\chi^2$ | P |
|---|---|---|---|---|---|---|
| Types of antidiabetic medications | | | | | | |
| GLP-1 receptor agonists | 2 (12.5) | 11 (23.9) | 5 (29.4) | 2 (18.2) | 11.077 | 0.208 |
| Metformin | 9 (56.3) | 21 (45.7) | 9 (52.9) | 6 (54.5) | | |
| SGLT-2 inhibitors | 2 (12.5) | 14 (30.4) | 3 (17.6) | 3 (27.3) | | |
| Thiazolidinediones | 3 (18.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | | |
| Number of antidiabetic medications | | | | | | |
| 0 | 5 (33.3) | 8 (25.8) | 2 (18.2) | 3 (33.3) | 2.873 | 0.987 |
| 1 | 6 (40.0) | 9 (29.0) | 4 (36.4) | 3 (33.3) | | |
| 2 | 2 (13.3) | 5 (50.0) | 2 (18.2) | 1 (11.1) | | |
| 3 | 2 (13.3) | 9 (29.0) | 3 (27.3) | 2 (22.2) | | |

**Notes**: P was calculated by Fisher's exact test and the chi-square test. Four groups of weight loss: G1, <10%; G2, 10% ~ 20%; G3, 20% ~ 30%; G4, >30. The values in parentheses indicate the proportions of different types and quantities of medication within the corresponding groups.
**Abbreviations**: GLP-1, Glucagon like peptide-1; SGLT-2, sodium-glucose transporter 2.

**Table 4** Correlation Between Weight Loss and Remission of HI

| Characteristic | Subgroups | P | OR (95% CI) |
|---|---|---|---|
| Age | | *0.026 | 0.95(0.91–0.99) |
| Gender | Male | 0.428 | 0.64(−0.46–1.74) |
| | Female | – | 1 (Reference) |
| T2D family history | No | 0.146 | 2.42(1.23–3.61) |
| | Yes | – | 1 (Reference) |
| Medications | 0 | 0.631 | 0.72(−0.65–2.08) |
| | 1 | 0.065 | 0.28(−1.08–1.64) |
| | 2 | 0.229 | 0.38(−1.20–1.96) |
| | 3 | – | 1 (Reference) |
| HI | Remission | *0.001 | 13.56(12.35–14.77) |
| | Non-remission | – | 1 (Reference) |

**Notes**: A significant P value (P < 0.05) is marked in bold in the results section. Ordinal multivariate multifactor logistic regression was performed to analyze the relationship between weight loss and the remission of HI. *p<0.05 was considered statistically significant.
**Abbreviations**: T2D, Type 2 diabetes; OR, odds ratio; CI: confidence intervals.

Losing weight too quickly leads to more loss of FFM during weight loss during the dynamic weight loss phase. This finding was reported by Fogarasi A et al.[24,25] But since weight loss has an effect on FFM, we calculated PFF to evaluate the contribution of FFM to lost weight, which is fat-free mass as a percentage of body weight. With our lifestyle and medicine interventions, PFF gradually increased after weight loss. These findings may suggest that a high-protein diet combined with a moderate-intensity exercise lifestyle may contribute to the preservation of fat-free mass during weight loss. Furthermore, FFM is a crucial factor of the magnitude of resting metabolic rate (RMR)[26] and also a risk factor for weight regain, so a weight-reduction plan that maintains the FFM may help prevent future weight regain.

Modest weight loss has a strong correlation with improved glycemia in people with obesity and either have diabetes or not,[13,27,28] and it is not limited to diabetes treatment. A study showed that improvement in FPG and HbA1c is observed beginning at 2<5% weight reduction,[29] and the benefits to glycemic outcomes increase in a direct and linear manner as the degree of weight loss increases. This is also confirmed by our results. Overweight and obesity have been confirmed to be

closely related to IR and HI.[30] Obesity can lead to a diminished response of the body to insulin, causing the pancreas to secrete more insulin to maintain normal blood glucose levels, which further exacerbates HI. Conversely, HI also promotes the development of insulin resistance and obesity. Recent studies have indicated that HI may occur earlier than IR and obesity.[31] The interactions among these three factors not only increase the risk of T2D but are also closely related to the progression of various pathological processes, such as aging, tumors, and inflammation.[8] Therefore, weight loss, as an effective strategy to improve insulin sensitivity and reduce circulating HI, can play a crucial role in preventing the early onset and progression of related diseases. We found that remission of HI began at <10% weight loss, and progressive decreases in HI are associated with further weight loss. Insulin sensitivity assessed by HOMA-IR, TyG and ISI also improved after progressive weight loss. The $IGI_{60}$ was unchanged in response to lifestyle-induced weight loss, which measures the β-cell response based on the change in plasma glucose level.[32] Consequently, the rise in DI following weight loss induced by the 12-month lifestyle intervention was primarily due to the improvement in IR. The trend of improvements in IR that we observed parallels the enhancements noted in a clinical trial that achieved 5%, 11% or 16% and weight loss.[28] Our results extend similar improvements to participants with obesity after 20~30%, >30% weight loss. Previous studies have shown that improvements in TC and SBP begin with a 2–5% weight loss. Decreases in DBP and HDL-C started with 5–10% weight loss, and the greater the weight loss, the greater the risk factor benefit.[29] In our results, SBP and DBP began to decrease at <10% weight loss, but we did not observe an increase in cardiovascular risk factor benefits with further weight loss, possibly because the trials were conducted in a small number of individuals, which may have limited their ability to detect statistically significant effects. HI and IR are two key early events in the path of an imbalance of glycemic homeostasis that influence each other and break the cascade of homeostasis that causes the occurrence and development of T2D. Recently, there has been growing evidence that suggests that HI is regarded as the primary event that secondarily causes IR and T2D.[30] Recent studies have shown that the combined use of antidiabetic medications, such as GLP-1 receptor agonists, along with lifestyle interventions leads to better weight loss and improved pancreatic function in obese patients compared to lifestyle interventions alone.[33] Therefore, medications may have a direct impact on insulin resistance and hyperinsulinemia. To minimize the influence of this impact on weight loss and the improvement of HI and IR, we conducted a multivariable logistic regression analysis, adjusting for medication use, age, gender, and family history. The results indicated that the improvement in HI still predicts better weight loss. Therefore, focusing on the relationships between progressive weight loss and remission of HI may help to prevent T2D in the early stage.

There were still some limitations in our study. One limitation of our study is that it was conducted at a single academic research center in China with a relatively small sample size; thus, the results obtained in this research might not be applicable to other populations. Secondly, as our intervention program includes moderate to high-intensity exercises, it may not be suitable for certain populations, such as older persons (>65 years of age), people with low adherence or those who are restricted in their ability to do moderate-intensity exercise. Additionally, this study is observational, and the treatments received by the participants could directly lead to weight reduction and the HI. Therefore, we only discuss the association between the two in this study and propose the hypothesis that there may be a causal relationship between them. However, the causality still needs to be confirmed by further clinical and mechanistic research.

The findings of the current study illustrate the significant therapeutic effects of progressive weight loss on metabolic function in individuals with obesity. Our current findings could facilitate the development of individualized prevention programs targeting obesity at-risk phenotypes and reinforce the key role of HI remission in the prevention and treatment of obesity and T2D. Weight loss brings numerous benefits, and only the relationships of glucose-insulin regulation and cardiovascular risk factors with weight loss and body composition were studied in this trial. The benefits of progressive weight reduction for other obesity comorbidities such as polycystic ovary syndrome, obstructive sleep apnea syndrome and long-term benefits need to be further studied. Furthermore, more research is required to determine whether the lifestyle intervention-induced remission of HI leads to better prevention of T2D and metabolic diseases and to further study the relevant molecular mechanisms.

## Conclusions

In summary, progressive weight loss brought persistent improvements in body composition and metabolism factors, strongly associated with stepwise improvements in HI and IR. Moreover, the treatment of hyperinsulinemia can facilitate more effective weight loss.

## Data Sharing Statement

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author, L.C.J (Email: li_chunjun@126.com), upon reasonable request.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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