Nutrition Journal

RESEARCH

Open Access

Low-calorie diets and remission of type 2 diabetes in Chinese: phenotypic changes and individual variability

Zhenxiu Liu[1†], Nannan Feng[2†], Sujing Wang[2], Yang Liu[3], Jie Wang[4], Yue Tan[1], Ying Dong[2], Zhewei Sun[5], Xihao Du[2], Yaqing Xu[2], Feng Tao[1] and Victor W. Zhong[2*]

Abstract

Background Chinese have distinct phenotypes of type 2 diabetes (T2D) and obesity compared with people of other ethnicities, but using low-calorie diets to achieve T2D remission has never been conducted in Chinese. This study aimed to assess if T2D remission can be achieved using low-calorie formula diet (LCFD) and low-calorie real food-based diet (LCRFD) in Chinese similarly to other populations and to identify determinants of individual variability in T2D remission.

Methods This 6-month intervention consisted of a 3-month isocaloric intensive weight loss phase (815–835 kcal/d) and a 3-month weight maintenance phase. Enrolled participants with T2D had BMI of 24–45 kg/m^2 and HbA1c level of 6.5-12.0% (< 6.5% if on medication). Everyone stopped anti-diabetic drugs on day 1 and was assigned to receive LCFD ($n = 21$) or LCRFD ($n = 20$).

Results At 6 months, 29.3% of participants had ≥ 12 kg weight loss, 39.0% lost ≥ 10% weight, and 56.1% achieved T2D remission. MRI-derived liver and pancreatic fat decreased significantly. Significant improvement was also seen in insulin sensitivity, continuous glucose monitoring-derived metrics, and various other cardiometabolic risk factors but not arginine-induced insulin secretory response. There was no difference in all outcomes between LCFD and LCRFD. Compared with responders for T2D remission, nonresponders were more likely to be women, and had more fat mass, longer diabetes duration, poorer glycemic control, and lower beta-cell function.

Conclusions T2D remission rate and weight loss amount following low-calorie diet intervention in Chinese people were comparable to those reported from other populations, although individual variability existed. LCFD and LCRFD were similarly effective.

Trial registration The trial was registered with ClinicalTrials.gov: NCT05472272.

[†]Zhenxiu Liu and Nannan Feng contributed equally to this work.

*Correspondence:
Victor W. Zhong
wenze.zhong@shsmu.edu.cn

Full list of author information is available at the end of the article

Highlights

What is already known?

•Remission of type 2 diabetes (T2D) can be achieved using low-calorie total diet replacement in populations of European descent.

•Chinese people have distinct phenotypes of obesity and T2D.

What this study has found?

•T2D remission rate and weight loss amount resulting from low-calorie diet intervention in Chinese people were comparable to those reported from other populations, but different phenotypic changes were also identified.

•Low-calorie formula diet and low-calorie real food-based diet were similarly effective. Several characteristics differed between responders for T2D remission and non-responders.

What are the implications of the study?

•Identifying people with T2D who are most responsive to low-calorie diet intervention is needed.

Keywords Low-calorie diet, Type 2 diabetes, Remission, Variability, Weight loss

Background

Overweight and obesity account for ~65–80% of new cases of T2D [1]. Excess body weight leads to insulin resistance, β-cell decompensation, and chronic inflammation, which are key pathophysiological processes underlying the T2D development [2]. Although the importance of weight management in T2D has been increasingly recognized, the current treatment paradigm for T2D still focuses on glucose-lowering [3]. Nationwide epidemiological studies have revealed poor risk factor control in diabetes. Only 4.4% of people with diabetes in China, 7.7% in India, and 21.2% in the US simultaneously achieved guideline-recommended targets for hemoglobin A1c (HbA1c), blood pressure, and cholesterol [4–6].

Growing evidence from intervention studies suggests that for people with T2D who are overweight or obese, in particular those with short diabetes duration, pharmacotherapy may be completely replaced by hypocaloric diets [7]. Published randomized controlled trials (RCTs) reported diabetes remission rates of ~40–60% by employing a low-calorie diet intervention (800–853 kcal/day). [8–10] However, the majority of the evidence comes from European populations [7]. China has the largest population of people with T2D who present distinct diabetes phenotypes including younger onset age, greater predisposition to β-cell failure, and lower body mass index (BMI) [11]. These distinctions likely result in different responses to a low-calorie diet intervention. Additionally, most trials used formula meal replacement products which may be challenging for long-term consumption [8–10, 12].

Therefore, we conducted this clinical trial in a Chinese population with T2D who were overweight or obese to (1) assess whether T2D remission could be achieved using low-calorie diets and (2) preliminarily compare the effectiveness in achieving T2D remission, reducing weight, and improving other cardiometabolic risk factors between low-calorie formula diet (LCFD) and low-calorie real food-based diet (LCRFD) intervention. Also, factors contributing to individual variability in T2D remission were explored.

Methods

Study design and participants

This study was a single-center, pilot, non-randomized, open-label trial. Participants were recruited from endocrinology clinics and by advertisement. Participants were sequentially assigned to the LCFD group and LCRFD group. This study was approved by the Ethics Committee of the Shanghai Municipal Hospital of Traditional Chinese Medicine. The trial was registered at ClinicalTrials.gov (NCT number: NCT05472272). Written consent was obtained from all participants.

Participants were eligible if they were aged 18 to 60 years, and had physician-diagnosed T2D, BMI of 24–45 kg/m^2, and HbA1c level of ≥6.5%. If HbA1c level was <6.5%, participants had to take antidiabetic medication(s) currently. A detailed exclusion criteria was listed in the Supplement.

Procedures

The intervention consisted of an intensive weight loss phase for 3 months and a weight loss maintenance phase for another 3 months. All antidiabetic drugs were discontinued on the first day. During the intensive weight loss period, participants consumed complimentary meals (815–835 kcal/day), either a commercial meal replacement product (Quaker Smart Calories) or dietitian-designed real food-based diet prepared by the central nutrition kitchen. The two types of diet were matched on macronutrient compositions: 43–48% carbohydrate, 27–29% protein, and 25–28% fat. Participants were recommended to drink at least 2 L of water and maintain habitual exercise level. Participants were contacted weekly or biweekly by trained staff to provide one-to-one support.

During the weight loss maintenance period, an individualized program was delivered to prevent weight regain during the supervised stepped transition to normal diet. Participants in the LCFD diet group gradually replaced the formula diet with real food-based diet over 7 days. Generally, all participants followed a stepped increase in daily energy intake with adding an additional 200 kcal/day every 1–2 weeks until the daily energy level reached the basal metabolic rate estimated by bioelectrical impedance analysis (Tanita MC-980MA, Tanita Corporation, Tokyo, Japan). Participants were recommended to increase physical activity level up to 15,000 steps per day. Participants were contacted weekly to monthly to provide individualized support.

Anthropometric and body composition measurements

Height and weight were measured in morning fasting state when participants wore light clothing without shoes. In an upright position, waist circumference was measured just above the iliac crest using a stretch-resistant measuring tape. Hip circumference was measured around the widest portion of the buttocks. Biceps, triceps, subscapular and suprailiac skinfold thickness were measured using a skinfold caliper. Body composition was determined with Tanita MC-980MA.

Liver and pancreatic fat determination

MRI IDEAL-IQ sequences were acquired by a 3T MR scanner (Signa Premier, GE Healthcare). Pancreatic and liver proton density fat fraction were calculated from the mean of all the pixels within three circular regions of interest on pancreas and liver images, which were manually selected by two analysts independently. The final results were determined as the average of the two analyses. Cases with significant discrepancies were reanalyzed.

Insulin tolerance test and arginine stimulation test

Insulin tolerance test and arginine stimulation test were performed after an overnight fast of at least 10–12 h on different days; details are described in the Supplement. Insulin sensitivity was assessed by the rate constant for plasma glucose disappearance (KITT; %/min), KITT=(0.693*100) / (t1/2).[13] T1/2 was the half-life of plasma glucose decay, calculated from the slope of least square analysis of plasma glucose concentrations between 3 and 15 min after insulin injection. Arginine-induced insulin secretory response was assessed with acute insulin response (AIR), acute C-peptide response (ACR), and area under curve of insulin (INS_{AUC}) [14, 15].

Glycemic measurements

Fasting plasma glucose and HbA1c were measured. All participants wore continuous glucose monitoring (CGM) device (Abbott Freestyle Libre Pro) during the entire 6 months. Time in range (TIR, 3.9–10.0 mmol/L), time above range (TAR, > 10.0 mmol/L) and time below range (TBR, < 3.9 mmol/L) were computed using % of readings spent in each range [16].

Other biochemical and body examination measurements

Fasting insulin, C-peptide, total cholesterol, low-density lipoprotein cholesterol (LDL-C), small dense LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, and free fatty acids as well as systolic and diastolic blood pressure were measured. The updated homeostatic model assessment (HOMA2) was used to evaluate beta-cell function (HOMA2-%B), insulin sensitivity (HOMA2-%S), and insulin resistance (HOMA2-IR).

Weight and glycemic outcomes

The co-primary outcomes of this study were weight loss ≥ 12 kg and T2D remission. A 12 kg target was chosen based on the 15 kg goal set by the DiRECT study and the proportional conversion according to the average weight of people with diabetes in China and the UK [8]. Diabetes remission was defined by HbA1c dropping to < 6.5% in the absence of glucose-lowering drugs for ≥ 3 months whereas normoglycemia required HbA1c < 5.7%. [17]

Statistical analysis

Within-group differences between baseline and follow-up were estimated using the paired t-test. Between group differences were assessed using linear mixed-effects models, adjusting for age, sex, diabetes duration, time and baseline value as fixed effects. A group*time interaction term was added. Participant ID was included as a random effect. Baseline differences and the differences resulting from the intervention were compared between responders and nonresponders. Responders were people who successfully achieved T2D remission. The intention-to-treat (ITT) principle was used for primary analysis. Complete cases analysis was conducted as sensitivity analysis. Abnormally distributed variables were log-transformed for modeling and back-transformation was performed for presenting results after modeling. Statistical analyses were executed with R 4.3.2. A 2-sided *P* value < 0.05 was considered statistical significance. Due to the exploratory nature of this study, multiple testing correction was not performed.

Results

Twenty-one individuals were assigned to the LCFD group and 20 assigned to the LCRFD group (Fig. 1). The mean (SD) of the key characteristics among 41 participants was 40.4 (8.8) years for age, 30.2 (5.3) kg/m^2 for BMI, 87.0 (20.3) kg for weight, 2.7 (2.5) years for diabetes duration, 8.0 (1.8) % for HbA1c; 68.3% were men (Table 1).

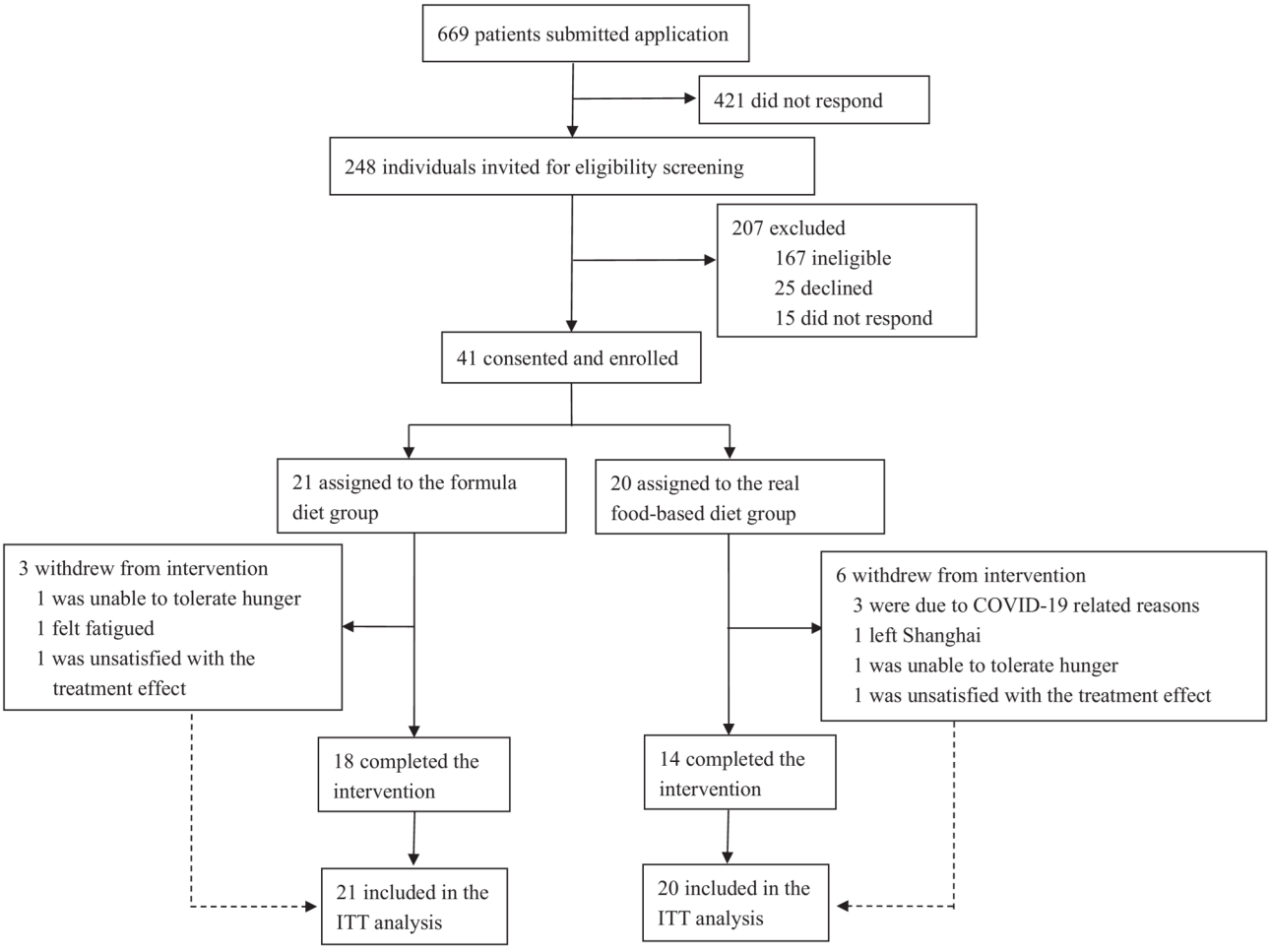

Fig. 1 Flow chart

The mean (SD) HbA1c was 7.9 (1.8) % in individuals on pharmacotherapy and 8.3 (1.8) % in those who were not treated with glucose-lowering medications. The characteristics between the two diet groups as well as between participants who completed the intervention ($n = 32$) and those who dropped out ($n = 9$) were similar (Table S1).

Weight loss and glycemic control

At 6 months in the overall sample, 29.3% of participants achieved weight loss ≥ 12 kg and 39.0% lost ≥ 10% of body weight by ITT analysis whereas the percentages were 37.5% and 50.0% respectively by complete case analysis (Fig. 2A and B). T2D remission rate was 56.1% by ITT analysis and 71.9% by complete case analysis (Fig. 3A). The mean weight loss was 9.7 kg (95% CI, 7.3–12.1) (Fig. 2C, Table S2). The mean decrease in HbA1c level was 1.7% (95% CI, 1.2–2.3) (Fig. 3B). The lost weight and decreased HbA1c level during the intensive weight loss period were well maintained in the subsequent 3 months.

Fasting glucose dropped from 7.4 mmol/L to 6.3 mmol/L during the intervention period (Fig. 3C). CGM data revealed more time spent in TIR and less time spent in TAR during follow-up than baseline (Fig. 3D). Approximately 20% of participants achieved normoglycemia (Fig. 3A). Greater weight loss was associated with a considerably higher probability of achieving normoglycemia, but not T2D remission (Fig. 3E). For example, the probability of achieving normoglycemia was 29.6%, 43.8%, and 66.7%, respectively, for people who lost at least 5%, 10%, and 15% of body weight. In contrast, the probability of achieving T2D remission was 70.4%, 75.0%, and 77.8%, respectively, for people who lost at least 5%, 10%, and 15% of body weight.

Body composition and adiposity measures

Fat mass loss (6.9 kg [95% CI, 4.3–9.5]) was greater than muscle mass loss (1.7 kg [95% CI, 0.7–2.7]) (Fig. 2D). BMI decreased by 3.4 kg/m^2 (95% CI, 2.7–4.1) and waist circumference decreased by 11.2 cm (95% CI, 8.8–13.6) (Table 2). Hip circumference and skinfold thickness at biceps, triceps, subscapular and suprailiac sites decreased.

Table 1 Baseline characteristics of the enrolled participants

	All (*n* = 41)	Low-calorie formula diet (*n* = 21)	Low-calorie real food-based diet (*n* = 20)	*P* value[a]
Age, mean (SD), years	40.4 (8.8)	38.5 (9.7)	42.4 (7.4)	0.11
Male, *n* (%)	28 (68.3)	15 (71.4)	13 (65.0)	0.06
Education, *n* (%)				0.20
< Bachelor's degree	14 (34.1)	9 (42.9)	5 (25.0)	
Bachelor's degree	23 (56.1)	9 (42.9)	14 (70.0)	
> Bachelor's degree	4 (9.8)	3 (14.3)	1 (5.0)	
Weight, mean (SD), kg	87.0 (20.3)	90.1 (24.5)	83.9 (14.6)	0.33
Body mass index, mean (SD), kg/m^2	30.2 (5.3)	30.6 (6.3)	29.7 (4.3)	0.61
Waist circumference, mean (SD), cm	102.7 (13.1)	104.5 (16.4)	100.9 (8.3)	0.39
MRI-derived liver fat content, mean (SD), %	13.8 (7.7)	12.9 (8.1)	14.7 (7.3)	0.46
MRI-derived pancreatic fat content, mean (SD), %	6.1 (4.6)	5.7 (4.7)	6.5 (4.7)	0.62
Duration of diabetes, mean (SD), years	2.7 (2.5)	2.6 (2.4)	2.8 (2.8)	0.86
Hemoglobin A1c, mean (SD), %	8.0 (1.8)	8.2 (1.9)	7.8 (1.7)	0.52
Fasting glucose, mean (SD), mmol/L	7.6 (2.5)	7.3 (1.8)	8.0 (3.1)	0.43
HOMA2 indexes, mean (SD)				
HOMA2-IR	2.7 (1.2)	2.5 (0.9)	3.0 (1.4)	0.32
HOMA2-%B	97.8 (51.1)	96.8 (49.1)	98.8 (54.4)	0.90
HOMA2-%S	43.2 (17.1)	45.7 (16.3)	40.5 (17.9)	0.34
Arginine stimulation test				
INS_{AUC}, median (Q1, Q3), pmol/L*min	1427 (869, 2242)	993 (725, 1697)	1777 (1192, 4085)	0.03
Acute insulin response, median (Q1, Q3), pmol/L	206 (97, 348)	183 (83, 232)	267 (155, 542)	0.09
Acute C-peptide response, mean (SD), ng/mL	2.7 (1.8)	2.3 (1.4)	3.1 (2.0)	0.16
KITT, mean (SD), %/min	1.2 (0.9)	1.1 (0.8)	1.3 (1.0)	0.70
No. of glucose-lowering drugs, n (%)				0.06
0	10 (24.4)	2 (9.5)	8 (40.0)	
1	16 (39.0)	10 (47.6)	6 (30.0)	
≥2	15 (36.6)	9 (42.9)	6 (30.0)	
Family history of diabetes, *n* (%)	26 (63.4)	12 (57.1)	14 (70.0)	0.60
Current smoking, *n* (%)	11 (26.8)	5 (23.8)	6 (30.0)	0.93
Hypertension, *n* (%)	10 (24.4)	8 (38.1)	2 (10.0)	0.08
Hyperlipidemia, *n* (%)	8 (19.5)	4 (19.1)	4 (20.0)	1.00
Systolic blood pressure, mean (SD), mm Hg	131.6 (17.0)	131.5 (16.2)	131.8 (18.2)	0.97
Diastolic blood pressure, mean (SD), mm Hg	85.2 (9.0)	86.6 (9.0)	83.8 (9.0)	0.32
Total cholesterol, mean (SD), mmol/L	5.2 (1.5)	5.1 (1.5)	5.3 (1.6)	0.65
LDL-C, mean (SD), mmol/L	3.3 (0.8)	3.4 (1.0)	3.3 (0.6)	0.65
HDL-C, mean (SD), mmol/L	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.87
Triglycerides, median (Q1, Q3), mmol/L	1.9 (1.5, 2.8)	1.8 (1.4, 2.1)	2.3 (1.6, 2.8)	0.18

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA2, Homeostasis Model Assessment 2; INS_{AUC}, area under curve of insulin; IR, insulin resistance; KITT, glucose disposal rate for insulin tolerance test; LDL-C, low-density lipoprotein cholesterol; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; MRI, magnetic resonance imaging; %B, beta-cell function; %S, insulin sensitivity

[a]Differences between groups were assessed using the t-test, Wilcoxon signed-rank test or chi-square test where relevant

Liver and pancreatic fat

MRI derived liver fat was 13.9% at baseline, 5.1% at 3 months, and 5.0% at 6 months; the decrease during the intervention was 8.9% (95% CI, 6.3–11.5) (Fig. 2E). MRI derived pancreatic fat was 5.4% at baseline, 4.3% at 3 months and 4.0% at 6 months; the decrease was 1.4% (95% CI, 0.0-2.8) (Fig. 2F).

Insulin sensitivity and insulin secretory response

Insulin sensitivity improved during the intervention, supported by the increase in insulin-induced glucose disposal rate (KITT, 0.8%/min [95% CI, 0.3–1.2]) and HOMA2-%S (14.2 [95% CI, 6.6–21.8) (Fig. 3F, Table S2, Table 2). However, there was no improvement in insulin secretory response assessed by AIR, ACR, and INS_{AUC} (Fig. 3G). No increase in HOMA2-%B was observed.

Blood pressure and serum lipids

Systolic blood pressure was 6.6 mm Hg (95% CI, 0.6–12.6) lower and diastolic blood pressure was 4.8 mm Hg (95% CI, 1.1–8.6) lower at 6 months than baseline. The serum cholesterol profile improved with decreased

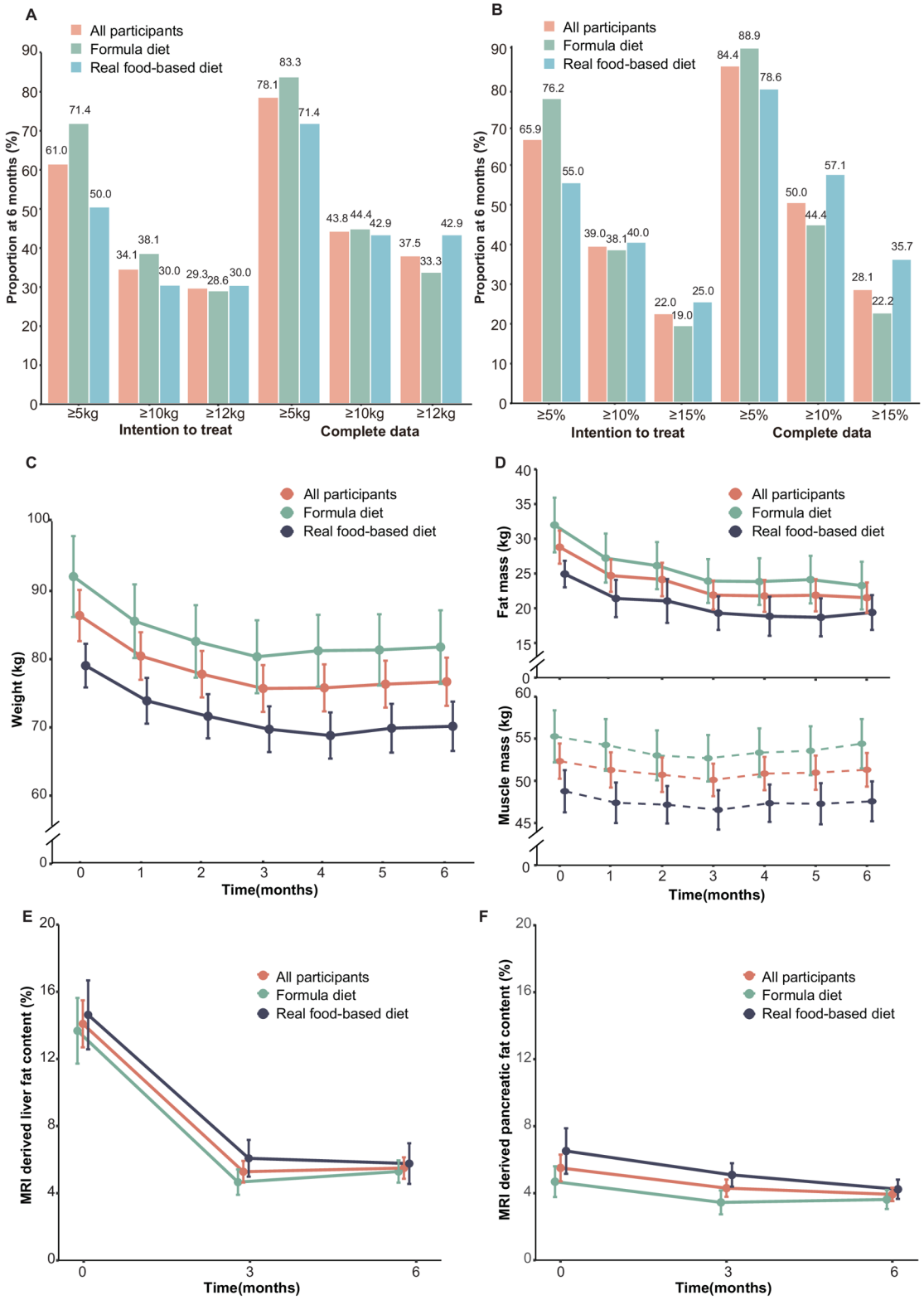

Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Changes in body weight, body composition, and intraorgan fat following the low-calorie diet intervention (**A**) Proportion of participants achieving weight loss ≥ 5 kg, ≥ 10 kg, and ≥ 12 kg at 6 months. (**B**) Proportion of participants achieving weight loss ≥ 5%, ≥ 10%, and ≥ 15% at 6 months. (**C**) Change in body weight during 6-month intervention. (**D**) Change in muscle mass and fat mass during 6-month intervention. (**E**) Change in liver fat during 6-month intervention. (**F**) Change in pancreatic fat during 6-month intervention. Error bars show the 95% confidence intervals. For binary outcomes, results from both the intention-to-treat analysis and complete case analysis are provided. Specific data are shown in Table S2

concentrations of small dense LDL-C and triglycerides and increased concentration of HDL-C.

LCFD vs. LCRFD

There was no difference between the two types of diet in any of the outcomes comparing 6 months with baseline (Tables S2 and S3). When comparing 3 months with baseline, LCRFD led to less muscle mass loss and a smaller reduction in hip circumference and LDL-C level than LCFD.

Responders and nonresponders

Compared with responders for T2D remission, nonresponders were more likely to be women, and had a higher percent of fat mass, lower percent of muscle mass, less muscle mass, longer diabetes duration, poorer glycemic control, and lower HOMA2-%B (Table S4). There was no difference in the post-intervention change in most outcomes between responders and nonresponders (Table S5). However, responders had a greater reduction in pancreatic fat content and a smaller reduction in HbA1c level, time spent in TAR, and diastolic blood pressure.

Adverse events

No serious adverse event was reported (Table S6). The most frequently reported adverse events were gastrointestinal disorders, especially constipation.

Discussion

During this 6-month low-calorie diet intervention in a Chinese sample with T2D who were overweight or obese, 29.3% of participants had weight loss of 12 kg or more, 39.0% lost at least 10% of weight, and 56.1% achieved T2D remission. Significant improvements in waist and hip circumference, subcutaneous skinfold thickness, blood pressure, serum cholesterol, and insulin sensitivity were observed, but not insulin secretion. More fat mass was lost than muscle mass. Both liver fat and pancreatic fat decreased. LCFD and LCRFD were similarly effective in reducing weight, achieving T2D remission, and improving other cardiometabolic risk factors. Various factors associated with individual variability in T2D remission were identified. No serious adverse event was reported.

Our study is the first low-calorie diet intervention targeting diabetes remission through rapid substantial weight loss in people with T2D in China. T2D remission rate of our study was comparable to other trials employing low-calorie diet programs (800–950 kcal/d): 43% in STANDby, 46% in DiRECT, 56% in DiRECT-Aus, and 61% in DIADEM-I [8–10, 12]. The relative weight loss was also comparable. For example, 22% of participants lost at least 15% of body weight in our study while 24%, 21%, and 21% of participants in DiRECT, DiRECT-Aus, and DIADEM-I achieved 15% weight loss, respectively [8, 9, 12]. Serious adverse events were rare or absent. Our study participants had the lowest BMI, the highest HbA1c level and comparable diabetes duration among all studies under comparison which were conducted in the UK (White and South Asian people), Qatar, and Australia [8–10, 12]. Taken together, low-calorie diet intervention is an effective and safe dietary strategy for substantial weight loss and T2D remission across populations of differing characteristics including different ethnicities and geographical locations.

A unique strength of our study was comparing two dietary approaches, LCFD and LCRFD. Previous low-calorie diet intervention studies for T2D remission predominantly used LCFD [7]. However, widely prescribing liquid formula meal replacement for therapeutic use faces certain challenges such as cultural acceptability, affordability, accessibility, and palatability [18, 19]. Furthermore, T2D remission achieved by short-term use of LCFD failed to maintain in the long run in many individuals [20–22]. Our study found that LCFD and LCRFD had similar effects on weight loss, T2D remission, and improving cardiometabolic risk profiles in 6 months. Whether T2D remission achieved by LCRFD is more durable than by LCFD requires further investigation. Macronutrient compositions did not appear to materially affect the effect of low-calorie diets on weight loss and T2D remission [7–10, 12].

An inconsistency between some of the previous studies (e.g., DiRECT and DiRECT-Aus) and our study is that we did not find a gradient relationship between weight loss amount and T2D remission rate, although such a gradient relationship existed for normoglycemia [8, 12]. Nonetheless, in line with the literature, the majority of the lost weight was fat mass which was accompanied by a significant decrease in liver and pancreatic fat [9, 10, 23–25]. Liver and pancreatic fat loss in our study were comparable to those reported from other low-calorie diet intervention studies, 6.7-12.9% for liver fat loss and 0.8-1.8% for pancreatic fat loss. Furthermore, these studies consistently found a significant improvement in insulin sensitivity assessed by homeostasis model assessment,

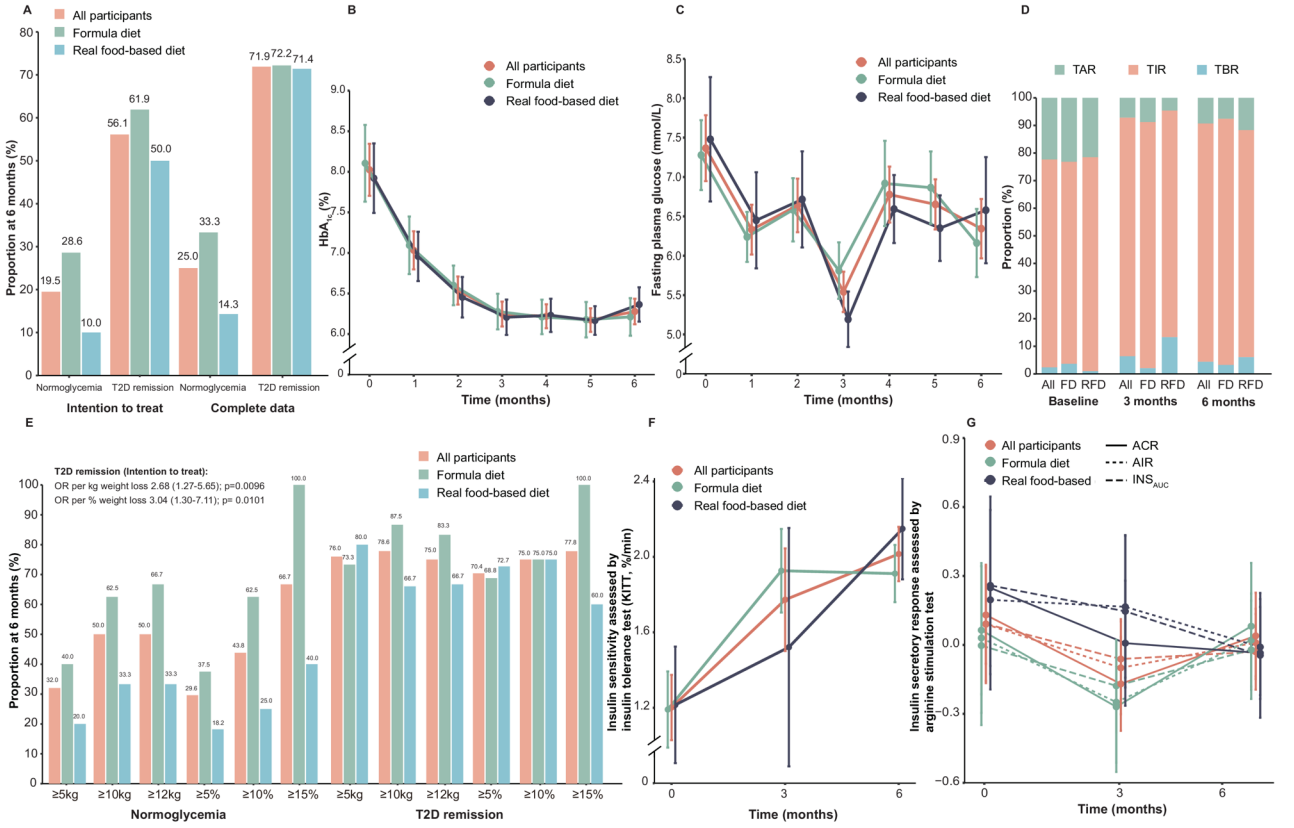

Fig. 3 Rates of T2D remission and normoglycemia as well as changes in glycemic control, insulin sensitivity, and insulin secretory response following the low-calorie diet intervention (**A**) Proportion of participants achieving T2D remission (HbA1c < 6.5% after being off medication for ≥ 3 months) and normoglycemia (HbA1c < 5.7% after being off medication for ≥ 3 months) at 6 months. (**B**) Change in HbA1c level during 6-month intervention. (**C**) Change in fasting plasma glucose during 6-month intervention. (**D**) Change in continuous glucose monitoring outcomes during 6-month intervention. (**E**) Rates of T2D remission and normoglycemia at different weight loss targets achieved at 6 months. (**F**) Change in insulin sensitivity assessed by insulin tolerance test during 6-month intervention. (**G**) Change in insulin secretory response assessed by arginine stimulation test during 6-month intervention. Error bars show the 95% confidence intervals. ACR = acute C-peptide response. AIR = acute insulin response. INS_{AUC} = area under the curve of insulin. FD = formula diet. OR = odds ratio. RFD = real food-based diet. T2D = type 2 diabetes. TAR = time above range (> 10 mmol/L). TBR = time below range (< 3.9 mmol/L). TIR = time in range (3.9–10 mmol/L). ACR, AIR and INS_{AUC} were standardized before analysis. For binary outcomes, results from both the intention-to-treat analysis and complete case analysis are provided. Specific data are shown in Table S2

isoglycemic-hyperinsulinemic clamp or insulin tolerance test [9, 10, 23, 24, 26]. However, arginine-induced insulin secretory response did not increase in our study but increased in the Counterpoint ($n = 11$) and Counterbalance ($n = 30$) studies after 8 weeks of a very low-calorie diet (600–700 kcal/d), among predominantly Caucasian people with T2D [23, 24]. Compared with people of European ancestry, Chinese people with T2D have more prominent impairment in insulin secretion [11]. Whether impaired beta-cell secretory capacity may not be recovered or requires a longer period of low-calorie diet intervention or more extreme energy restriction is unclear. Fat accumulation in the pancreas has been associated with impaired insulin secretion, but this relationship depends on factors such as the degree of disrupted glucose homeostasis, genetic predisposition to diabetes, and possibly liver fat content [27, 28]. Also, there is currently no data describing what degree of reduction in pancreatic fat may result in the recovery of insulin secretion.

Our study revealed similar and distinct characteristics between responders and nonresponders compared with the published findings [24, 25]. Consistently, nonresponders had a longer diabetes duration and a higher HbA1c level than responders whereas pancreatic fat content was similar at baseline [24, 25]. Comparable amount of body weight loss and liver fat loss were observed. However, more inconsistencies were revealed [24, 25]. For example, compared with responders, nonresponders had a greater reduction in HbA1c in our study and a smaller reduction in the Steven et al.' study [24], but had no decrease in the Taylor et al.'s study [25]. Weight loss lowered fasting glucose in both groups in our and Steven et al.' studies, but only in responders in the Taylor et al.' study. Pancreatic fat content decreased only in

Table 2 Changes in adiposity measures, body composition, and other cardiometabolic risk factors following the low-calorie diet intervention[a]

	n	Baseline	3 months	Intervention effect	*n*	Baseline	6 months	Intervention effect
		Mean (SD)	Mean (SD)	Difference[b] (95% CI)		Mean (SD)	Mean (SD)	Difference[b] (95% CI)
Adiposity measures								
Body mass index, kg/m^2	32	29.8 (5.4)	26.0 (5.3)	-3.7 (-4.3 to -3.2)	32	29.8 (5.4)	26.3 (5.5)	-3.4 (-4.1 to -2.7)
Waist circumference, cm	32	102.5 (13.9)	91.6 (14.1)	-10.8 (-12.9 to -8.8)	32	102.5 (13.9)	91.3 (13.7)	-11.2 (-13.6 to -8.8)
Hip circumference, cm	32	105.2 (12.6)	97.1 (11.6)	-8.1 (-10.0 to -6.3)	32	105.2 (12.6)	97.7 (10.5)	-7.5 (-9.6 to -5.4)
Biceps skinfold, mm	29	15.8 (6.9)	11.0 (5.0)	-4.9 (-6.8 to -2.9)	29	15.8 (6.9)	11.1 (3.7)	-4.7 (-6.8 to -2.7)
Triceps skinfold, mm	29	18.3 (7.5)	12.9 (4.1)	-5.3 (-7.5 to -3.2)	29	18.3 (7.5)	13.3 (4.7)	-4.9 (-7.1 to -2.7)
Subscapular skinfold, mm	29	25.9 (6.8)	20.6 (4.6)	-5.4 (-7.3 to -3.5)	29	25.9 (6.8)	21.8 (5.1)	-4.1 (-6.2 to -2.0)
Suprailiac skinfold, mm	30	22.6 (7.4)	14.8 (5.4)	-7.7 (-10.5 to -4.9)	30	22.6 (7.4)	14.5 (5.1)	-8.1 (-10.5 to -5.6)
Body composition								
Body fat percentage, %	30	32.8 (9.2)	28.2 (9.9)	-4.6 (-6.3 to -2.9)	30	32.3 (8.9)	27.2 (9.6)	-5.1 (-7.4 to -2.7)
Body muscle percentage, %	30	61.9 (9.8)	67.7 (9.7)	5.7 (4.5 to 7.0)	30	62.5 (9.5)	68.6 (9.7)	6.1 (4.2 to 8.0)
HOMA2 indexes								
HOMA2-IR	29	2.6 (1.3)	1.7 (0.6)	-0.9 (-1.3 to -0.5)	32	2.6 (1.3)	2.0 (0.9)	-0.6 (-1.0 to -0.2)
HOMA2-%B	29	101.9 (53.3)	126.4 (52.8)	24.4 (3.3 to 45.5)	32	101.4 (53.4)	108.3 (45.2)	6.8 (-9.5 to 23.2)
HOMA2-%S	28	46.6 (18.2)	68.2 (24.3)	21.7 (16.5 to 26.8)	32	45.7 (17.5)	59.9 (24.5)	14.2 (6.6 to 21.8)
Blood pressure, mm Hg								
Systolic blood pressure	32	128.7 (14.9)	118.8 (14.3)	-9.9 (-16.2 to -3.6)	32	128.7 (14.9)	122.1 (17.0)	-6.6 (-12.6 to -0.6)
Diastolic blood pressure	32	84.1 (9.0)	78.6 (9.0)	-5.5 (-9.7 to -1.3)	32	84.1 (9.0)	79.3 (10.0)	-4.8 (-8.6 to -1.1)
Serum lipids, mmol/L								
Total cholesterol	32	5.2 (1.5)	4.6 (1.0)	-0.6 (-1.0 to -0.2)	32	5.2 (1.5)	4.9 (0.9)	-0.3 (-0.8 to 0.2)
LDL-C	29	3.4 (0.7)	3.0 (0.8)	-0.3 (-0.6 to -0.1)	32	3.3 (0.7)	3.2 (0.7)	-0.2 (-0.4 to 0.0)
HDL-C	28	1.0 (0.2)	1.1 (0.2)	0.0 (-0.0 to 0.1)	31	1.0 (0.2)	1.2 (0.2)	0.2 (0.1 to 0.2)
Triglycerides	29	2.0 (0.9)	1.2 (0.4)	-0.7 (-1.0 to -0.5)	32	2.0 (0.8)	1.4 (0.9)	-0.5 (-0.8 to -0.3)
Small dense LDL-C	27	1.1 (0.5)	0.8 (0.3)	-0.4 (-0.6 to -0.2)	30	1.1 (0.5)	0.9 (0.3)	-0.2 (-0.4 to -0.1)
Free fatty acids	29	0.7 (1.0)	0.5 (0.2)	-0.2 (-0.6 to 0.2)	32	0.7 (1.0)	0.4 (0.1)	-0.3 (-0.6 to 0.0)

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA2, Homeostasis Model Assessment 2; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; %B, beta-cell function; %S, insulin sensitivity

[a] Results by the type of low-calorie diets are shown in Table S3

[b] Differences were estimated using the paired-t test

responders in our study, but a similar decrease in both groups was reported from the other two studies. Unlike the findings from the Steven et al.'s study, we did not find that responders had a higher degree of insulin resistance and higher arginine-induced insulin secretory response at baseline. Arginine-induced first-phase insulin secretory response increased in both groups in the Steven et al.'s study and only in responders in the Taylor et al.'s study; it however did not increase in both groups in our study. Responders in our study had a higher baseline HOMA2-%B, a measure of steady-state insulin secretion during fasting instead of post-challenge insulin secretory response [29], but HOMA2-%B may not robustly assess beta-cell function in people with T2D and obesity [30].

Based on 6 months of CGM data, our study revealed that low-calorie diet intervention reduced glycemic variability by decreasing the time spent in hyperglycemic range and increasing the time spent in a desired target range, while the time spent in hypoglycemic range did not increase significantly. Some of these findings are supported by the CGM results from the DIADEM-I study [9]. Blood pressure improvement was not seen in STANDby, DIADEM-I, and DiRECT studies, but both systolic and diastolic blood pressure decreased in our study [8–10]. Serum cholesterol control improved in our study and some of the published studies [9, 24], but not all [10]. Differences in these results may be attributable to a number of reasons including different intervention time and characteristics of participants. Nevertheless, the improvement in many facets of cardiometabolic health is expected following a substantial amount of weight loss.

Our study has limitations. First, between group comparisons are subject to confounding bias due to the non-randomized design. Second, this is a small pilot study, although the sample size is comparable to or even larger than many other published pilot studies [7, 10]. Therefore, some estimates, in particular subgroup results, may be imprecise. Third, a control group following guideline-based care was not designed, because T2D remission rate is expected to be low [8, 9]. Fourth, our study had a slightly high drop-out rate of 22% (9/41), but three left the study due to COVID-19 related lockdowns and

restrictions and one relocated to another city. Fifth, 6 months are insufficient to determine the long-term effectiveness of low-calorie diet intervention. Sixth, we did not have participants with long duration greater than 8 years. Seventh, micronutrients and vitamins were not matched between the two diets. Also, micronutrients and vitamins may not be adequately consumed, but it is unlikely that 3 months of low-calorie diet would lead to micronutrient deficiency in people who are overweight or obese. Eighth, the enrolled participants were motivated patients, ~68% were men, and ~66% had a bachelor's degree or higher. Thus, findings of this study may not be generalized to the general population of Chinese people with T2D. Given these limitations, future intervention studies should consider a randomized study design, longer intervention period, larger sample size through recruiting participants from multiple sites, and inclusion of a standard care group for comparison and patients with longer diabetes duration.

Conclusions

Findings of this study suggest that T2D remission rate and weight loss amount resulting from the low-calorie diet intervention in Chinese people were comparable to those reported in other populations of distinct body composition and T2D phenotypes. A few factors contributing to individual variability in T2D remission were identified. LCRFD was an alternative dietary strategy to LCFD for weight loss and diabetes remission.

Abbreviations

ACR	Acute C peptide response
AIR	Acute insulin response
BMI	Body mass index
CGM	Continuous glucose monitoring
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HOMA2	Updated homeostatic model assessment
HOMA2-%B	Updated homeostatic model assessment of beta-cell function
HOMA2-%S	Updated homeostatic model assessment of insulin sensitivity
HOMA2-IR	Updated homeostatic model assessment of insulin resistance
INS_{AUC}	Area under curve of insulin
ITT	Intention-to-treat
KITT	Rate constant for plasma glucose disappearance
LCFD	Low-calorie formula diet
LCRFD	Low-calorie real food-based diet
LDL-C	Low-density lipoprotein cholesterol
RCT	Randomized controlled trial
T2D	Type 2 diabetes
TAR	Time above range
TBR	Time below range
TIR	Time in range

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01101-z.

Supplementary Material 1

Supplementary Material 2

Author contributions

VWZ, FT, ZL, and NF designed the study. ZL and FT screened and recruited participants. SW, JW, YT, and YD were responsible for data and biospecimen collection and patient follow-up. YL and ZS were responsible for all diet-related work. NF, XD, and YX contributed to data curation and provided statistical expertise. VWZ and FT supervised and coordinated the entire study. VWZ drafted the manuscript. All authors contributed to the interpretation of the data and critical revision of the manuscript for important intellectual content and approved the final draft. VWZ is the guarantor of this work and, as such, had 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.

Funding

This study was supported by the National Natural Science Foundation of China (82373551, 82304117), the National Key R&D Program of China (2023YFC2506700), the program of Shanghai Clinical Key Specialty (B01A3), the Shanghai Municipal Commission of Science and Technology Medical Innovation Research Project (23Y11921500), Traditional Chinese Medicine Inheritance and Development Project of Shanghai Medical Innovation & Development Foundation (WLJH2021ZYGZS005), Traditional Chinese Medicine Science and Technology Development Project of Shanghai Medical Innovation & Development Foundation (WL-XJRY-2021001K, WL-LCZD-2022001K), the Shanghai Key Discipline of Public Health Grants Award (GWVI-11.1-20), and the Innovative Research Team of High-Level Local Universities in Shanghai.

Data availability

Data used for this study are available from the corresponding author upon reasonable request for an approved study.

Declarations

Ethical approval and consent to participate

All participants provided written informed consent before participating in this intervention study. The study protocol was approved by the Ethics Committee of the Shanghai Municipal Hospital of Traditional Chinese Medicine (Approval ID: 2022SHL-KY-23-02).

Consent for publication

Not applicable.

Competing interests

The authors have no relevant conflict of interest to disclose.

Author details

[1]Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200025, China
[2]Department of Epidemiology and Biostatistics, School of Public Health, Shanghai Jiao Tong University School of Medicine, 415 East No. 1 Building 227 South Chongqing Rd, Shanghai, China
[3]Department of Clinical Nutrition, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[4]Department of Chinese Medicine & Integrative Medicine, Shanghai Geriatric Medical Center, Zhongshan Hospital, Fudan University, Shanghai, China
[5]Department of Health and Behavioral Studies, Teachers College, Columbia University, New York, USA

Received: 2 December 2024 / Accepted: 21 February 2025
Published online: 14 March 2025

References

1. World Health Organization. Diabetes data and statistics. Available from: https://who-sandbox.squiz.cloud/en/health-topics/noncommunicable-diseases/diabetes/data-and-statistics. Accessed September 9 2024.
2. Klein S, Gastaldelli A, Yki-Järvinen H, Scherer PE. Why does obesity cause diabetes? Cell Metabol. 2022;34(1):11–20. https://doi.org/10.1016/j.cmet.2021.12.012

3. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in Diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S158–78. https://doi.org/10.2337/dc24-S009
4. Zhong VW, Yu D, Zhao L, et al. Achievement of Guideline-Recommended targets in diabetes care in China: A nationwide Cross-Sectional study. Ann Intern Med. 2023;176(8):1037–46. https://doi.org/10.7326/M23-0442
5. Anjana RM, Unnikrishnan R, Deepa M, et al. Achievement of guideline recommended diabetes treatment targets and health habits in people with self-reported diabetes in India (ICMR-INDIAB-13): a National cross-sectional study. Lancet Diabetes Endocrinol. 2022;10(6):430–41. https://doi.org/10.1016/S2213-8587(22)00072-9
6. Wang L, Li X, Wang Z, et al. Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999–2018. JAMA. 2021;326(8):1–13. https://doi.org/10.1001/jama.2021.9883
7. Churuangsuk C, Hall J, Reynolds A, Griffin SJ, Combet E, Lean MEJ. Diets for weight management in adults with type 2 diabetes: an umbrella review of published meta-analyses and systematic review of trials of diets for diabetes remission. Diabetologia. 2022;65(1):14–36. https://doi.org/10.1007/s00125-021-05577-2
8. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541–51. https://doi.org/10.1016/S0140-6736(17)33102-1
9. Taheri S, Zaghloul H, Chagoury O, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. Lancet Diabetes Endocrinol. 2020;8(6):477–89. https://doi.org/10.1016/S2213-8587(20)30117-0
10. Sattar N, Welsh P, Leslie WS, et al. Dietary weight-management for type 2 diabetes remissions in South Asians: the South Asian diabetes remission randomised trial for proof-of-concept and feasibility (STANDby). Lancet Reg Health Southeast Asia. 2023;9:100111. https://doi.org/10.1016/j.lansea.2022.100111
11. Hu C, Jia W. Diabetes in China: epidemiology and genetic risk factors and their clinical utility in personalized medication. Diabetes. 2017;67(1):3–11. https://doi.org/10.2337/dbi17-0013
12. Hocking SL, Markovic TP, Lee CMY, Picone TJ, Gudorf KE, Colagiuri S. Intensive lifestyle intervention for remission of early type 2 diabetes in primary care in Australia: DiRECT-Aus. Diabetes Care. 2024;47(1):66–70. https://doi.org/10.2337/dc23-0781
13. Bonora E, Moghetti P, Zancanaro C, et al. Estimates of in vivo insulin action in man: comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. J Clin Endocrinol Metab. 1989;68(2):374–8. https://doi.org/10.1210/jcem-68-2-374
14. Tangphao O, Grossmann M, Chalon S, Hoffman BB, Blaschke TF. Pharmacokinetics of intravenous and oral L-arginine in normal volunteers. Br J Clin Pharmacol. 1999;47(3):261–6. https://doi.org/10.1046/j.1365-2125.1999.00883.x
15. Clinical application of. Arginine stimulation test in estimating islet β-cell function in individuals with different abnormalities of glucose metabolism. Chin J Endocrinol Metabolism. 2005;21(03):215–8.
16. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593–603. https://doi.org/10.2337/dci19-0028
17. Riddle MC, Cefalu WT, Evans PH, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. Diabetes Care. 2021;44(10):2438–44. https://doi.org/10.2337/dci21-0034
18. Farhat G, Majeed S, Rutter MK, Issa B, Harvie M. Comparing the acceptability of total diet replacement and food-based low energy diets for type 2 diabetes remission amongst South Asians: a public and patient involvement activity. NIHR Open Res. 2022;1:24. https://doi.org/10.3310/nihropenres.13233.4
19. Gazan R, Brouzes CMC, Vieux F, Maillot M, Lluch A, Darmon N. Mathematical optimization to explore tomorrow's sustainable diets: A narrative review. Adv Nutr. 2018;9(5):602–16. https://doi.org/10.1093/advances/nmy049
20. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the direct open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019;7(5):344–55. https://doi.org/10.1016/S2213-8587(19)30068-3
21. Lean ME, Leslie WS, Barnes AC, et al. 5-year follow-up of the randomised diabetes remission clinical trial (DiRECT) of continued support for weight loss maintenance in the UK: an extension study. Lancet Diabetes Endocrinol. 2024;12(4):233–46. https://doi.org/10.1016/S2213-8587(23)00385-6
22. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA. 2012;308(23):2489–96. https://doi.org/10.1001/jama.2012.67929
23. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54(10):2506–14. https://doi.org/10.1007/s00125-011-2204-7
24. Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very Low-Calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. Diabetes Care. 2016;39(5):808–15. https://doi.org/10.2337/dc15-1942
25. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for B cell recovery. Cell Metabol. 2018;28(4):547–e5563. https://doi.org/10.1016/j.cmet.2018.07.003
26. Umphonsathien M, Prutanopajai P, Aiam-O-Ran J, et al. Immediate and long-term effects of a very-low-calorie diet on diabetes remission and glycemic control in obese Thai patients with type 2 diabetes mellitus. Food Sci Nutr. 2019;7(3):1113–22. https://doi.org/10.1002/fsn3.956
27. Wagner R, Eckstein SS, Yamazaki H, et al. Metabolic implications of pancreatic fat accumulation. Nat Rev Endocrinol. 2022;18(1):43–54. https://doi.org/10.1038/s41574-021-00573-3
28. Gerst F, Wagner R, Kaiser G, et al. Metabolic crosstalk between fatty pancreas and fatty liver: effects on local inflammation and insulin secretion. Diabetologia. 2017;60(11):2240–51. https://doi.org/10.1007/s00125-017-4385-1
29. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008;294(1):E15–26. https://doi.org/10.1152/ajpendo.00645.2007
30. Cao C, Koh HCE, Reeds DN, Patterson BW, Klein S, Mittendorfer B. Critical evaluation of indices used to assess β-Cell function. Diabetes. 2023;73(3):391–400. https://doi.org/10.2337/db23-0613

Publisher's note