BMC Medicine

RESEARCH

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Effect of hypoglycemic agents with weight loss effect plus a high protein diet and moderate exercise on diabetes remission in adults with obesity and type 2 diabetes: a randomized controlled trial

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Abstract

Background This study aimed to explore the effects of hypoglycemic agents with weight loss effect plus a high protein diet and moderate exercise on weight loss and diabetes remission in adults with obesity and newly diagnosed prediabetes/type 2 diabetes (T2D).

Methods Participants with obesity and newly diagnosed prediabetes or T2D ($n=61$) were randomly allocated to standard treatment group (conventional medication and lifestyle guidance for 12 months) and intensive treatment group (in addition to conventional medication, a high protein diet and moderate exercise were given for 12 months).

Results By month 12, 60 (98.4%) participants completed the 12-month follow-up visit. In the intensive treatment group, 73.33% patients in the prediabetes subgroup returned to normoglycemia and the diabetes remission rate was 86.67% in the diabetes subgroup, which were much higher than the remission rate of prediabetes subgroup (7.69%) and diabetes subgroup (16.67%) in the standard treatment group ($P<0.001$). The mean weight change was − 19.29 kg (95% CI, − 22.95 to − 15.63) in the intensive treatment group and − 1.52 kg (95% CI, − 5.12 to 2.07) in the standard treatment group from baseline after intervention. The weight change between the two groups was significantly different (net difference, − 17.77 kg; 95% CI, − 22.90 to − 12.64; $P<0.001$). Percent of body fat, visceral fat area, and hepatic controlled attenuation parameter value reduced significantly in the intensive treatment group compared to the standard treatment group ($P<0.001$).

Conclusions Hypoglycemic agents with weight loss effect plus a high protein diet and moderate exercise could lead to a considerable proportion of patients with diabetes achieving diabetes remission.

Trial registration chictr.org.cn ChiCTR2100044305.

Keywords Obesity, Type 2 diabetes, Remission, Hypoglycemic agents, Weight loss effect, High protein diet, Moderate exercise

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Background

The prevalence of obesity is increasing drastically in China in the past decades due to westernized dietary patterns and lack of physical activity [1]. Obesity can cause insulin resistance (IR) and the development of type 2 diabetes (T2D) through a variety of biological pathways. T2D and its related severe complications have become major public health issues both in China and abroad [2]. Effective lifestyle intervention in people with prediabetes can lead to a significantly reduced incidence of diabetes, which has been confirmed in the China Da Qing Diabetes Prevention Study (CDQDPS) [3], Diabetes Prevention Program (DPP) in the USA [4], and Diabetes Prevention Study (DPS) in Finland [5]. Moreover, sustained diabetes remission had been achieved through effective weight management in the Diabetes Remission Clinical Trial (DiRECT) conducted in the UK [6], which has challenged the long-held view that diabetes is an unremittable condition requiring permanent pharmacotherapy. Regarding the approaches of lifestyle intervention in DiRECT and the subsequent Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) trial done in the Middle East and north Africa region [7], low-calorie formula meal products were adopted to replace total diet in the early phase of dietary intervention followed by stepwise food reintroduction. In addition, the frequency, intensity of aerobic exercise and resistance exercise were less concerned in both the two studies. Although no serious adverse events leading to withdrawal were reported in DiRECT and DIADEM-I study [6, 7], the relatively high dropout rate suggested that this dietary pattern might be unacceptable to some people. The dropout rates in the DiRECT and DIADEM-I studies were 8% and 7%, respectively. Thus, improving the acceptability of lifestyle intervention approaches might be of critical importance to raise the patients' compliance, improve weight loss effect and even increase diabetes remission rate. Therefore, this study aimed to conduct a randomized controlled study in patients with obesity and newly diagnosed prediabetes or T2D to assess the effects of supervised weight management that involved a high protein diet and moderate exercise plus hypoglycemic agents with weight loss effect, on weight loss, body composition and diabetes remission, and further explore the potential pathophysiological mechanisms that might contribute to diabetes remission.

Methods

Study design and participants

This study was a randomized, controlled clinical trial conducted in people aged 18 to 60 years with obesity and new-onset of prediabetes or T2D (history of hyperglycemia less than 6 months) who came to our outpatient clinic from April 2022 to November 2022. Obesity was defined as body mass index (BMI) $\geq$ 28 kg/m^2, according to the diagnostic criterion for obesity in China. The diagnosis of prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), and T2D was based on the Chinese Guidelines for the Prevention and Treatment of T2D (2020 Edition) [8](same as the diagnostic criteria from WHO 1999 version and WHO 2011 supplement. Diabetes could be diagnosed if any of the following criteria are met: fasting plasma glucose (FPG), $\geq$ 7.0 mmol/L; 2-h plasma glucose during oral glucose tolerance test (OGTT), $\geq$ 11.1 mmol/L; glycated hemoglobin (HbA1c), $\geq$ 6.5%; random plasma glucose, $\geq$ 11.1 mmol/L, accompanied by classic symptoms of diabetes, e.g., polyuria, polydipsia, and weight loss. If not having the classic symptoms, need to test again. Prediabetes could be diagnosed if any of the following criteria are met: fasting glucose levels between 6.1 and 6.9 mmol/L and 2-h plasma glucose during OGTT between 7.8 and 11.0 mmol/L). Individuals were excluded if they (1) had severe cerebro-cardiovascular diseases; (2) were complicated with serious hepatic or renal insufficiency; (3) had uncontrolled psychological conditions; (4) were during pregnancy or lactation; and (5) were unwilling to sign the informed consent. After excluding patients with the above-mentioned conditions, a total of 61 patients were recruited in this study. Only 1 patient in the intensive treatment group withdrew from the study for moving to another city after the study began and 60 patients were included in the final statistical analysis. Assessments of height, weight, body composition, blood pressure, 12-lead electrocardiogram, biochemical tests, 75-g oral glucose tolerance test (OGTT), and measurements of cytokines related to obesity and diabetes including adiponectin, myonectin, and pregnancy zone protein (PZP) were conducted at baseline. Then the participants were randomly allocated to either the standard treatment group or the intensive treatment group. The randomization scheme was generated using the sample function in R software (version 4.3.2) and hidden until an eligible participant was ready to be enrolled. The flowchart of study design and participant enrollment can be found in Fig. 1. The study protocol was approved by the Ethics Committee of Tianjin Union Medical Center (approval number: 2021C06). All participants provided written informed consent. This study was not masked, but the research assistants and statistical analysts collected and analyzed the study data without knowing intervention group assignments.

Intervention programs

For standard treatment group, we gave the conventional medication same as intensive treatment group, and

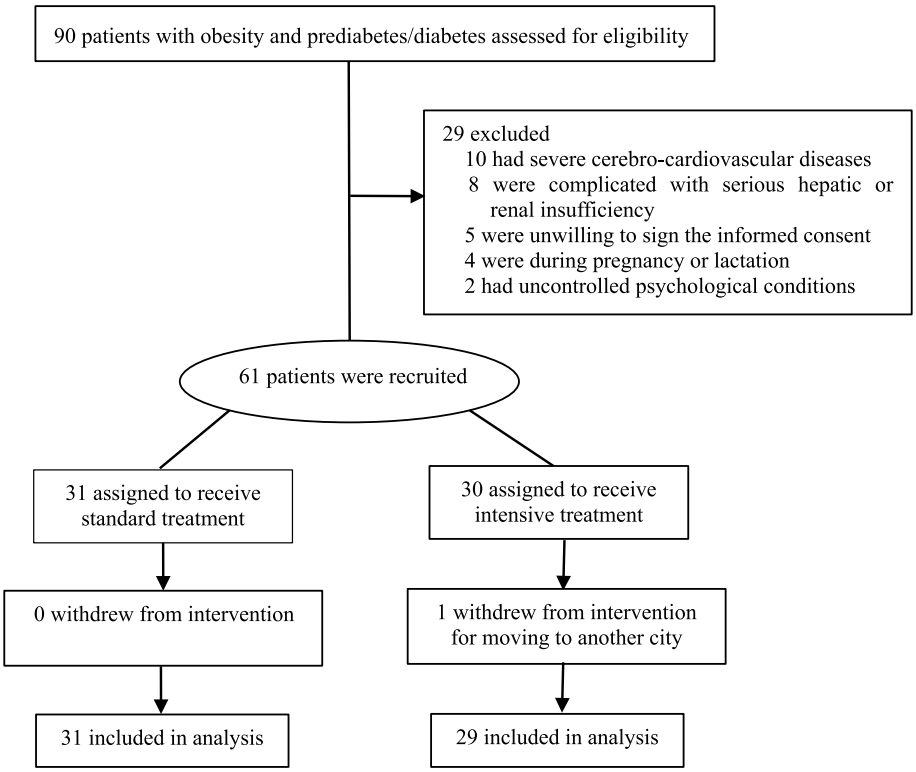


Fig. 1 Flowchart of study design and participants recruitment in this study

lifestyle guidance (all participants were recommended to practice the following items: not drink sugar sweetened beverages, no food intake before 4 h of sleep, daily vegetable intake of at least 500 g, eating out no more than once per week, at least 30 min of physical exercises daily 5 days per week) for 12 months. In addition to conventional individual medication (major hypoglycemic agents included metformin, sodium-dependent glucose transporters 2 inhibitors and glucagon-like peptide-1 receptor agonists), the intensive treatment group received supervised lifestyle therapy, including dietary and exercise intervention. For the dietary intervention, after excluding renal dysfunction, participants were prescribed a high-protein diet consisting of 25% protein, 50% carbohydrate, and 25% fat [9], with around 500 kcal of calories subtracted from their estimated total daily energy requirements. Total daily energy intake was adjusted periodically to achieve a weight loss of 0.5–1.0 kg per week. All participants will be encouraged to weigh foods to ensure the accuracy of intake. During the 12-month weight loss phase, all participants will be asked to periodically record a 3-day diet questionnaire, recording food names, types, and weights. Dietitians will assess calorie intake based on each participant's 3-day dietary questionnaire and the nutrient content listed in the Chinese food composition list. Participants will receive follow-up calls twice a week and meet individually with a dietitian every two weeks/a month to assess their adherence to the plan and provide recommendations for improvement and personalized energy target weight maintenance. Scientific and personalized exercise prescription, including aerobic and resistance exercises, was made according to the FITT-VP (Frequency, Intensity, Time, Type of exercise, Volume, Progression) principle recommended by the American College of Sports Medicine [10], combining with the participant's exercise habit and physical condition. Aerobic exercise of moderate intensity was recommended, with a target heart rate monitored by an exercise bracelet gradually increasing to 60% to 70% of the maximum heart rate, and 150–200 min per week was preferred. In the meanwhile, resistance exercise should be performed 20 min each time and 2–3 times per week. Notably, doctors, nurses, dietitians, and exercise therapists jointly led care in the intensive treatment group and biweekly individual visit and counseling were required. Doctors would reduce hypoglycemic medications based on self-monitoring blood glucose of the patients to decrease the risk of hypoglycemia. When fasting blood glucose decreases to 7 mmol/L and postprandial blood glucose falls below 11.1 mmol/L, the dosage of hypoglycemic medication may be appropriately reduced. In this study, with reference to the "Chinese Expert Consensus on Alleviating

Type 2 Diabetes," the glycosylated hemoglobin within 6.5% after 3 months of drug withdrawal can be defined as "remission." Dietitians and exercise therapists adjusted the dietary and exercise prescriptions depending on the weight change of each subject. It was emphasized that trained nurses should give participants in this group one-to-one education on obesity, diabetes and diabetes remission. Patients in the standard treatment group were given medication and lifestyle guidance solely by doctors in accordance with the recommendations of the Chinese Guidelines for the Prevention and Treatment of T2D (2020 Edition) [8].

Sociodemographic and clinical information collection

At baseline, detailed information on age, gender, ethnicity, and past medical history including hypertension, hyperuricemia, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease were collected. Blood pressure was measured by an automatic electronic sphygmomanometer after a 10-min rest. A 12-lead electrocardiogram examination was undertaken to exclude heart diseases and ensure the safety of exercise training.

Study outcomes

The primary outcomes were the percentage of patients returning to normoglycemia in prediabetes subgroup (fasting plasma glucose (FPG) < 7.0 mmol/L) and diabetes remission rate in diabetes subgroup after 12 months of intervention. T2D remission is defined as glycated hemoglobin (HbA1c) < 6.5% after discontinuation of hypoglycemic drugs for at least 3 months, and the factors that may affect HbA1c results are excluded, which is based on the expert consensus on diabetes remission by American Diabetes Association in 2021 [11]. The secondary outcomes included changes in weight, percent of body fat (PBF), visceral fat area (VFA), and hepatic controlled attenuation parameter (CAP) value. HbA1c was assessed by high-performance chromatography. PBF and VFA were determined by the direct segmental multi-frequency bioelectrical impedance analysis (BIA) (InBody 770, Bio-space Inc., Korea). Skeletal muscle mass also used BIA to measure. Hepatic CAP value was obtained by transient elastography examination (FibroScan 502 Touch, Echosens). HbA1c was detected at baseline and after intervention and discontinuation of hypoglycemic agents for at least 3 months, and the other study outcomes were evaluated at baseline and 12-month visit.

Blood sample determinations

Blood samples were taken after an overnight fasting. Biochemical tests including fasting plasma glucose (FPG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), uric acid (UA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), free fatty acid (FFA), and C reactive protein (CRP) levels were measured by an automatic biochemical analyzer (TBA-120FR, Toshiba, Tokyo). Fasting insulin (FINS) was determined by chemiluminescent immunoassay. Serum concentrations of adiponectin, PZP and myonectin were detected using human enzyme-linked immunosorbent assay (ELISA) kits (Catalog No. JL12255, JL30433, JL47317; JiangLai Bioscience, Shanghai, China). The detection ranges were 0.9375–30 μg/mL for adiponectin, 0.25–8 μg/mL for PZP, and 2.5–80 ng/mL for myonectin, respectively. The intra-assay and inter-assay coefficients of variation of the ELISA kits were < 9% and < 12%.

Evaluations of IR

The homeostatic model assessment of insulin resistance (HOMA-IR) was used to evaluate whole-body IR. The correction of HOMA-IR by adiponectin was indicated by the homeostasis model assessment-adiponectin (HOMA-AD). Additionally, adipose tissue IR (Adipo-IR) was assessed. The calculation formulas for HOMA-IR, HOMA-AD and Adipo-IR were as follows: HOMA-IR = FPG (mmol/L) × FINS (IU/L) /22.5 [12], HOMA-AD = (FPG (mmol/L) × FINS (IU/L))/(22.5 × adiponectin (μg/mL)) [13], Adipo-IR = FFA (mmol/L) × FINS (IU/L) [14].

Statistical analysis

Regarding the sample size calculation, we calculated that 28 participants per group would provide greater than 80% statistical power to detect a significant difference of 2.5 kg in body weight (± 3.3) between the standard and the intensive treatment group with $\alpha = 0.025$. We planned to enroll 66 participants, assuming that 56 participant (28 per group) would complete the trial with an anticipated dropout rate of 20%. The analysis was conducted based on the intention-to-treat principle. Continuous variables were presented as means (95% confidence interval (CI)). A two-sided *P* value of less than 0.05 was considered to be statistically significant. As for the analyses of differences in the trial outcomes between groups, the Wilcoxon signed-rank test for continuous data and the chi-square test for categorical data was used, respectively. A mixed-effects model with an autoregressive correlation matrix was performed to correct for the correlations of repeated measurements to assess the effects of each treatment regimen on changes in the trial outcomes. In this model, participants were assumed to be random effects, and intervention group, time and their 2-factor interactions were assumed to be estimable fixed effects. The linear trend test was conducted by entering the median value of each category of weight loss as a continuous variable

Table 1 Characteristics of the participants at baseline

Characteristics	Standard treatment group		Intensive treatment group	
	Prediabetes (*N* = 13)	Diabetes (*N* = 18)	Prediabetes (*N* = 15)	Diabetes (*N* = 15)
Female sex—no. (%)	7 (53.85)	9 (50.00)	6 (40.00)	10 (66.67)
Age—years	36.08 ± 9.16	39.28 ± 13.19	34.27 ± 11.40	38.73 ± 12.94
Han ethnicity—no. (%)	12 (92.31)	16 (88.89)	14 (93.33)	13 (86.67)
Time since glucose abnormality—months	3.42 ± 1.21	3.91 ± 1.62	3.78 ± 1.55	4.00 ± 1.24
History of other diseases—no. (%)				
Hypertension	8 (61.54)	9 (50.00)	10 (66.67)	7 (46.67)
Dyslipidemia	4 (30.77)	9 (50.00)	7 (46.67)	11 (73.33)
MASLD	8 (61.54)	16 (88.89)	9 (60.00)	11 (73.33)
Hyperuricemia	8 (61.54)	4 (22.22)[a]	11 (73.33)[d]	4 (26.67)[cf]
Oral hypoglycemic agents—no. (%)				
Metformin	11 (84.61)	14 (77.78)	14 (93.33)	12 (80.00)
TZD	2 (15.38)	0 (00.00)	1 (6.67)	2 (13.33)
SGLT-2i	5 (38.46)	8 (44.44)	11 (73.33)	11 (73.33)
GLP-1RA	4 (30.77)	8 (44.44)	10 (66.67)	8 (53.33)
weight (kg)	100.43 ± 18.51	99.06 ± 16.49	112.11 ± 16.92	101.21 ± 19.05
BMI (kg/m^2)	35.21 ± 5.97	34.56 ± 5.53	38.87 ± 4.73	36.49 ± 5.78
PBF (%)	41.42 ± 5.94	40.96 ± 7.83	43.70 ± 4.87	44.49 ± 6.72
VFA (cm^2)	194.73 ± 44.03	204.57 ± 34.09	221.13 ± 26.98	212.43 ± 50.63
SMM (kg)	32.00 ± 5.58	32.41 ± 6.00	35.51 ± 6.65	31.07 ± 6.24
CAP (dB/m)	332.77 ± 53.66	334.89 ± 38.81	319.27 ± 48.44	303.20 ± 68.69
FPG (mmol/L)	5.34 ± 0.72	8.36 ± 2.45[a]	5.10 ± 0.65[d]	8.15 ± 3.19[cf]
2hPG (mmol/L)	8.37 ± 0.89	15.89 ± 3.47[a]	9.02 ± 1.08[d]	15.56 ± 4.30[cf]
FINS (μU/mL)	22.85 (17.59 to 29.10)	22.62 (17.39 to 32.90)	19.55 (14.42 to 29.51)	30.40 (17.09 to 60.49)
HbA_{1c} (%)	5.79 ± 0.34	7.77 ± 1.78[a]	5.77 ± 0.37[d]	7.53 ± 2.06[cf]
TC (mmol/L)	4.74 ± 0.62	5.48 ± 1.27	5.29 ± 1.02	5.52 ± 1.15
TG (mmol/L)	1.99 (1.72 to 3.28)	1.69 (1.26 to 2.77)	1.54 (1.05 to 2.77)	2.23 (1.81 to 3.17)
HDL-C (mmol/L)	1.26 ± 0.33	1.26 ± 0.29	1.20 ± 0.30	1.25 ± 0.34
LDL-C (mmol/L)	2.95 ± 0.48	3.50 ± 1.05	3.29 ± 0.86	3.41 ± 0.82
Urea (mmol/L)	4.82 ± 0.82	4.60 ± 1.09	5.06 ± 1.13	4.90 ± 1.09
Creatinine (μmol/L)	70.00 ± 22.89	57.70 ± 13.33[a]	64.33 ± 11.96	63.73 ± 13.58
UA (μmol/L)	446.23 ± 122.49	364.28 ± 102.16[a]	453.93 ± 105.49[d]	366.33 ± 75.75[cf]
ALT (IU/L)	37.60 (20.50 to 57.05)	59.75 (30.60 to 109.70)	28.00 (18.20 to 44.30)	45.40 (34.50 to 63.00)
AST (IU/L)	27.80 (17.55 to 42.00)	41.45 (22.93 to 60.55)	21.40 (14.40 to 31.90)	28.40 (25.80 to 48.60)

Abbreviations MASLD metabolic dysfunction-associated steatotic liver disease, *BMI* body mass index, *PBF* percent of body fat, *VFA* visceral fat area, *SMM* skeletal muscle mass, *CAP* controlled attenuation parameter, *FPG* fasting plasma glucose, *2hPG* 2-h Postprandial Glucose, *FINS* fasting insulin, *HbA1c* hemoglobin A1c, *TC* total cholesterol, *TG*, triglyceride *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *UA* uric acid, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

[a] indicated that significant difference between patients with prediabetes and those with diabetes in the standard treatment group

[b] indicated that significant difference between patients with prediabetes in the standard treatment group and those in the intensive treatment group

[c] indicated that significant difference between patients with prediabetes (standard treatment) and patients with diabetes (intensive treatment)

[d] indicated that significant difference between patients with diabetes (standard treatment) and patients with prediabetes (intensive treatment)

[e] indicated that significant difference between patients with diabetes in the standard treatment group and those in the intensive treatment group

[f] indicated that significant difference between patients with prediabetes and diabetes within the intensive treatment group

in the models. Missing data were handled by multiple imputations using the Monte Carlo method. For comparing the differences in values of patients in each group at baseline and after intervention, non-normally distributed data were analyzed by Wilcoxon signed-rank test. Categorical variables were tested by chi-squared test. All the analyses were conducted with the use of R software (version 4.3.2).

Results

After excluding patients who did not meet the inclusion criteria and 1 patient who withdrew during the study period, a total of 60 patients completed the study, including 31 in the control group and 29 in the intervention group. The baseline characteristics of the study participants are shown in Table 1. Both sexes were about equally represented in both the two groups. Other clinical characteristics including age, ethnicity, duration of prediabetes or T2D and other comorbidities were similar between groups.

Primary outcomes

In the intensive treatment group, 78.57% patients in the prediabetes subgroup returned to normoglycemia and the diabetes remission rate was 75% in the diabetes subgroup at 12 months, which were much higher than the remission rates in the standard treatment group ($P<0.001$) (Fig. 2A). In a secondary analysis, all participants were divided into four groups according to the quartiles of weight loss and the remission rates in the four quartile groups were calculated. Results showed that with the increase of weight loss, the remission rates of prediabetes and diabetes significantly improved (Fig. 2B).

Changes in weight, body composition and metabolic indices

The mean weight change was − 19.29 kg (95% CI, − 22.95 to − 15.63) in the intensive treatment group and − 1.52 kg (95% CI, − 5.12 to 2.07) in the standard treatment group from baseline after intervention. The weight change between the two groups was significantly different (net difference, − 17.77 kg; 95% CI, − 22.90 to − 12.64; $P<0.001$) (Table 2). Body weight change was significantly different in the intensive treatment group compared to the standard treatment group during 12 months of follow-up (Fig. 3). Likewise, PBF, VFA, CAP and FINS reduced significantly in the intensive treatment group compared to the standard treatment group ($P<0.001$). And there were obvious differences in the changes of TC and HDL-C between the two treatment groups ($P<0.05$). Whereas, the skeletal muscle mass (SMM) change between the two groups was not significantly different (Table 2).

IR before and after intervention

In the intensive treatment group, HOMA-IR, Adipo-IR and HOMA-AD significantly decreased from baseline in both the prediabetes and diabetes subgroups ($P<0.001$). However, HOMA-IR, Adipo-IR and HOMA-AD did not significantly change in the control group (Fig. 4).

CRP, adiponectin, myonectin, and PZP levels before and after intervention

Compared with baseline, the concentration of CRP decreased, while adiponectin, myonectin and PZP levels increased significantly after intervention in both the prediabetes and diabetes subgroups of the intensive treatment group ($P<0.001$). However, the levels of these four indexes did not change significantly in subjects of the

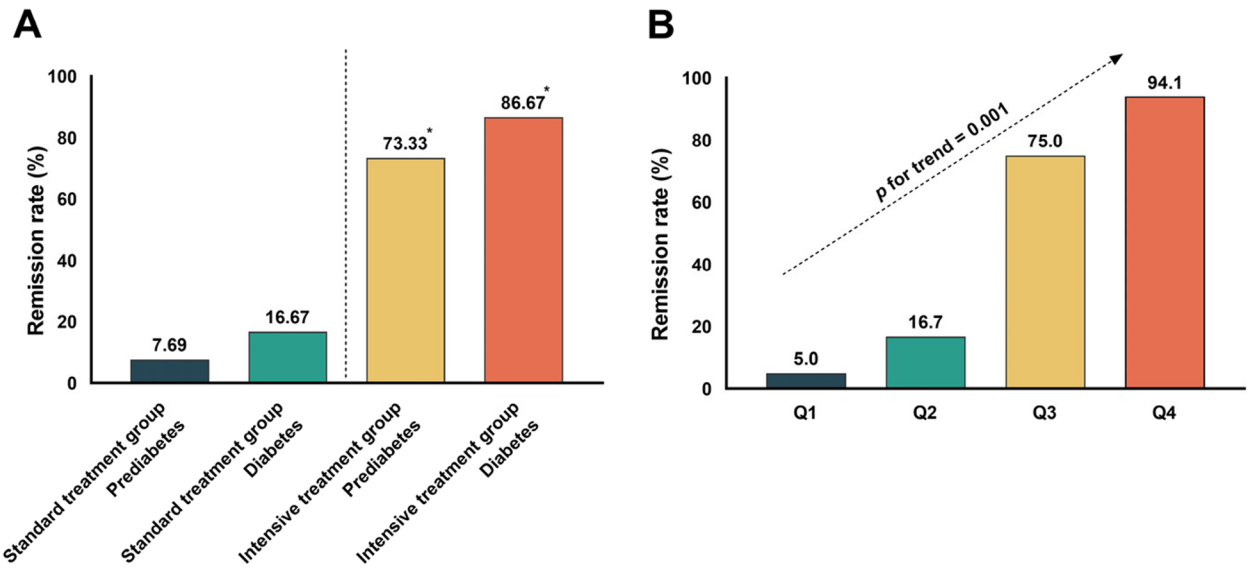


Fig. 2 Diabetes remission following 12 months of intensive and standard treatment. **A** Proportion of patients returning to normoglycemia in prediabetes subgroup and diabetes remission rate in diabetes subgroup of the standard and intensive treatment groups. **B** Remission rates of the four quartile groups based on weight loss. *$P<.001$ vs standard treatment group. Remission rates were compared by chi-squared test. Four quartiles of weight loss: Q1, < 5%; Q2, 5% ~ 10%; Q3, 10% ~ 15%; Q4, > 15%

Table 2 Effects of treatment regimens on weight loss, body composition, and metabolic indices[a]

Variables	Standard treatment group (*N* = 31)		Intensive treatment group (*N* = 30)	Difference between Groups (95% CI)
	N	*Change from baseline (95% CI)*		
Weight (kg)	60	−1.52 (−6.43 to 3.38)	−19.29 (−24.30 to −14.30)‡	−17.77 (−22.90 to −12.64) ‡
BMI (kg/m^2)	60	−0.52 (−2.30 to 1.27)	−6.86 (−8.68 to −5.05)‡	−6.35 (−8.21 to −4.48) ‡
PBF (%)	60	−0.64 (−3.55 to 2.28)	−6.28 (−9.24 to −3.32)‡	−5.64 (−8.69 to −2.60) ‡
VFA (cm^2)	60	−11.30 (−33.66 to 11.00)	−53.80 (−76.51 to −31.12)‡	−42.49 (−65.82 to −19.15) ‡
SMM (kg)	60	−0.07 (−1.37 to 1.23)	−0.48 (−1.80 to 0.84)	−0.41 (−1.76 to 0.94)
CAP (dB/m)	60	−10.60 (−32.50 to 11.30)	−59.10 (−81.42 to −31.80)‡	−48.55 (−71.46 to −25.64) ‡
TC (mmol/L)	60	−0.38 (−1.00 to 0.25)	−1.26 (−1.90 to −0.60)‡	−0.89 (−1.54 to −0.24)†
TG (mmol/L)	60	−0.37 (−1.76 to 1.03)	−1.08 (−2.49 to 0.34)	−0.71 (−2.17 to 0.74)
HDL-C (mmol/L)	60	−0.02 (−0.14 to 0.10)	0.15 (0.03 to 0.27)†	0.17 (0.05 to 0.30)†
LDL-C (mmol/L)	60	−0.07 (−0.53 to 0.39)	−0.44 (−0.90 to 0.03)	−0.36 (−0.84 to 0.12)
FPG (mmol/L)	60	−1.50 (−2.72 to −0.28)†	−2.09 (−3.33 to −0.85)‡	−0.59 (−1.86 to 0.68)
2hPG (mmol/L)	53	−4.41 (−6.43 to −2.93)‡	−5.57 (−7.62 to −3.51)‡	−1.16 (−3.27 to 0.95)
FINS (μU/mL)	60	−2.89 (−10.96 to 5.18)	−18.74 (−26.94 to −10.53)‡	−15.85 (−24.28 to −7.41)‡
HbA_{1c} (%)	60	−0.71 (−1.36 to −0.06)†	−1.40 (−2.04 to −0.76)‡	−0.69 (−1.36 to −0.20)†
Urea (mmol/L)	56	0.64 (−0.02 to 1.30)	0.58 (−0.09 to 1.25)	0.07 (−0.75 to 0.62)
Creatinine (μmol/L)	56	−0.05 (−4.17 to 4.08)	1.92 (−2.27 to 6.12)	1.97 (−2.34 to 6.28)
UA (μmol/L)	60	−61.30 (−106.50 to −15.99)†	−98.00 (−144.00 to −51.99)‡	−36.74 (−84.05 to 10.56)
ALT (IU/L)	60	−9.33 (−28.38 to 9.71)	−21.46 (−40.81 to −2.10)†	−12.12 (−32.02 to 7.78)
AST (IU/L)	60	−2.82 (−13.79 to 8.16)	−9.91 (−21.07 to 1.24)	−7.10 (−18.57 to 4.37)

Abbreviations CI confidence interval, *BMI* body mass index, *PBF* percent of body fat, *VFA* visceral fat area, *SMM* skeletal muscle mass, *CAP* controlled attenuation parameter, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *FPG* fasting plasma glucose, *FINS* fasting insulin, HbA_{1c} hemoglobin A_{1c}, *UA* uric acid, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

[a] Analyses were conducted with the use of a mixed-effects model, with randomized treatment as a factor and the use of a multiple imputation method for missing data. Bonferroni method was used for pairwise group comparisons

† and‡ indicated significant difference in the changes of weight loss, body composition, and clinical indices between the two treatment groups

† $P < 0.05$

‡ $P < 0.001$

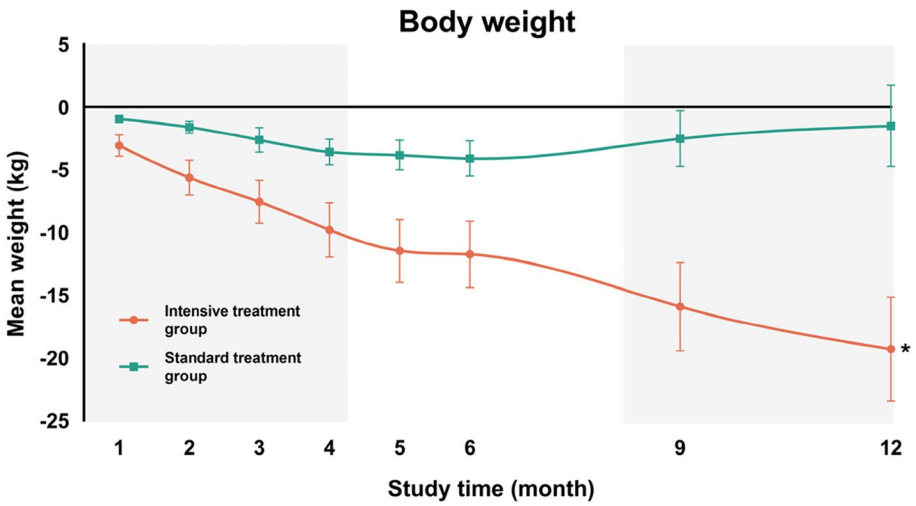


Fig. 3 Body weight change following 12 months of intensive and standard treatment. * $P < 0.01$ vs Standard treatment group. Data were included for 61 participants, means were evaluated using a mixed-effects model by an intention-to-treat analysis. Error bars represent 95% confidence interval for weight loss

standard treatment group. The results are exhibited in Fig. 5.

Serious adverse events and program adherence

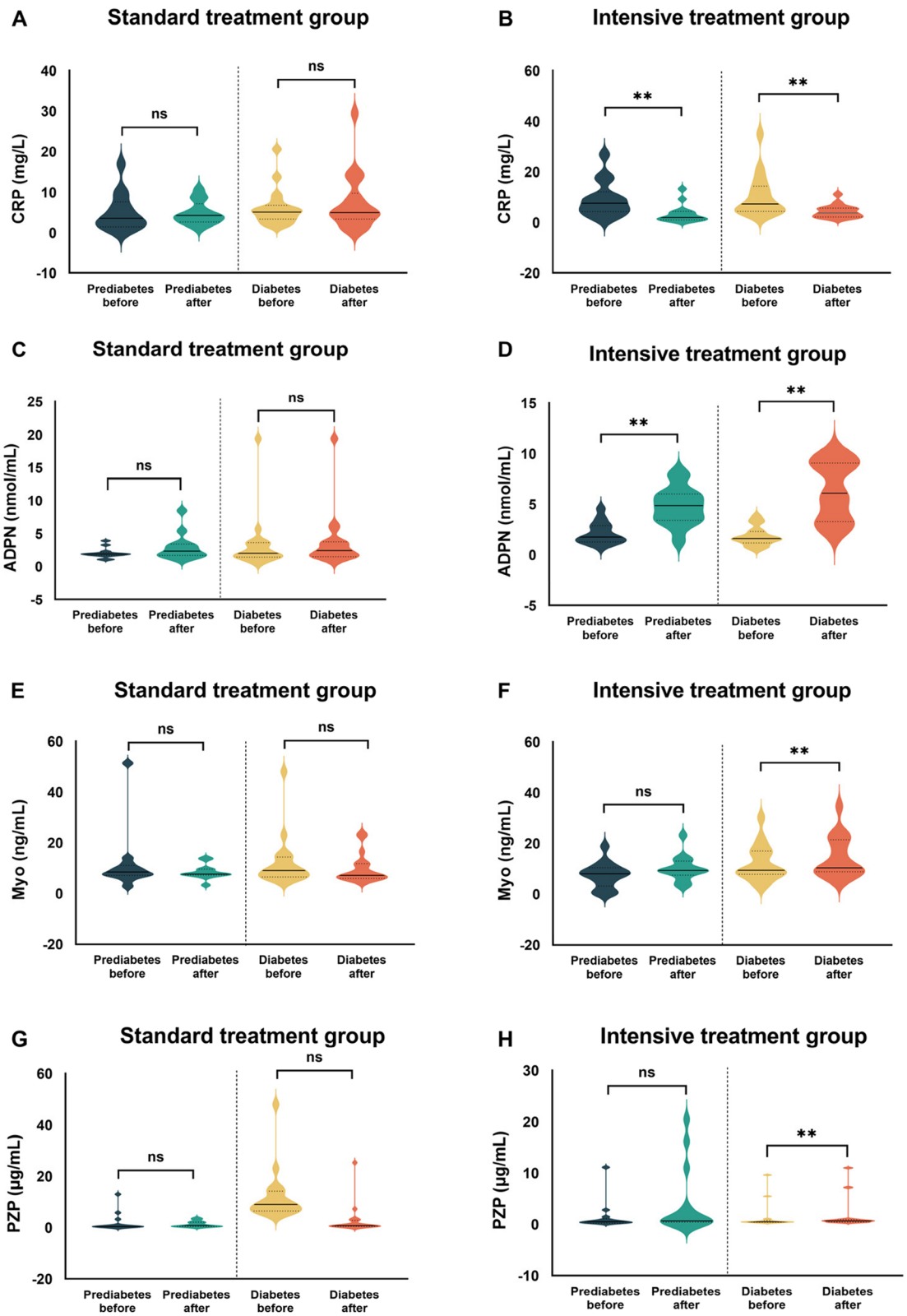
There were no serious adverse events reported in the intensive treatment group or the standard treatment group. Renal function, including serum creatinine and urea nitrogen, did not change significantly before and after the intervention in the intensive treatment group in which participants were given a high-protein diet. In the intensive treatment group, the average percentage of days that participants adhered to the dietary prescription during the 12-month intervention was 86.9 ± 5.4% (Supplementary Table 1). The overall compliance rate with the exercise prescription in participants of the intensive treatment group was 83.8 ± 2.0% (Supplementary Fig. 1).

Discussion

The findings in this study demonstrate that a high protein diet combined with moderate exercise plus hypoglycemic agents with weight loss effect could lead to significant weight loss in adults with obesity and new-onset of prediabetes or T2D. We also find dramatic decrease in body fat mass; visceral and liver fat content; amelioration of cardiometabolic risk factors; beneficial changes in inflammation marker; adipocytokine, myokine, and hepatokine; and even a considerable proportion of diabetes remission from the trial data. To our knowledge, this is the first study conducted in a Chinese population, mainly Han ethnicity, to show that calorie restricted diet and increased physical exercise, which are considered the first-line treatment for obesity and T2D [15], can induce diabetes remission in patients with obesity and T2D. Previous studies, including the DiRECT and DIADEM-I trial, had confirmed that intensive lifestyle intervention could cause significant weight loss and result in diabetes remission. In DiRECT and DIADEM-I study, sufficient weight loss and diabetes remission were achieved by use of a low-energy formula meal products replacing normal diet in the first 3–5 months [6, 7]. Low calorie diets (LCDs) and very low calorie diets (VLCDs) have been shown to be effective in weight management and glucose control by a plethora of studies [16, 17]. However, there exist some problems in this pattern of diet, which to some extent restricts energy intake too much, especially VLCDs, defined as less than 800 kcal energy intake per day [18]. Firstly, hunger caused by excessively low calorie intake may prevent patients from adhering to the intervention regimen, or even cause patients to withdraw from the intervention. DiRECT reported that in the intervention group there were 4% of the participants never adhere to the intervention protocol and the withdrawal rate was 17% during the first year of treatment, which mainly happened during the phase of total diet replacement. This study also investigated the specific reasons for dropout from intervention, with social reasons, other and not known reasons accounting for the vast majority [6]. The acceptability of this low calorie meal replacement dietary intervention approach might be one of the reasons, although it was not stated in the study. In addition, too low energy intake may lead to some side effects, including constipation, dizziness, hair loss, menstrual disorders, fatigue, depression or even exacerbation of gout, acute psychosis, cholelithia and fatal dysrhythmias [19]. While only two severe adverse events were considered potentially correlated to the intervention in DiRECT and none was reported in DIADEM-I trial [6, 7], the potential harm of too low energy intake should be paid attention to. Excessive loss of lean body mass resulting from the very energy-restricted diet is also a matter of concern, although the difference of reduction in lean mass did not reach statistical significance between the intervention and control group in DIADEM-I trial [7]. Most importantly, weight regain and the consequent re-elevation of blood glucose are worth of concern after VLCDs. Numerous studies have shown that weight loss is not sustainable at 1-year and 5-year follow-up after VLCDs treatment, and weight regain may be even higher than the initial lost weight [20, 21]. The 2-year follow-up of DiRECT revealed the durability of weight loss and diabetes remission, with 11% of intervention participants maintaining at least 15 kg weight loss and 36% remaining in remission at 24 months [22], compared with 24% and 46% of the corresponding outcomes at 12 months [6]. These results suggested that weight regain and hyperglycemia without medications might occur in some participants as time went on. Previous researches demonstrated high-protein diet was significantly effective in reducing

(See figure on next page.)

Fig. 4 Changes of HOMA-IR, Adipo-IR, and HOMA-AD of the prediabetes and diabetes subgroups in the standard and intensive treatment groups from baseline after intervention. HOMA-IR, homeostatic model assessment of insulin resistance; Adipo-IR, adipose tissue insulin resistance; HOMA-AD, homeostasis model assessment-adiponectin. **A** Changes of HOMA-IR in the standard treatment group from baseline after intervention. **B** Changes of HOMA-IR in the intensive treatment group from baseline after intervention. **C** Changes of Adipo-IR in the standard treatment group from baseline after intervention. **D** Changes of Adipo-IR in the intensive treatment group from baseline after intervention. **E** Changes of HOMA-AD in the standard treatment group from baseline after intervention. **F** Changes of HOMA-AD in the intensive treatment group from baseline after intervention. *P* values were assessed by comparing the values before and after intervention using Wilcoxon signed-rank test



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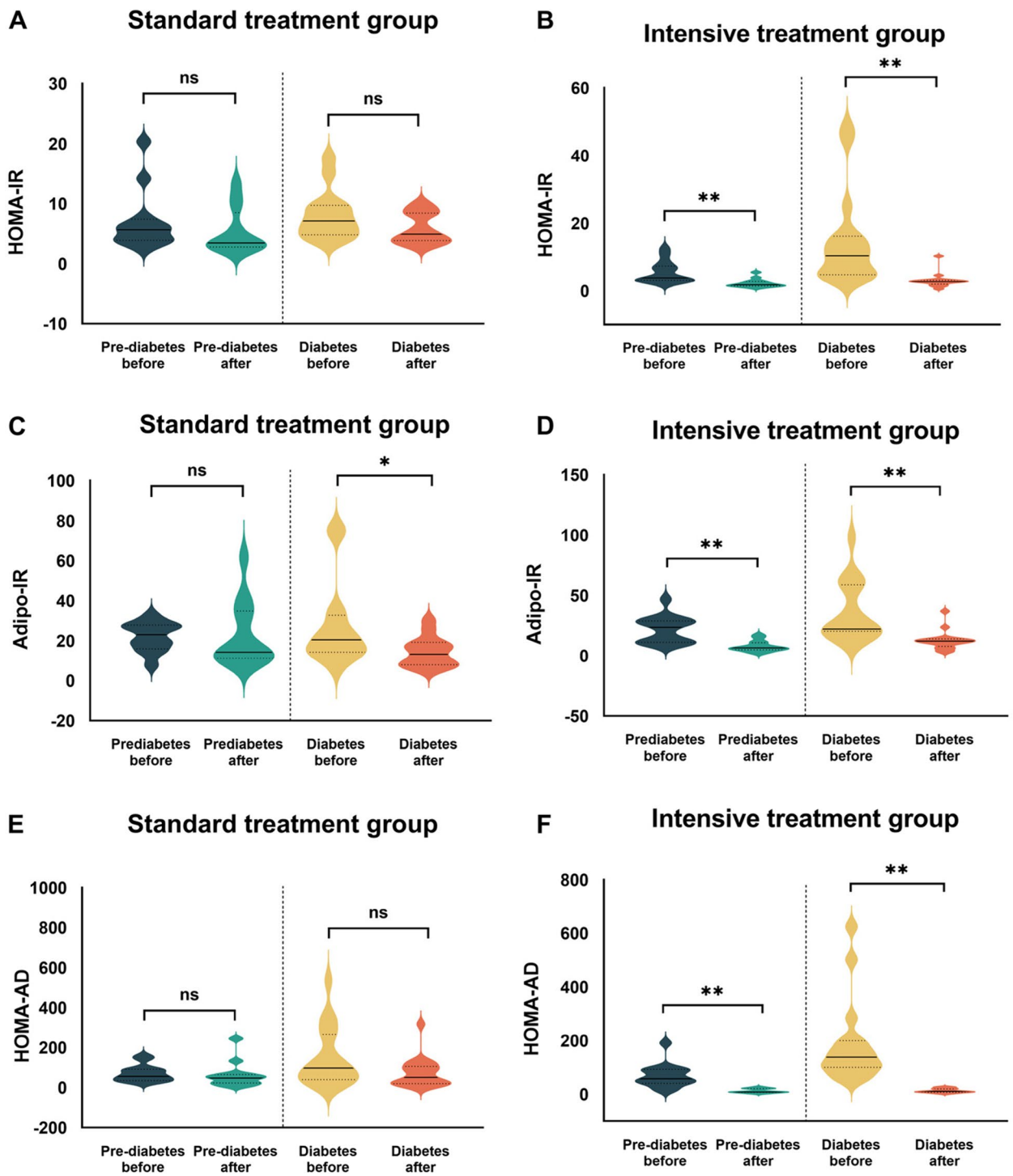

Fig. 5 Changes of cytokines of the prediabetes and diabetes subgroups in the standard and intensive treatment groups from baseline after intervention. CRP, C reactive protein; ADPN, adiponectin; Myo, myonectin; PZP, pregnancy zone protein. **A** Changes of CRP of the prediabetes and diabetes subgroups in the standard treatment group from baseline after intervention. **B** Changes of CRP of the prediabetes and diabetes subgroups in the intensive treatment group from baseline after intervention. **C** Changes of ADPN of the prediabetes and diabetes subgroups in the standard treatment group from baseline after intervention. **D** Changes of ADPN of the prediabetes and diabetes subgroups in the intensive treatment group from baseline after intervention. **E** Changes of Myo of the prediabetes and diabetes subgroups in the standard treatment group from baseline after intervention. **F** Changes of Myo of the prediabetes and diabetes subgroups in the intensive treatment group from baseline after intervention. **G** Changes of PZP of the prediabetes and diabetes subgroups in the standard treatment group from baseline after intervention. **F** Changes of PZP of the prediabetes and diabetes subgroups in the intensive treatment group from baseline after intervention

fasting glucose[23]. HPDs were an effective alternative to reduce hyperglycemia in patients with T2DM[24], in addition, it could downregulate total insulin AUC[25] and HOMA-IR levels in T2DM patients[26]. Different from the approaches of lifestyle intervention in the DiRECT and DIADEM-I study, lifestyle treatments including a high-protein diet and moderate exercise training were implemented in this study. The diet protocol makes an energy deficit of about 500 kcal per day, which is more than 1200 kcal in most cases and higher than that of LCDs and VLCDs. Exercise following the FITT-VP principle not only helps increase energy expenditure, but also benefits cardiorespiratory endurance, although cardiorespiratory function was not assessed in this study. Moreover, the adequate protein intake and resistance exercise make no obvious reduction of muscle mass in the case of significant decrease of weight and body fat mass. The percentage of carbohydrate was around 50% in the diet regimen undertaken in this study, for low carbohydrate diets may have some harmful effects on human body and long-term restriction of carbohydrate (< 40%) is even related to increased mortality [27]. Under this approach of lifestyle intervention, most participants in this study had no feelings of obvious hunger, the adherence was excellent, and no one withdrew from the study because of the adaption issue related to the intervention approach. What is more, the participants' weight and body fat mass decreased significantly while their muscle mass remained unchanged. Notably, the diabetes remission rate of the intensive treatment group was relatively high in this study, which was attributed to their significant weight and fat loss and good adherence. We are also continuing to focus on the sustainability of weight loss and diabetes remission under this lifestyle intervention method. IR plays a crucial role in the pathogenesis of T2D and other cardiometabolic diseases [28]. Systemic IR, attributed to excessive accumulation of adipose tissue in liver and skeletal muscle, causes a variety of cardiometabolic diseases and is generally assessed by HOMA-IR in clinical practice [29]. Whereas, HOMA-IR, based on FPG and FINS levels, does not distinguish well between hepatic and peripheral IR [30]. Adiponectin, an adipocytokine that can enhance insulin sensitivity, has been shown to decrease in individuals with obesity and T2D and increase after weight loss [31]. Thus HOMA-AD, incorporating circulating adiponectin level in the calculation formula of HOMA-IR, may be more indicative of adiposity and IR in individuals [32]. Increased insulin sensitivity in the liver and adipose tissue contribute to reduction of hepatic glucose output, enhancement of the antilipolytic effect of insulin and decrease of ectopic fat deposition, which will lead to improvement in glycemic control [33]. Therefore, significant improvements of HOMA-IR, HOMA-AD and Adipo-IR after weight loss might be the potential pathophysiological mechanisms of diabetes remission. Inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 secreted from increased adipose tissue will cause low-grade inflammation in the body, and it is one of the major mechanisms by which obesity leading to IR and metabolic diseases [34]. On the contrary, myokines such as myonectin may be protective cytokines in IR and metabolic diseases, for their roles in increasing FFA oxidation, browning of white adipose tissue and promotion of thermogenesis [35]. Although the aforementioned inflammatory cytokines were not detected in this study, we evaluated the concentrations of CRP, which is also an indicator reflecting the inflammatory status of the body [36], before and after intervention. The significant decrease of CRP and increase of myonectin suggested that the alleviation of chronic inflammation and enhancement of myokines' impacts might be vital pathophysiological changes involved in weight loss and diabetes remission. Adiponectin is an adipocytokine secreted mainly by adipocytes and many studies have confirmed that hypoadiponectinemia plays a central role in obesity and cardiometabolic disorders [37]. The results in this study suggested that adiponectin levels increased significantly with the obvious loss of weight and remission of diabetes, which proved the beneficial effect of adiponectin on obesity and metabolic diseases from another aspect. A study conducted by Lin et al. found that PZP, a novel identified hepatokine, might have some potential therapeutic roles in obesity and its related metabolic diseases by promoting brown adipose tissue thermogenesis [38]. In this study, the significant increase of circulating PZP after weight loss in the intensive treatment group also suggested that PZP was negatively correlated to obesity and diabetes and it might become a protective effect marker on obesity and diabetes. It is worth noting that the marked effect of this lifestyle therapy on weight loss and diabetes remission was mainly due to the fact that the treatment and care in the intensive treatment group were led by a team, including doctors, nurses, dietitians and exercise therapists, rather than just doctors. Previous studies have documented the efficacy and importance of nurse-led or pharmacist-delivered education and patient involvement in chronic disease management, such as gout, coronary heart disease, asthma and chronic obstructive pulmonary disease [39–41], which is particularly central to weight and diabetes management. Much time should be spent in explaining the disease and making the explanations easy to understand in order to help patients in decision making, however, this is usually suboptimum in clinical practice, for time limitation on communication between doctors and patients [42]. Especially

in China, with a large population and limited medical resources in big cities, there is usually little time for doctor-patient communication. In this study, for the successful implementation of the diet and exercise therapy, in addition to the treatment strategy prescribed by physicians, dietitians and exercise therapists, education on diabetes, especially that weight loss can induce diabetes remission was delivered by professionally trained nurses. The patients enrolled in this study were relatively young and almost were prediabetes or short clinical course of diabetes, so their motivations to lose weight were very strong and the adherence was extremely excellent after they knew the significance of losing weight, which ensured the remarkable weight loss and diabetes remission. Diabetes Remission remains controversial. Remission as a primary objective of therapy in non-obese patients is "sidelined" in the current American/European guidelines[43, 44]. The findings of the present study compliment and are reinforced by remission in obesity patients with T2D following bariatric surgery[45]. This is the first study to demonstrate the effect of a high-protein diet and moderate exercise plus hypoglycemic agents with weight loss effect on diabetes remission in Chinese adults with obesity and newly diagnosed T2D or prediabetes. Moreover, we explored the changes of systemic IR, HOMA-AD and Adipo-IR, and several potential cellular factors (inflammation marker, adipocytokine, myokine and hepatokine), which might be involved in the pathogenesis of obesity and diabetes. However, this study has several limitations. Firstly, the follow-up of this study is relatively short and the sustainability of this lifestyle intervention therapy for weight loss and diabetes remission is unknown yet. And we will continue to focus on the durability of weight loss and diabetes remission with longer follow-up. Secondly, the number of participants in this study is relatively small, and we will still recruit more participants in the future to expand the sample size and confirm the results obtained in this study. Finally, this study cannot tell the causal relationship between the improvements of cellular factors and weight loss and diabetes remission, and animal studies are needed to further confirm the causality between them.

Conclusions

In conclusion, this study indicates that a high-protein diet and moderate exercise plus hypoglycemic agents with weight loss effect could lead to diabetes remission in people with obesity and new-onset T2D, and this intervention regimen has demonstrated extremely good safety and adherence. The beneficial improvements in IR, inflammation marker, adipocytokine, myokine and hepatokine, might be crucial pathophysiological changes involved in weight loss and diabetes remission.

Abbreviations

IR	Insulin resistance
T2D	Type 2 diabetes
CDQDPS	China Da Qing Diabetes Prevention Study
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
DiRECT	Diabetes Remission Clinical Trial
DIADEM-I	Diabetes Intervention Accentuating Diet and Enhancing Metabolism
BMI	Body mass index
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
OGTT	Oral glucose tolerance test
PZP	Pregnancy zone protein
HbA1c	Glycated hemoglobin
PBF	Percent of body fat
VFA	Visceral fat area
CAP	Hepatic controlled attenuation parameter
BIA	Bioelectrical impedance analysis
FPG	Fasting plasma glucose
TC	Total cholesterol
LDL-C	Low density lipoprotein cholesterol
HDL-C	High density lipoprotein cholesterol
TG	Triglycerides
UA	Uric acid
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
FFA	Free fatty acid
CRP	C reactive protein
FINS	Fasting insulin
ELISA	Enzyme-linked immunosorbent assay
HOMA-IR	Homeostatic model assessment of insulin resistance
HOMA-AD	Homeostasis model assessment-adiponectin
Adipo-IR	Adipose tissue insulin resistance
CI	Confidence interval
SMM	Skeletal muscle mass
LCDs	Low calorie diets
VLCDs	Very low calorie diets

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04072-4.

Additional file 1: Table S1, Fig S1. Table S1-Diet adherence and nutrient distribution during intervention. Fig S1-Compliance rate with the exercise prescription during intervention

Additional file 2: Table S2-S5. Table S2-Details of weight, fasting blood glucose and treatment plans for Pre-diabetes patients in Intensive treatment group. Table S3-Details of weight, fasting blood glucose and treatment plans for Diabetes patients in Intensive treatment group. Table S4-Details of weight, fasting blood glucose and treatment plans for Pre-diabetes patients in Standard treatment group. Table S5-Details of weight, fasting blood glucose and treatment plans for Diabetes patients in Standard treatment group.

Additional file 3: Table S6. Table S6-Effects of Treatment Regimens on Cytokines and indicators of Insulin Resistance.

Acknowledgements

The authors would like to acknowledge gratefully all the participants in this study and the contribution of Ying Chen, Xiaochen Yan and Lili Li in Health Management Center of Tianjin Union Medical Center.

Authors' contributions

SZ designed the research and wrote the manuscript. YW conducted the clinical trial and wrote the manuscript. XCW performed the statistical analysis. MXL, RJL, ZHL, JL, JXX, DMH, LBL and XYG assisted with the recruitment and conduction of the clinical trial. CJL designed and supervised the research.

All authors helped interpret the data and approved the final version of the manuscript.

Funding
This study was supported by the Tianjin Science and Technology Committee (C.J.L, Grant Number 23 JCZDJC01040) and the Science and Technology Project of the Tianjin Municipal Health Commission (S.Z, Grant Number TJWJ2022MS019).
Tianjin Union Medical Center,2021YJ002,Tianjin Health Research Project,TJWJ2022MS019

Data availability
Data is provided within the manuscript or supplementary information files

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles of the Helsinki declaration. All participants provided the written informed consent and the study protocol was approved by the Medical Ethics Committee of Tianjin Union Medical Center (No. 2021C06).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 24 June 2024 Accepted: 10 April 2025
Published online: 07 May 2025

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