*The Journal of Clinical Endocrinology & Metabolism*, 2023, **108**, 1415–1424
https://doi.org/10.1210/clinem/dgac661
Advance access publication 14 December 2022
**Clinical Research Article**

# Effect of an Intermittent Calorie-restricted Diet on Type 2 Diabetes Remission: A Randomized Controlled Trial

**Xiao Yang,[1,2,3] Jiali Zhou,[1,4] Huige Shao,[5] Bi Huang,[5] Xincong Kang,[1,6,7] Ruiyu Wu,[1,8] Fangzhou Bian,[9] Minghai Hu,[10] and Dongbo Liu[1,2,11]**

[1]Horticulture College, Hunan Agricultural University, Changsha 410128, China
[2]Clinical Research Center, State Key Laboratory of Subhealth Intervention Technology, Changsha 410128, China
[3]Nutrition and Food Catering, Changsha Commerce and Tourism College, Changsha 410116, China
[4]Department of Shizi Mountain Primary Care, Changsha 410007, China
[5]Endocrinology Department, Changsha Central Hospital, Changsha 410004, China
[6]National Research Center of Engineering Technology For Utilization Ingredients From Botanicals, Changsha 410128, China
[7]Chinese Medicine Nutrition Center, Hunan Provincial Engineering Research Center of Medical Nutrition Intervention Technology for Metabolic Diseases, Changsha 410128, China
[8]Jinheyuan Outpatient Department, State Key Laboratory of Subhealth Intervention Technology Achievement Application Center, Changsha 410205, China
[9]Biological Sciences, University of California Irvine, Irvine, CA 92697, USA
[10]Department of Neurobiology and Human Anatomy, School of Basic Medical Science, Central South University, Changsha 410013, China
[11]College of Food Science and Technology, Hunan Agricultural University, Changsha 410128, China

**Correspondence:** Dongbo Liu, PhD, Horticulture College, Hunan Agricultural University, No. 1 Nongda Rd, Changsha 410128, China. Email: liudongbo@hunau.net; or Minghai Hu, MD, Department of Neurobiology and Human Anatomy, School of Basic Medical Science, Central South University, Changsha 410013, China. Email: 274854457@qq.com.

## Abstract

**Context:** The 2021 consensus report on the definition and interpretation of remission of type 2 diabetes (T2D) has been released. Although intermittent fasting diets (IF) are becoming very popular, no studies have investigated their benefit in diabetes remission.

**Objective:** The present study examined the effectiveness of IF in diabetes remission and potential remission durability.

**Methods:** Participants between ages 38 and 72 years with a duration of T2D of 1 to 11 years, a body mass index (BMI) of 19.1 to 30.4, 66.7% male, and antidiabetic agent use and/or insulin injection were randomly allocated at a ratio of 1:1 to the Chinese Medical Nutrition Therapy (CMNT) or control group. The primary outcome was diabetes remission, defined as a stable glycated hemoglobin $A_{1c}$ ($HbA_{1c}$) level of less than 48 mmol/mol (< 6.5%) for at least 3 months after discontinuing all antidiabetic medications. The secondary outcomes included $HbA_{1c}$ level, fasting blood glucose level, blood pressure, weight, quality of life, and medication costs. We conducted a 12-month follow-up to assess the continuation of remission.

**Results:** On completing the 3-month intervention plus 3-month follow-up, 47.2% (17/36) of participants achieved diabetes remission in the CMNT group, whereas only 2.8% (1/36) of individuals achieved remission in the control group (odds ratio 31.32; 95% CI, 2.39-121.07; $P < 0.0001$). The mean body weight of participants in the CMNT group was reduced by 5.93 kg (SD 2.47) compared to 0.27 kg (1.43) in the control group. After the 12-month follow-up, 44.4% (16/36) of the participants achieved sustained remission, with an $HbA_{1c}$ level of 6.33% (SD 0.87). The medication costs of the CMNT group were 77.22% lower than those of the control group (60.4/month vs 265.1/month).

**Conclusion:** This study demonstrated the clinical efficacy of CMNT in achieving diabetes remission for at least 1 year.

**Key Words:** randomized controlled trial, diet, diabetes remission, intermittent calorie-restricted diet

**Abbreviations:** BMI, body mass index; CMNT, Chinese Medical Nutrition Therapy; DiRECT, Diabetes Remission Clinical Trial; EQ-5D-5L, 5-level EuroQol 5 Dimensions; FBG, fasting blood glucose; FFQ, Food Frequency Questionnaire; $HbA_{1c}$, glycated hemoglobin $A_{1c}$; IF, intermittent fasting; T2D, type 2 diabetes.

Type 2 diabetes (T2D) is a lifelong progressive disease characterized by insulin resistance and hyperglycemia. Intensive therapy is required over time, with most patients ultimately requiring 2 or more medications to achieve and maintain glycemic control goals (1). T2D causes a significant increase in premature mortality, comorbidity, and health care costs and lowers quality of life (2–5). According to the International Diabetes Federation, diabetes-related health expenditure has grown considerably 316% over 15 years, from $232 billion in 2007 to $966 billion in 2021 (6).

Despite a widespread public consensus that T2D is irreversible and requires drug treatment escalation (7, 8), there is some evidence for the possibility of remission (9–12). The randomized controlled Diabetes Remission Clinical Trial (DiRECT) in the United Kingdom showed that 46% of non–insulin-taking participants achieved remission through energy

**Received:** 23 July 2022. **Editorial Decision:** 10 November 2022. **Corrected and Typeset:** 14 December 2022

restriction (11). An intensive lifestyle intervention led to diabetes remission in more than 60% of Middle Eastern participants who were younger (aged 18-50 years) and had a shorter duration of diabetes (0-3 years) (12). Increasing evidence of sustained improvement of glucose levels into the normal range has prompted a reevaluation of terminology and definitions (13). In 2021, a consensus statement initiated by the American Diabetes Association proposed a new diabetes remission criteria of glycated hemoglobin $A_{1c}$ ($HbA_{1c}$) less than 6.5% (48 mmol/mol) measured at least 3 months after cessation of glucose-lowering pharmacotherapy. Subsequent measurements of $HbA_{1c}$ at least annually are advised to confirm the continuation of remission (14).

Intermittent fasting (IF) is defined as periods of fasting interspersed with periods of *ad libitum* eating and has been a dietary strategy in managing chronic disorders. Three types of IF have received the most research attention: alternate-day fasting, the 5:2 diet, and time-restricted eating (15). Numerous animal studies have demonstrated improvements in insulin resistance, $HbA_{1c}$, long-term weight, and cardiometabolic benefits (16). Meta-analyses of randomized controlled trials indicated that intermittent energy restriction involving 2 to 3 days of periodic fasting led to reduced weight loss and body fat (17). Although some studies have investigated the health benefits of IF in humans, the efficiency in the context of diabetes remission remains to be elucidated and the long-term sustainability of dietary patterns needs further observation. The Chinese Medical Nutrition Therapy (CMNT) diet is a new proposed dietary approach based on IF involving 5 fasting days followed by 10 days of reintroducing everyday food items. The CMNT diet contains daily foods such as wheat, barley, rice, rye, and oat, and features reduced glycemic loads, calories, and carbohydrates, as well as increased unsaturated fatty acids (18, 19).

Here we present a randomized, controlled clinical study to investigate the efficacy of the CMNT diet on the induction of diabetes remission. We evaluated diabetes remission as the primary outcome, which was defined as stable $HbA_{1c}$ levels less than 6.5% (48 mmol/mol) after discontinuing antidiabetic medication for at least 3 months. We conducted a 12-month follow-up to confirm the continuation of remission. Secondary outcomes included $HbA_{1c}$ level, fasting blood glucose (FBG), blood pressure, weight, quality of life, and medication costs of the participants before and after the intervention.

## Materials and Methods

### Study Design and Participants

This was a parallel-design, open-label, randomized controlled trial. The study was performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the ethical principles described in the Declaration of Helsinki. It was conducted at primary care centers in the local community. Patients were independently recruited on various dates from January 2, 2019, to June 2, 2020. Each patient was closely monitored for 3 months during the intervention and for 12 months during follow-up. Their last days of intervention fell between May 2, 2019, and November 10, 2020. The study was approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20200235). All patients signed a written informed consent form prior to their participation.

Eligible participants were those who had been diagnosed with T2D based on the 1999 World Health Organization recommendations; who were between ages 18 and 75 years; who had a body mass index (BMI) between 18 and 35; who took T2D medications such as sulfonylureas, meglitinides, metformin, dipeptidyl peptidase-4 inhibitors (DPP4i), glucagon like peptide-1 agonist (GLP1-RA), thiazolidinedione, and insulin; and who could understand and carefully follow study directions.

Individuals were excluded if they had a diabetes type other than T2D; had used other medications that may affect blood glucose levels within 2 months; had used nonspecific dosages of antihypertensive or blood lipid–regulating drugs before screening; had New York Heart Association grade III or IV decompensated cardiac insufficiency; had unstable angina pectoris, coronary artery bypass grafting, myocardial infarction, or stent implantation history; had a history of 2 or more episodes of severe hypoglycemia within 6 years; had a past or present history of eating disorders; had systolic blood pressure greater than or equal to 160 mm Hg and/or diastolic blood pressure greater than or equal to 100 mm Hg; were pregnant or breastfeeding; or had other conditions that were unsuitable for participation as judged by the investigator or a medical expert in this study.

### Randomization and Masking

Participants were randomly allocated at a ratio of 1:1 to the CMNT or the control group with SAS/Base statistical software (SAS Inc) based on random numbers generated by the trial statistician. The study was assessor-blinded, as the nurses who performed the data collection (eg, weight, height, diabetes duration, medication dosage, and blood samples) and the technicians who conducted laboratory work were blinded to the assignment.

### Procedures

Individuals were randomly allocated at a ratio of 1:1 to the CMNT group or the control group using a computer-based random number generator. Then, they entered a 3-month intervention period that included 6 cycles of 15 intervention days. In each cycle, the CMNT group was assigned a diet with 5 modified fasting days (~840 kcal/day), during which patients were given CMNT kits at their regular meal schedule (ingredients see Table 1). During the fasting period, participants were instructed to choose a habitual time between 06:30 and 08:30 to start eating breakfast and to consume lunch and dinner between 11:00 and 13:00 and between 17:00 and 19:00, respectively. In the following 10 days of the ad libitum diet period, participants consumed ad libitum diets, as was done for the entire period in the control group (Fig. 1). Both groups followed Dietary Guidelines for Diabetes in China (2017 Edition) with foods of their choice during the consumption of ad libitum diets. During the period of follow-up, the CMNT and control groups both followed the ad libitum diets instead of the CMNT diet. The guidelines recommended a dietary approach that is rich in fiber (≥ 5 g fiber per serving) with low glycemic index carbohydrates. The macronutrient recommendations are as follows: approximately 50% to 65% of total energy intake from carbohydrates, 15% to 20% from protein, and approximately 20% to 30% from fat. The saturated fatty acid intake was not to exceed 7% of total calories. Both groups were supervised by nurses trained with the clinical standard protocol. Participants were reviewed by the study team to collect outcome data at baseline, postintervention (3 months), and

**Table 1. Chinese Medical Nutrition Therapy diet calorie content and ingredients**

| Calorie information | | | | |
|---|---|---|---|---|
| | Solid beverages | Fruit and vegetable gruel | Composite nutritional rice | Meal replacement biscuit |
| Energy density (kcal/100g) | 576.24 | 533.22 | 358.75 | 489.96 |
| Protein (g/100g) | 7.20 | 3.40 | 10.50 | 7.10 |
| Protein % | 5.28 | 2.52 | 11.86 | 5.97 |
| Fat (g/100g) | 50.00 | 30.80 | 1.80 | 18.20 |
| Fat % | 84.09 | 52.39 | 4.66 | 35.13 |
| Carbohydrates (g/100g) | 14.50 | 60.80 | 73.90 | 70.00 |
| Carbohydrates % | 10.63 | 45.09 | 83.48 | 58.90 |
| Fiber (g/100g) | 23.90 | — | — | 8.20 |
| Sodium (mg/100g) | 63.00 | 95.00 | 41.20 | 264.00 |

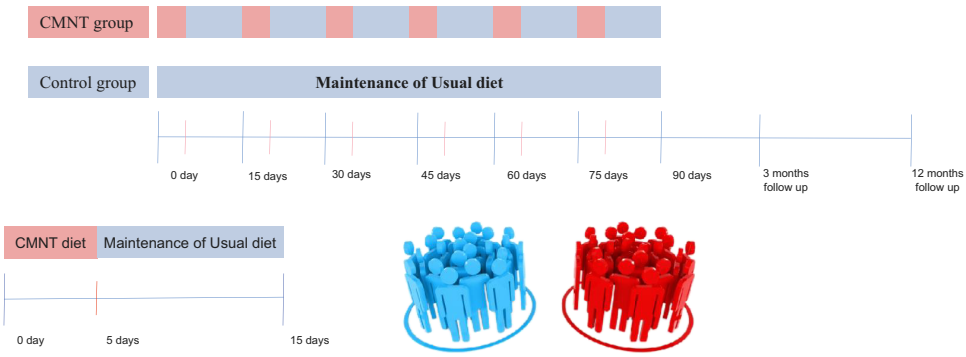
| Diet ingredients | | |
|---|---|---|
| | Daily intake | Note |
| **Breakfast** | | |
| Fruit and vegetable gruel | 50 g (266.61 kcal) | Fresh pumpkins, pumpkin seed kernel oil, maltodextrins, isomalto-oligosaccharide, casein, resistant dextrin, sodium ascorbate, potassium citrate, monoglycerides and diglycerides of fatty acids esters, vitamin E, tea polyphenols, and silicon dioxide |
| **Lunch** | | |
| Solid beverages | 25 g (144.06 kcal) | Pumpkin seed kernel oil, isomalto-oligosaccharide, casein, resistant dextrin, sodium ascorbate, potassium citrate, Monoglycerides and diglycerides of fatty acids esters, vitamin E, tea polyphenols, and silicon dioxide |
| Composite nutritional rice | 60 g (215.25 kcal) | Rice, millet, corn, buckwheat, quinoa, oat, spinach powders, lily root flour, cucumber powders, mushroom powder, wheat dietary fiber, bitter melon, pumpkins, potato, purple potato, sweet potato, mung bean, Konjac flour, inulin, *Fructus lyci, Ganoderma lucidum, Folium Mori, Poria cocos, Dioscorea opposita Thunb*. (Chinese yam), *Radix puerariae, Cordyceps militaris, Momordica grosvenori*, and edible refined salt |
| **Dinner** | | |
| Solid beverages | 25 g (144.06 kcal) | Pumpkin seed kernel oil, isomalto-oligosaccharide, casein, resistant dextrin, sodium ascorbate, potassium citrate, mono-and diglycerides of fatty acids esters, vitamin E, tea polyphenols, and silicon dioxide |
| Biscuit | 30 g (146.99 kcal) | Wheat flour, MAIKERENJIA, mix powder (quinoa, white kidney, wheat germ, azuki bean, black beans, yellow beans, *Liriopes radix*, glutinous rice, black rice, maize, round bract Plantago ovata husk powder, oat, buckwheat, Chinese yam, hawthorn, roselle, millet, brown rice, Chinese jujube, Chinese wolfberry, pecan nuts, chia seed, black sesame, white sesame, shiitake mushroom, Laminaria hyperborean, coffee), edible vegetable oils, potato protein, wheat dietary fiber powder, resistant dextrin, maltodextrin, and L-arabinose |

follow-up (3 and 12 months). All participants completed an informed consent form and guaranteed to supply real data about food intake at the beginning of the trial. Assessment was based on participant adherence to the diet and meal timing schedule. To assess compliance, participants were required to record in diet diaries and send them privately to the investigators. Food Frequency Questionnaires (FFQs) were used to record the food items and quantity consumed during the *ad libitum* diet periods for both groups (20). The records were collected at baseline and 3 months' intervention and 12 months' follow-up to assess the energy content of the foods consumed (Supplementary Table S2 [21]). The FFQ recorded the numbers of various types of food. An investigator who had obtained a good clinical practice certificate estimated the energy content of the daily meal, and another investigator double-checked the data.

All dosages of antidiabetic medications were stable at least 2 months before the initiation of the study. All patients continued taking their initially prescribed antidiabetic medications at the beginning of the study. The ingredients of the CMNT kit are commercially available and are listed in Table 1. The State Key Laboratory of Subhealth Intervention Technology in China standardized prepared precooked meals and distributed them to participants. The meals were in the form of rice, biscuits, and solid beverages. To prepare a meal, the participant needed to mix the given material with boiling water. The kit contains approximately 840 kcal/day (46% carbohydrates, 46% fat, 8% protein, Table 1). Participants in the CMNT group were limited to consuming the provided kits during the 5 fasting days. Intake of noncaloric beverages was allowed. Both groups maintained their usual exercise habits.

## Medication Reduction

Dosages of antidiabetic medications were adjusted and recorded by physicians depending on blood glucose levels (classification of antidiabetic agents based on action duration see Supplementary Approaches [21]). Adverse events were recorded and monitored using standardized questionnaires,




| Time point* | Screening | Baseline | 90days | 3 months follow up | 12 months follow up |
|---|---|---|---|---|---|
| Participant characteristics | ○ | | | | |
| Medication history | ○ | | | | |
| Anthropometrics | ○ | ○ | ○ | | ○ |
| Medication dosage | | ○ | ○ | ○ | ○ |
| Medication cost | | ○ | ○ | | ○ |
| Diabetes remission | | | | ○ | ○ |
| HbA1c | | ○ | | ○ | ○ |
| FBG | | ○ | ○ | | ○ |
| Blood pressure | | ○ | ○ | | ○ |
| Quality of life | | ○ | ○ | | ○ |

**Figure 1.** A chart of the Chinese Medical Nutrition Therapy (CMNT) intervention. Individuals were randomly allocated to the CMNT group or the control group. They were followed for 90 days, which included 6 cycles of 15 intervention days. During each cycle, the CMNT group was assigned a diet with 5 modified fasting days, during which time patients were given CMNT kits on their regular meal schedule. In the following 10 days of the ad libitum period, patients were able to reintroduce everyday food items. The control group consumed their ad libitum diet for 15 days.

diaries, and interviews at each study visit. According to the protocol, the participants consumed for 5 days an intermittent calorie-restricted CMNT diet followed by 10 days of the *ad libitum* diet as a cycle. When participants reached the criteria of antidiabetic medication reducing, the physician followed the principles to adjust the medication:

1. When participants achieved FBG or postprandial blood glucose (PBG) less than or equal to 5 mmol/L, the physician reduced the usage of antidiabetic medications.
2. If FBG was less than or equal to 5 mmol/L, priority would be given to reduce medium, long-acting and ultra-long-acting hypoglycemic agents; if PBG was less than or equal to 5 mmol/L, it would reduce the short-acting and ultra-short-acting hypoglycemic agents of corresponding meals.
3. If the action duration of the agents is the same or similar, the agents were reduced according to the following priority: insulin > insulin secretagogues agent > noninsulin secretagogues agent.

## Outcomes

The primary outcome was diabetes remission, which was defined as a stable $HbA_{1c}$ level less than 48 mmol/mol (< 6.5%) after at least 3 months of not taking antidiabetic medication.

The secondary outcomes included $HbA_{1c}$ level, FBG level (specification attached in Supplementary Approaches [21]), blood pressure, weight, quality of life, and medication costs. All measurements, including anthropometric, blood pressure, and biochemical assessments, were performed at baseline and at the end of the intervention. Anthropometric measurements were conducted while participants were barefoot and wearing light clothing after an overnight fast. Body weight was measured to the nearest 0.1 kg while participants were in light clothing without shoes, and height was measured to the nearest 0.1 cm. BMI was calculated as weight [kg]/height$^2$ [m$^2$]. Blood pressure was measured twice on the right arm using an automatic sphygmomanometer, with a 15-minute interval between measurements after the participants had been seated quietly for 5 minutes. The 5-level EuroQol 5 Dimensions (EQ-5D-5L) is a validated quality-of-life questionnaire that measures the effects of disease and health status on perceived quality of life (Supplementary Approaches [21]). The EQ-5D-5L is measured on a visual analog scale, and general well-being was measured by the Health Utility Score; both scales were obtained from the EQ-5D-5L. Five health-related quality-of-life dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) have been described, all of which can be reflected by 1 of 5 responses depending on the level of severity (22). The questionnaires

used in this study have been validated or used in similar settings. Participants brought all prescription medications to the baseline and 12-month follow-up visits to ensure recording accuracy. Physicians entered the dosage and usage of medications into the study database. Medication costs were estimated as the cost of a 1-month supply of medication as listed on the website of a national online pharmacy (https://mall.jd.com/index-1000015441.html). When the cost varied by medication dose, a dosage of 50% of the maximal recommended or effective dose was used. Costs are presented in 2020 China prices (CNY).

### Statistical Analysis

The primary outcome was diabetes remission. A type I error of 5% ($\alpha = 0.05$) and a type II error of 20% ($\beta = 0.20$, power = 80%) were assumed. According to primary care-led weight management for remission of T2D (DiRECT) (11), calculations assumed diabetes remission would occur in 22% of participants in the intervention group (the effect size deemed clinically meaningful difference) compared with an estimated 5% in the control group. Allowing for an approximate 15% dropout rate, a total of 72 participants were recruited. We calculated the required sample size using the following formula:

$$n = \frac{\pi 1(100 - \pi 1) + \pi 2(100 - \pi 2)}{(\pi 2 - \pi 1)2} \times f(\alpha, \beta)$$

An interim analysis for futility and efficacy was planned at the midpoint of the trial. At this point, the sample size was also reassessed.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 23.0 version, SPSS Inc). For continuous outcomes, model fit was assessed visually with normal probability plots. Continuous variables were compared between the 2 groups using independent sample *t* tests. When a departure from a normal distribution was observed, Mann-Whitney-Wilcoxon tests were applied. The chi-square test was used to compare categorical variables. Normally distributed continuous variables are reported as the mean ± SD. We adjusted our final results for potential confounding factors by conducting multivariable regression modeling with adjustments for age, sex, diabetes duration, number of diabetes medications, baseline BMI, $HbA_{1c}$, FBG, blood pressure, and quality of life. Two-tailed statistical significance was accepted at *P* less than 0.05.

Electronic data capture was used for data management, including data entry, security, coding, query, and storage. Data were collected in source documents, transferred onto paper case-report forms, and then uploaded to the electronic data capture system. To improve accuracy, data entries were double-checked to ensure the proper format and expected range. Overall data quality was ensured by independent monitoring throughout the study, and all documentation was managed by an independent manager. Four nutritional scientists oversaw the implementation of interventions and communicated with the physicians frequently. Investigators supervised and reviewed the study progress and discussed the therapeutic regimen and adverse events every month. A safety report was submitted to the medical research ethics committee every year.

## Results

Between January 2, 2019, and June 2, 2020, a total of 246 potential participants were recruited through specific study calls on the diabetes website and holding of lectures invited by letter. Furthermore, 129 did not meet the inclusion criteria and were excluded, 117 were potentially eligible and invited to give consent, 45 excluded for 34 were excluded at further eligible screening and 11 did not respond (Fig. 2). A total of 72 participants were enrolled and randomly assigned to the CMNT group (n = 36) or the control group (n = 36). Four participants withdrew from the CMNT diet group during the intervention phase because of relocation (n = 1), time conflict (n = 1) or loss to follow-up (n = 2). Five participants withdrew from the control group because of time conflict (n = 1), loss to follow-up (n = 1), or lack of desire to continue (n = 3) (see Fig. 2). There were no serious adverse events in the study, and no events led to withdrawal. The intention-to-treat population consisted of 72 participants (see Fig. 2).

The baseline characteristics of the participants were similar between the 2 groups (Table 2). There was no significant difference in the types of medication taken by the 2 groups at baseline, which included insulin nonsecretagogues and secretagogues antidiabetic medicines and insulin injection. Participants in both groups took a similar number of diabetes medications at baseline (1.86 ± 0.76 vs 1.81 ± 0.67; see Table 2). The $HbA_{1c}$ level was 7.63% (SD 1.80) in the CMNT group and 7.52% (1.30) in the control group. The FBG of the CMNT group was 8.10 (SD 2.70) mmol/L, and that of the control group was 7.70 (2.95) mmol/L (see Table 2). The baseline BMI measurements were 20.4 to 30.4 in the CMNT group and 19.1 to 29.6 in the control group.

### After 3 Months of Intervention

After 3 months of the intervention, 50.0% (18/36) of participants in the CMNT group and 2.8% (1/36) in the control group ceased using antidiabetic medications. Moreover, 68.4% (13/19) of participants in the CMNT group and 2.8% (1/35) in the control group reduced their diabetes medication intake. The average number of medications taken by the intervention group was significantly lower than that by the control group (0.59 ± 0.63 vs 1.81 ± 0.67; $P < 0.0001$).

The FBG level in the CMNT group was 6.30 (SD 0.84) mmol/L, and that in the control group was 7.66 (1.72) mmol/L ($P < 0.0001$; Table 3). The reduction in FBG was statistically significant in the CMNT group (see Table 3; 1.85 mmol/L vs 0.21 mmol/L). The mean body weight of participants in the CMNT group was reduced by 5.93 kg (SD 2.47) compared to 0.27 kg (1.43) in the control group ($P < 0.0001$; see Table 3). Between baseline and 3 months' intervention, the mean reduction in BMI was −2.41 (SD 1.00) in the CMNT group and −0.18 (1.01) in the control group.

The mean blood pressure decreased in both groups, by 0.41 mm Hg (SD 3.22) in the CMNT group and 1.35 mm Hg (6.39) in the control group (adjusted mean difference −0.32 mm Hg; 95% CI, −3.16~2.52; $P = 0.122$). Mean systolic blood pressure was reduced by 0.75 mm Hg (SD 4.0) in the CMNT group and 2.58 mm Hg (7.39) in the control group (adjusted mean difference −1.04 mm Hg; 95% CI, −2.47~0.38; $P = 0.519$). There was no statistically significant difference between the 2 groups in either diastolic or systolic blood pressure (see Table 3). The quality-of-life scores of the CMNT group increased by 4.57 (SD 6.52) compared with the baseline scores, but decreased by 1.77 (3.71) in the control group (adjusted mean difference 3.2; 95% CI, 1.2~5.24; $P < 0.05$; see Table 2). According to the FFQ, the food items

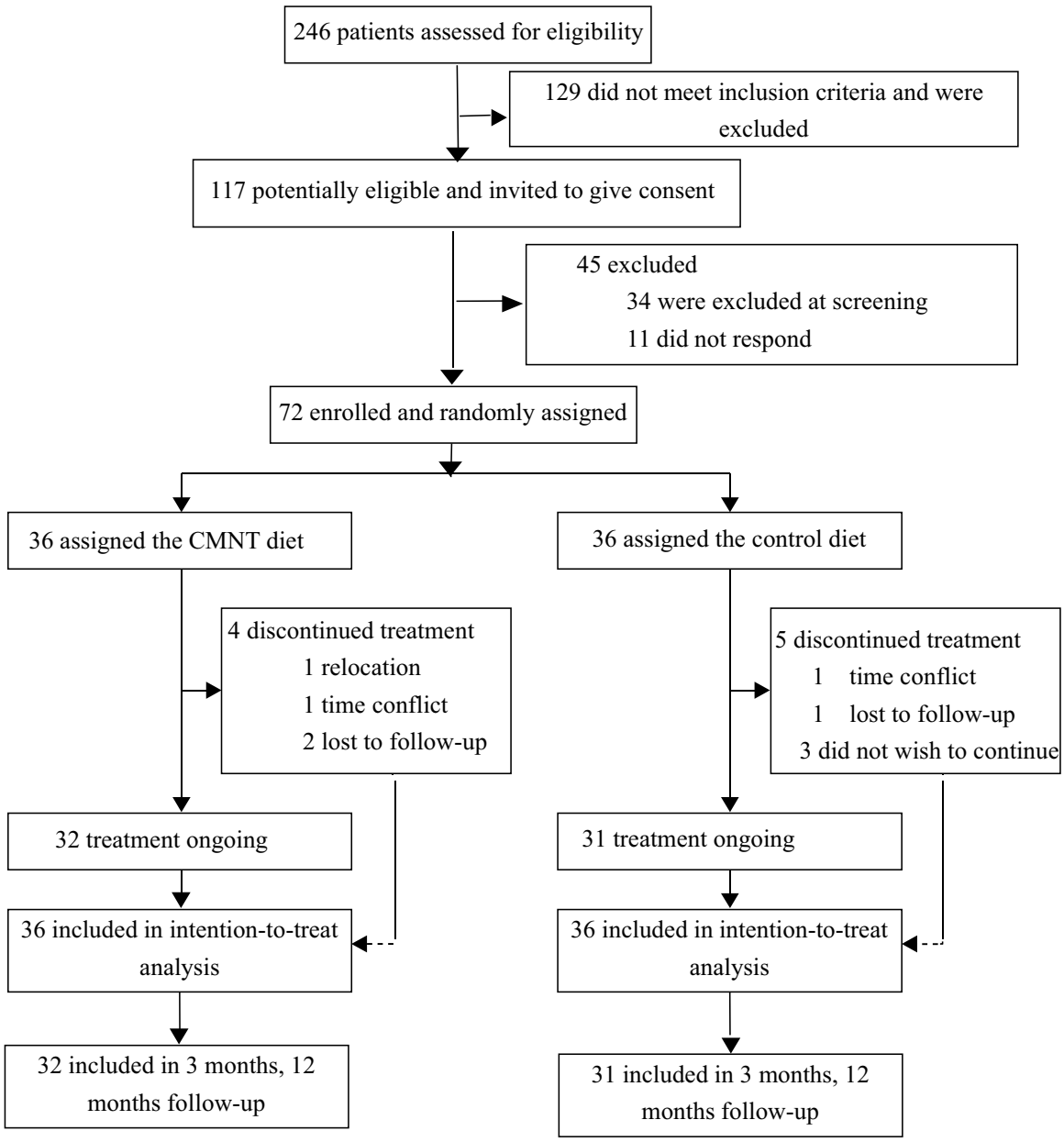



**Figure 2.** Diagram showing participant flow through the trial. Seventy-two individuals provided consent to participate in the study. A total of 72 participants were enrolled and randomly assigned to the Chinese Medical Nutrition Therapy (CMNT) group (n = 36) or the control group (n = 36). Four participants withdrew from the CMNT group during the intervention phase because of relocation or time conflict or were lost to follow-up. Five participants withdrew from the CMNT group during the intervention phase because they did not wish to continue, experienced a time conflict, or were lost to follow-up.

and quantity consumed during the ad libitum diets were not different between the groups (see Supplementary Table S2 [21]).

## After 3 Months of Follow-up

After 3 months of follow-up, 47.2% (17/36) of individuals achieved diabetes remission in the CMNT group, whereas only 2.8% (1/36) achieved diabetes remission in the control group (odds ratio [OR] 31.32; 95% CI, 2.39-121.07; $P < 0.0001$). Among the 17 medication-withdrawal participants in the CMNT group, 10 took insulin nonsecretagogue antidiabetic medicines, 4 took insulin secretagogue antidiabetic medicines, 3 took hypoglycemic agents plus insulin, and 1 in the control group took metformin only.

$HbA_{1c}$ level was 5.66% (SD 0.58) in the CMNT group and 7.87% (1.63) in the control group. The reduction in mean $HbA_{1c}$ was statistically significantly greater in the CMNT group (1.75%, SD 1.52) than in the control group (0.37%, SD 1.05) (adjusted difference −1.06% [95% CI, −1.48∼−0.65]; $P < 0.0001$; Table 4). The FBG of the CMNT group was 5.84 (0.67) mmol/L, and that of the control group was 7.64 (1.74) mmol/L ($P < 0.0001$).

## After 12 Months of Follow-up

After 12 months of follow-up, there were 16 of 36 (44.4%) participants who achieved diabetes remission in the intervention group, with an $HbA_{1c}$ level of 5.90% (SD 0.33), and 0 of

**Table 2. Baseline characteristics of participants**

| | CMNT group (n = 36) | Control group (n = 36) | *P* |
|---|---|---|---|
| Sex | | | |
| Male | 25 (63.4%) | 23 (57.4%) | 0.62 |
| Age, y | 52.2 (7.38) | 53.4 (11.72) | 0.64 |
| Anthropometry | | | |
| BMI mean (SD) | 24.23 (2.58) | 23.85 (2.50) | 0.53 |
| Duration of type 2 diabetes, y | 6.65 (3.25) | 6.51 (3.22) | 0.86 |
| Therapeutic manner | | | 0.76 |
| Insulin nonsecretagogue antidiabetic medicines | 13 (36.1%) | 15 (41.7%) | |
| Insulin secretagogue antidiabetic medicines | 17 (47.2%) | 14 (38.9%) | |
| Hypoglycemic agent(s) + insulin | 6 (16.7%) | 7 (19.4%) | |
| No. of glucose-lowering medications | 1.86(0.76) | 1.81(0.67) | 0.86 |
| 1 | 13 (36.1%) | 15 (41.7%) | |
| 2 | 15 (41.7%) | 13 (36.1%) | |
| 3 | 8 (22.2%) | 8 (22.2%) | |
| $HbA_{1c}$ | | | 0.62 |
| % | 7.63 (1.80) | 7.52 (1.30) | |
| mmol/mol | 59.73 (20.50) | 57.24 (14.69) | |
| Fasting plasma glucose, mmol/L | 8.10 (2.70) | 7.70 (2.95) | 0.46 |
| Cardiovascular disease risk factors | | | |
| Blood pressure | | | |
| Systolic, mm Hg | 129.39 (8.73) | 129.72 (12.71) | 0.62 |
| Diastolic, mm Hg | 84.50 (5.65) | 83.22 (5.93) | 0.96 |
| EQ-5D scale score | 76.22 (7.03) | 77.00 (6.12) | 0.93 |

Data are n (%), mean (SD) unless otherwise indicated. The degree of insulin administration was higher than that of secretagogues, and the former 2 were higher than that of nonsecretagogues. Participants who used the upper level of antidiabetic agents were classified into this category, regardless of whether they used the next level of drugs.
Abbreviations: CMNT, Chinese Medical Nutrition Therapy; EQ-5D, EuroQol 5 Dimensions; $HbA_{1c}$, glycated hemoglobin $A_{1c}$.

36 in the control group. In the CMNT group, the number of antidiabetic medications in baseline was statistically significantly different between responders (those with diabetes remission) and nonresponders (did not achieved diabetes remission), while baseline weight, type of antidiabetic medications, diabetes duration, and $HbA_{1c}$ were not significantly different. The $HbA_{1c}$ level was 6.33% (SD 0.87) among all participants in the CMNT group and 7.76% (1.15) in the control group ($P < 0.0001$; see Table 4). The FBG of the CMNT group was 6.17 (0.79) mmol/L, and that of the control group was 7.47 (1.38) mmol/L ($P < 0.0001$; see Table 3). The participants in the control group were taking an average of $1.85 \pm 0.61$ medications at an estimated cost of CNY 265.1/month, while those in the CMNT diet group required fewer medications ($0.61 \pm 0.56$) at lower cost (CNY 60.4/month) ($P < 0.0001$). BMI was 22.14 (SD2.53) in the CMNT group and 23.51 (2.68) in the control group. Weight fell from 67.60 kg (SD 6.58) to 61.67 (SD 5.58) and remained stable over 12 months (61.82 kg [SD5.46]) in the CMNT group. Weight changed from 66.25 kg (SD 7.26) to 65.98 kg (SD 7.16) and 66.05 kg (SD 7.03) at 12 months in the control group. Quality-of-life scores increased by 6.19 (SD 6.52) in the CMNT group and decreased by 2.82 (3.70) in the control group compared with baseline scores ($P < 0.05$; see Table 3).

## Discussion

A study examining utility analysis values employing the time trade-off method showed that diabetes patients were willing to trade 12% of their remaining life in return for being permanently in a nondiabetic health state (23). Although an increasing number of studies have verified the potential health benefits of IF in humans, no clinical investigations have been published regarding its effectiveness in diabetes remission (24). We showed that an IF diet, the CMNT, resulted in a 47.2% (17/36) diabetes remission rate when remission was defined as $HbA_{1c}$ less than 6.5% (48 mmol/mol) measured at least 3 months after cessation of glucose-lowering pharmacotherapy (14). This remission rate markedly exceeded the threshold level of 22% diabetes remission, which is considered a minimal clinically important difference (25), implying that IF is robust in the remission of patients and contributing to the clinical management of diabetes. A large study reported a diabetes remission rate of 0.23% with standard care (26). The results could be generalized because the sample characteristics are very similar to those of the general population with T2D.

As proposed, remission is a state in which diabetes is not present, but continued observation is nonetheless required because hyperglycemia frequently recurs (14). After an intensive lifestyle program, including calorie restriction and exercise for 6 months, 8 of the 10 individuals with recently diagnosed T2D achieved partial remission (27). Therefore long-term sustainability was not assessed. In our study, during the follow-up period, the CMNT and control groups both followed the Dietary Guidelines for Diabetes in China (2017 Edition) with ad libitum diets instead of the CMNT diet. A total of 44.0% (16/36) of the participants in the CMNT group still maintained a diabetes remission state with an $HbA_{1c}$ level of 5.90% after 1 year. Even with the more stringent criteria for "complete remission," which describes a return to "normal" measures of glucose metabolism ($HbA_{1c}$ in the normal range, FBG 100 mg/dL [5.6 mmol/L]) of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures (28), 33.3% (12/36) of participants in the CMNT group achieved complete remission. Preclinical data in our study team showed that CMNT could promote β-cell proliferation of pancreatic islets to reverse β-cell failure and alter gut microbiota, which, in turn, can modulate host metabolism (18).

Diabetes remission was more likely reported in those who had a shorter diabetes duration, lower baseline $HbA_{1c}$, and were prescribed fewer antidiabetes medications at baseline (29). In our study, baseline predictors of diabetes remission is the number of antidiabetic medications. Participants prescribed fewer antidiabetics medications were more likely to achieve diabetes remission. A systematic review of published meta-analyses reported that people with T2D diagnosed after a longer disease duration (6 years) were less likely to achieve remission (30). This 6-year diabetes duration as a predictor of T2D remission is consistent with the pathophysiology of

**Table 3. Secondary outcomes measured at 3-month intervention and 12-month follow-up**

| | n | Mean (SD) | | | Intervention effect | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | 3-mo intervention | Change between baseline and 3-mo intervention | Estimate (SD) | 95% CI | $P^a$ | 12-mo follow-up | $P^b$ |
| Fasting blood glucose, mmol/L | | | | | | | | | |
| Intervention | 32 | 8.15 (2.31) | 6.30 (0.84) | −1.85 (2.25) | −1.82 (0.27) | −2.13 to −0.26 | 0.002 | 6.17 (0.79) | 0.22 |
| Control | 31 | 7.83 (2.14) | 7.66 (1.72) | −0.21 (1.66) | | | | 7.47 (1.38) | 0.72 |
| Weight, kg | | | | | | | | | |
| Intervention | 32 | 67.60 (6.58) | 61.67 (5.58) | −5.93 (2.47) | −5.42 (0.32) | −6.07 to −4.22 | < 0.0001 | 61.82(5.46) | 0.81 |
| Control | 31 | 66.25 (7.26) | 65.98 (7.16) | −0.27 (1.43) | | | | 66.05(7.03) | 0.97 |
| Systolic blood pressure, mm Hg | | | | | | | | | |
| Intervention | 32 | 129.41 (6.94) | 128.66 (6.87) | −0.75 (4.00) | −1.04 (0.71) | −2.47 to 0.38 | 0.519 | 129.10 (5.24) | 0.77 |
| Control | 31 | 132.77 (8.49) | 130.19 (7.31) | −2.58 (7.39) | | | | 129.61 (6.96) | 0.80 |
| Diastolic blood pressure, mm Hg | | | | | | | | | |
| Intervention | 32 | 84.41 (4.33) | 84.00 (3.56) | −0.41 (3.22) | −0.32 (1.42) | −3.16 to 2.52 | 0.122 | 83.17 (5.24) | 0.81 |
| Control | 31 | 83.06 (4.90) | 81.71 (5.55) | −1.35 (6.39) | | | | 80.94 (4.92) | 0.45 |
| Quality of life | | | | | | | | | |
| Intervention | 32 | 76.31 (5.38) | 80.88(4.86) | 4.57 (6.52) | 3.2 (1.00) | 1.20 to 5.24 | 0.002 | 82.50 (4.86) | 0.34 |
| Control | 31 | 77.32 (5.49) | 75.55(5.67) | −1.77 (3.71) | | | | 74.50 (5.67) | 0.40 |

Intervention effects reported as estimated mean differences (intervention – control) adjusted for age, sex, diabetes duration, number of diabetes medications, baseline body mass index, glycated hemoglobin $A_{1c}$, fasting blood glucose, blood pressure, and quality of life. *T* test was used for comparison between groups. Means ± SD and means (range) were used to represent variables with normal distribution and variables with skewed distribution. The data applied Mann-Whitney-Wilcoxon tests when a departure from a normal distribution was observed.
Abbreviation: CMNT, Chinese Medical Nutrition Therapy.
[a]*P* value is a comparison of the difference between the CMNT group and control group from baseline to 3 months.
[b]*P* value is a comparison between 3-month and 12-month follow-up for both CMNT and control groups.
The difference was statistically significant ($P < 0.05$).

**Table 4. Diabetes remission and glycated hemoglobin $A_{1c}$ outcomes measured at 3-month follow-up and 12-month follow-up**

| | n | Mean (SD) | | | Intervention effect | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | 3-mo follow-up | Change between baseline and 3-mo follow-up | Estimate (SD) | 95% CI | $P^a$ | 12-mo follow-up | $P^b$ |
| Diabetes remission | | | | | | | | | |
| Intervention | 36 | 0/36 | 17/36 | – | – | – | < 0.0001 | 16/36 | 0.82 |
| Control | 36 | 0/36 | 1/36 | | | | | 0/36 | 0.31 |
| $HbA_{1c}$, % | | | | | | | | | |
| Intervention | 32 | 7.65 (1.41) | 5.66 (0.58) | −1.75 (1.52) | −1.06 (0.20) | −1.48 to −0.65 | < 0.0001 | 6.33 (0.87) | 0.24 |
| control | 31 | 7.50 (1.38) | 7.87 (1.63) | 0.37(1.05) | | | | 7.76 (1.15) | 0.56 |
| $HbA_{1c}$, mmol/mol | | | | | | | | | |
| Intervention | 32 | 59.92 (2.7) | 40.32 (5.50) | −19.60 (16.74) | −11.91 (4.31) | −12.15 to 2.39 | < 0.0001 | 45.68 (16.01) | 0.24 |
| Control | 31 | 58.47 (15.10) | 62.51 (17.83) | −4.04 (11.46) | | | | 60.21 (12.02) | 0.56 |

Intervention effects reported as estimated mean differences (intervention – control) adjusted for age, sex, diabetes duration, number of diabetes medications, baseline body mass index, $HbA_{1c}$, fasting blood glucose, blood pressure, and quality of life. *T* test was used for comparison between groups.
Abbreviations: CMNT, Chinese Medical Nutrition Therapy; $HbA_{1c}$, glycated hemoglobin $A_{1c}$.
[a]*P* value is a comparison between CMNT group and control group at 3 months.
[b]*P* value is a comparison between 3-month and 12-month follow-up for both CMNT and control groups.
The difference was statistically significant ($P < 0.05$).

T2D, in which the onset of pancreatic β-cell loss and secretory insufficiency represent a key clinical transition from insulin resistance to T2D (31). As reported, some participants in the DiRECT and DIADEM-I studies achieved diabetes remission through lifestyle intervention, but the duration of the studies was relatively short (11, 12). Individuals in DiRECT had a duration of T2D less than 6 years and participants in DIADEM-I had a shorter duration of diabetes (0-3 years). In our study, the average duration of T2D in the CMNT group was 6.63 years, with the longest duration being 11 years. Sixty-five percent (11/17) of the participants who achieved diabetes remission had a diabetes duration of more than 6 years. This suggests the possibility of remission for patients with longer duration.

A conventional diet recommended for T2D is a balanced diet with continuous, moderate calorie restriction (32). However, it is difficult for patients to adhere to this diet (33). IF is often considered to be less complicated than traditional forms of dieting, such as calorie restriction (16, 34). CMNT can be defined as periods of calorie restriction alternating with periods of ad libitum eating. According to the program acceptability feedback from participants, it was relatively effortless to complete the CMNT intervention cycles; 88.9% (32/36) of participants completed the clinical trial. It was relatively effortless for patients to complete the CMNT intervention cycles: First, it is not necessary for patients to track calories every day when following a CMNT diet. Second, the CMNT diet is a food-based diet instead of meal-replacement diet that excludes virtually all usual foods. Finally, the CMNT diet is characterized by the ability to engage in habitual social eating patterns with preference time points. The food is made of ordinary material and the processing procedure is standard, which guarantees its qualification for industrialization. This food can be prepared by simply mixing with boiling water. Its form, taste, and satiety closely catered to the average participants' food preference. So it is easy to implement in the real-world setting. The trial was designed to be pragmatic in nature, which could indicate the ability to implement similar interventions in the community, demonstrating CMNT as an appropriate dietary intervention for diabetes remission.

The long-term prognosis of diabetes is related to quality of life (35). More sustained improvements in quality of life, especially in regard to anxiety/depression and medical burden, were observed in the intervention group. Compared with baseline, medication costs decreased by 77.2% for CMNT participants and by only 3.0% in the control group. After the intervention, almost half of the participants (16/36) returned to a nondiabetic state, were off antidiabetic drugs, and were in remission that lasted at least 1 year. The CMNT diet also reduced the mean $HbA_{1c}$ by 1.33% (19.66 mmol/mol), which is an important reduction considering the UK Prospective Diabetes Study's finding that a 1% (10 mmol/mol) reduction in $HbA_{1c}$ over 10 years significantly decreased the risk of microvascular complications in T2D patients (36).

Some limitations are inevitable in studies conducted in real-life settings. Because of the nature of the dietary intervention, it was not possible to blind participants, physicians, or some of the researchers after allocation. Although participants were encouraged to maintain their usual physical activity in both groups, the formal recording of physical activity is needed in this study. The participants were followed up for 1 year, and a follow-up of 5 years or more is ongoing to explore the stability of the CMNT diet, its effects, and any complications.

In conclusion, the program allowed almost half of participants to revert to a nondiabetic state and discontinue their use of antidiabetic drugs, and these effects lasted at least 1 year. This study was performed under real-life conditions, and the intervention was delivered by trained nurses in primary care rather than by specialized staff at a research institute, making it a more practical and achievable way to manage T2D. It could be a paradigm shift in the management goals in diabetes care.

## Acknowledgments

The authors thank the study participants for their involvement and the research nurses and research assistants for their help conducting the study.

## Financial Support

This work was supported by the National Natural Science Foundation of China (No. 81773850).

## Author Contributions

Dongbo Liu is the guarantor of this work and 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. Xiao Yang contributed to designing the study, plotting the figures, and writing the manuscript. Xincong Kang contributed to study design and data analysis. Huige Shao and Bi Huang contributed to the protocol and data collection. Ruiyu Wu contributed to data collection. Jiali Zhou and Fangzhou Bian contributed to designing the study and plotting the figures.

## Disclosures

The authors have nothing to disclose.

## Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

## Clinical Trial Information

Clinical trial registry, clinical trials chictr.org.cn registration number ChiCTR2000038036 (registered on 9 September 2020).

## References

1. Taylor R, Ramachandran A, Yancy WS Jr, Forouhi NG. Nutritional basis of type 2 diabetes remission. *BMJ*. 2021;374:n1752.
2. DeFronzo RA, Ferrannini E, Groop L, *et al*. Type 2 diabetes mellitus. *Nat Rev Dis Primers*. 2015;1(1):1–22.
3. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88-98.
4. Porta M, Bandello F. Diabetic retinopathy. *Diabetologia*. 2002;45(12):1617-1634.

5. Moran C, Beare R, Phan TG, Bruce DG, Callisaya ML, Srikanth V. Type 2 diabetes mellitus and biomarkers of neurodegeneration. *Neurology*. 2015;85(13):1123-1130.
6. International Diabetes Federation. Diabetes Atlas. 10th ed. Accessed April 21, 2021. https://www.diabetesatlas.org/en/
7. Thrasher J. Pharmacologic management of type 2 diabetes mellitus: available therapies. *Am J Cardiol*. 2017;120(1):S4-S16.
8. Lipscombe L, Booth G, Butalia S, *et al*. Pharmacologic glycemic management of type 2 diabetes in adults. *Can J Diabetes*. 2018; 42(Suppl 1):S88-S103.
9. Li G, Zhang P, Wang J, *et al*. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet*. 2008;371 (9626):1783-1789.
10. Turner-McGrievy GM, Barnard ND, Cohen J, Jenkins DJ, Gloede L, Green AA. Changes in nutrient intake and dietary quality among participants with type 2 diabetes following a low-fat vegan diet or a conventional diabetes diet for 22 weeks. *J Am Diet Assoc*. 2008;108(10):1636-1645.
11. 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):344-355.
12. 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, randomized controlled trial. *Lancet Diabetes Endocrinol*. 2020;8(6):477-489.
13. Hallberg SJ, Gershuni VM, Hazbun TL, Athinarayanan SJ. Reversing type 2 diabetes: a narrative review of the evidence. *Nutrients*. 2019;11(4):766.
14. Riddle MC, Cefalu WT, Evans PH, *et al*. Consensus report: definition and interpretation of remission in type 2 diabetes. *J Clin Endocrinol Metab*. 2022;107(1):1-9.
15. Varady KA, Cienfuegos S, Ezpeleta M, Gabel K. Clinical application of intermittent fasting for weight loss: progress and future directions. *Nat Rev Endocrinol*. 2022;18(5):309-321.
16. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. *N Engl J Med*. 2019;381(26):2541-2551.
17. Borgundvaag E, Mak J, Kramer CK. Metabolic impact of intermittent fasting in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of interventional studies. *J Clin Endocrinol Metab*. 2021;106(3):902-911.
18. Wu R, Tang X, Kang X, *et al*. Effect of a Chinese medical nutrition therapy diet on gut microbiota and short chain fatty acids in the simulator of the human intestinal microbial ecosystem (SHIME). *J Funct Foods*. 2019;62:103555.
19. Luo W, Zhou JL, Yang X, *et al*. A Chinese medical nutrition therapy diet accompanied by intermittent energy restriction alleviates type 2 diabetes by enhancing pancreatic islet function and regulating gut microbiota composition. *Food Res Int*. 2022;161: 111744.
20. Huang MC, Lin KD, Chen HJ, *et al*. Validity of a short food frequency questionnaire assessing macronutrient and fiber intakes in patients of Han Chinese descent with type 2 diabetes. *Int J Environ Res Public Health*. 2018;15(6):1142.
21. Yang X, Zhou JL, Shao HG, *et al*. Supplementary data for "Effect of an intermittent calorie-restricted diet on type 2 diabetes remission: a randomized controlled trial." Zenodo Repository. Deposited October 6, 2022. https://doi.org/10.5281/zenodo.7151067
22. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35(11):1095-1108.
23. Brown GC, Brown MM, Sharma S, *et al*. Quality of life associated with diabetes mellitus in an adult population. *J Diabetes Complications*. 2000;14(1):18-24.
24. Muñoz-Hernández L, Márquez-López Z, Mehta R, Aguilar-Salinas CA. Intermittent fasting as part of the management for T2DM: from animal models to human clinical studies. *Curr Diab Rep*. 2020;20(4):13.
25. Goldenberg JZ, Day A, Brinkworth GD, *et al*. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. *BMJ*. 2021;372: m4743.
26. Karter AJ, Nundy S, Parker MM, Moffet HH, Huang ES. Incidence of remission in adults with type 2 diabetes: the Diabetes & Aging Study. *Diabetes Care*. 2014;37(12):3188-3195.
27. Ades PA, Savage PD, Marney AM, Harvey J, Evans KA. Remission of recently diagnosed type 2 diabetes mellitus with weight loss and exercise. *J. Cardiopulm Rehabil Prev*. 2015;35(3): 193-197.
28. Buse JB, Caprio S, Cefalu WT, *et al*. How do we define cure of diabetes? *Diabetes Care*. 2009;32(11):2133-2135.
29. Thom G, Messow CM, Leslie WS, *et al*. Predictors of type 2 diabetes remission in the Diabetes Remission Clinical Trial (DiRECT). *Diabet Med*. 2021;38(8):e14395.
30. Churuangsuk C, Hall J, Reynolds A, *et al*. 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.
31. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Investi*. 1999;104(6): 787-794.
32. Jensen MD, Ryan DH, Apovian CM, *et al*. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *Circulation*. 2014;129(25 Suppl 2):S102-S138.
33. Diabetes Prevention Program Research Group; Knowler WC, Fowler SE, Hamman Richard F, *et al*. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686.
34. Templeman I, Gonzalez JT, Thompson D, Betts JA. The role of intermittent fasting and meal timing in weight management and metabolic health. *Proc Nutr Soc*. 2020;79(1):76-87.
35. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, depression, and quality of life: a population study. *Diabetes Care*. 2004;27(5):1066-1070.
36. Maddaloni E, Coleman RL, Agbaje O, Buzzetti R, Holman RR. Time-varying risk of microvascular complications in latent autoimmune diabetes of adulthood compared with type 2 diabetes in adults: a post-hoc analysis of the UK Prospective Diabetes Study 30-year follow-up data (UKPDS 86). *Lancet Diabetes Endocrinol*. 2020;8(3):206-221.