A randomized controlled trial on the effects of the Chinese Medical Nutrition Therapy (CMNT) diet on type 2 diabetes: study protocol

xiao yang
State Key Laboratory of Subhealth Intervention Technology https://orcid.org/0000-0001-7906-2201
Xincong Kang
Hunan Key Laboratory of Crop Germplasm Innovation and Utilization
Ruiyu Wu
Jinheyuan Outpatient Department
Xihu Lai
State Key Laboratory of Subhealth Intervention Technology
Wu Luo
State Key Laboratory of Subhealth Intervention Technology
Lan Yang
State Key Laboratory of Subhealth Intervention Technology
Jiali Zhou
State Key Laboratory of Subhealth Intervention Technology
Ligang Yi
Shizhi Mountain Community Health Service
Dongbo Liu (hengxin1113@163.com)
Shizhi Mountain Community Health Service https://orcid.org/0000-0002-6623-9327

Study protocol

Keywords: Type 2 diabetes, a randomized controlled trial, Chinese Medical Nutrition Therapy (CMNT), diet

Posted Date: April 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-462944/v1

Abstract

Background:

Type 2 diabetes (T2D) has become a serious clinical problem since it has affected more than 463 million people. The importance of individual nutrients, foods, and dietary patterns in the prevention and management of type 2 diabetes is highlighted. Chinese Medical Nutrition Therapy (CMNT) is a special dietary intervention pattern featuring traditional Chinese medicine (TCM). The aim of the study is to determine the effect of the CMNT diet on medical nutritional rehabilitation of T2D. The withdrawal rate of anti-diabetic medications will be used to evaluate whether the CMNT diet can improve the blood glucose level and achieve the purpose of nutritional rehabilitation of T2D.

Methods:

This study is a randomized, controlled, parallel-group study. Seventy T2D patients will be randomly allocated to receive the CMNT diet (n = 35) or to continue their usual diet (as a control, n =35) at a 1:1 ratio for 90 days. Anthropological measures and biochemical assessments, including glycosylated haemoglobin (HbA1c) and plasma lipid profiles, will be performed in from patients at baseline and at the end of the study. The primary outcome is the withdrawal rate of antidiabetic medications. Secondary outcomes are HbA1c, fasting blood glucose (FBG), 2-h postprandial blood glucose (PBG), plasma lipid profiles, blood pressure, body mass index, treatment satisfaction and quality of life.

Discussion:

Preclinical data showed that the CMNT diet decreased the blood glucose level, improved insulin resistance and promoted β-cell regeneration. However, clinical evidence is lacking. The present study will help in understanding the potential effect of the CMNT diet on the medical nutritional rehabilitation of T2D patients. Consumption of the CMNT diet might decrease the blood glucose level and improve glucose and lipid metabolism. If the CMNT diet demonstrates a significant clinical effect for T2D, it will inform clinical guidelines for the management of T2D in the future.

Trial registration:

The trial was registered on chictr.org.cn. (Chinese Clinical Trial Registry, ChiCTR) Identifier: ChiCTR2000038036. Registered 9th of September, 2020; retrospectively registered.

Background

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by persistent hyperglycaemia[1]. An abnormal increase in blood glucose may be due to insufficient insulin secretion and/or insulin resistance, resulting in metabolic disorders of carbohydrate, fat and protein[2]. In 2019, the 9th edition of the International Diabetes Federation (IDF) Diabetes Atlas showed that approximately 463 million adults aged 20 to 79 years develop diabetes globally (1 in 11 will be diabetic) and that 4.2 million people die

from diabetes or its complications[3]. Diabetes is a potent risk factor for cardiovascular disease (CVD), blindness, renal failure, and lower limb amputation [4–6].

Medical nutrition therapy (MNT) is essential for the optimal management of T2D in adults [7]. It is an evidence-based application of nutrition care process interventions, including nutrition therapy, energy restriction and carbohydrate counting [8]. The evidence from randomized controlled trials, observational studies, and meta-analyses reveals that nutrition intervention improves metabolic outcomes, such as blood glucose and HbA1c levels, in individuals with diabetes. In randomized controlled trials in 2,595 patients who received intensive nutrition therapy, HbA1c decreased by 1.9% (from 8.9 to 7%) during 3 months of intervention[9]. A systematic review and meta-analysis suggested that healthy plant-based foods, such as fruits, vegetables, whole grains, legumes, and nuts, are associated with a lower risk of T2D[10]. Fasting blood glucose levels can be normalized by instituting a substantial negative calorie balance by dietary intervention. This rapid change relates to a substantial decrease in liver fat content and the return of normal hepatic insulin sensitivity [11].

Intermittent fasting is increasing in popularity as a means of losing weight and controlling chronic diseases [12]. It is an effective way to increase insulin sensitivity[13], reduce weight and fat mass[14] and improve blood lipid levels[15]. A randomized controlled trial compared participants who followed 3 months of an unrestricted diet to participants who consumed fasting-mimicking diets (FMDs) for 5 consecutive days per month for 3 months. Three FMD cycles reduced body weight, trunk, and total body fat, lowered the fasting glucose and blood pressure and decreased insulin-like growth factor 1 (IGF-1)[16]. A randomized noninferiority trial shows that intermittent energy restriction is an effective alternative diet strategy for the reduction of HbA1c levels that is comparable to continuous energy restriction in patients with T2D[17].

Diabetes is well known as ‘Xiao Ke’ in traditional Chinese medicine (TCM)[18]. Treatment with TCM has been shown to yield stable efficacy, lower toxicity and few adverse reactions[19] for at least 2000 years. Some TCM themselves are foods, which is a concept referred to as ‘medicine and food homology (MFH)’. The concept was mentioned in Huang Di Nei Jing as follows: ‘eating on an empty stomach as food and administering to the patient as medication’[20]. In addition to nutritional value, MFH materials also have bioactive compounds that are useful in the prevention and treatment of disease [21].

CMNT is proposed on the basis of MNT and is an intervention for improving the health status or treat diseases by adding TCM nutrition and trace elements with medicine food homology (MFH) to change the nutritional status [22]. CMNT emphasizes a low glucose index (GI), low calories and low carbohydrates, high unsaturated fatty acids, high intestinal nutrition and high homology of medicine and food [23–24]. Preclinical data from our team, which compared the db/db mice fed a usual diet (n = 20) to the CMNT diet (n = 20) for 91 days, showed that the CMNT diet significantly reduced fasting glucose, improved insulin resistance and increased fasting insulin levels. Immunofluorescence double staining (insulin + PCNA) showed that the CMNT diet promoted cell proliferation, reversed db/db mice cell defects, and increased α-

cells and β-cells to restore islet structure. The CMNT diet might remit diabetes and improve the quality of life in clinical practice.

We present the protocol of a randomized, controlled clinical study investigating the effects of the CMNT diet compared to a usual diet. We evaluated the withdrawal rate of antidiabetic medications, which was defined as HbA1c within normal range (≤7.0%) and without antidiabetic medications for three months. In addition, we observed the HbA1c, fasting blood glucose, and 2-hour postprandial blood glucose levels of the participants before and after the intervention. We hypothesize that the CMNT diet will be superior to the usual diet after intervention compared to baseline, achieving the purpose of nutritional rehabilitation of T2D.

Methods And Design

Study design

The study is a randomized, controlled intervention trial examining the effects of the CMNT diet in T2D patients. The trial is designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist. After recruitment, participants' general information on diet, physical activity, and type and dosage of medications will be obtained. After written informed consent, the participants will be screened further for eligibility. Individuals likely to be ineligible or unsuitable to approach because of comorbidity or other practical or medical obstacles to participation will be removed from the investigation. Each participant will receive a unique identifier upon study entry. This identifier will be used for all data documentation to ensure the participant's confidentiality.

Randomization sequence of participants will be done by a statistician not involved in the trial using SAS software, version 9.4 (SAS Institute). Then, participants will be randomized at a ratio of 1:1 to the CMNT group or control group. Participants in the intervention group will receive the CMNT diet, whereas the other participants will receive the usual diet for 90 days. To evaluate participants' compliance, five 24-h dietary recalls will be taken throughout the intervention. All measurements, including anthropometric and biochemical assessments, will be examined at baseline and at the end of the trial. The coordinating centre holds trained physician for conducting study visits and taking informed consent, a study nurse for coordinating study visits and obtaining data during study visits. Any modification to the current study protocol will be submitted to the institutional review board, all trial participants and the trial investigators.

Recruitment

Patient recruitment strategies include specific study calls on the diabetes website and the holding of lectures for patients in specialized diabetes practices. When potentially eligible subjects are interested in participation, physicians will fully explain and discuss the study. The diagram (Figure 1) shows the participant flow through the trial.

Participants

Seventy T2D patients will be randomly allocated to receive the CMNT diet or to continue their usual diet as a control for 90 days.

Inclusion criteria

Participants who meet all the following criteria can be included in this trial:

- Patients with a diagnosis of T2D
- Patients with age > 18 years and < 75 years
- Patients with T2D who meet the diagnostic criteria for diabetes issued by the World Health Organization in 1999
- Patients taking T2D medications
- Patients with a body mass index between 18 and 35 kg/m^2
- Patients who are willing and able to accurately use a home glucose metre for the self-monitoring of blood glucose
- T2D patients who have an urgent desire to fully understand the CMNT theory to improve their physical conditions
- Patients who can understand and follow the trial procedures and voluntarily participate in the trial
- Patients who provide informed consent

Exclusion criteria

Patients who meet any of the following criteria will not be allowed to participate in this trial:

- Type 1 diabetes or secondary diabetes due to pancreatic injury (such as Cushing's syndrome or acromegaly)
- Having used other drugs that may affect blood glucose metabolism in the last two months, including systemic glucocorticoids (except inhaled or topical), growth hormones, etc.
- Having used antihypertensive drugs or blood lipid regulating drugs used, but with the dose before screening not reaching a stable state

A history or condition of any of the following heart problems within the last 6 months:

- Decompensated cardiac insufficiency (NYHA grade III or IV)
- Unstable angina pectoris, myocardial infarction, coronary artery bypass grafting or stent implantation history
- Uncontrolled or severe arrhythmias (such as long QT syndrome, etc.) that have been evaluated by the investigator as inappropriate to participate in this clinical trial
- Haemorrhagic stroke or ischaemic stroke in the last 6 months rendering the individual ineligible to participate in this clinical trial as assessed by the investigator

- Presence of cerebral thrombosis, cerebral vascular blockage, cerebral haemangioma, mini-stroke, cerebral haemorrhage, cerebral stroke, cerebral infarction, cerebral infarction, hydrocephalus, brain tumour (malignant) and other diseases
- History of carotid artery stent implantation
- Urinary system with nephrotic syndrome, uraemia, polycystic kidney, kidney transplantation, lateral kidney removal/congenital single kidney, renal atrophy, renal tumour
- Digestive system with liver ascites, liver cirrhosis, liver flukes, severe hepatitis, varicose gastric fundus
- Nervous system with cerebellar atrophy, demyelination, cerebral palsy, Parkinson's disease, mania, schizophrenia
- Pulmonary embolism and pulmonary heart disease in the respiratory system
- Circulatory system with arterial rupture
- Immune system with Bezier's disease or eruption of lupus erythaematosus
- Presence of chondrosarcoma, liposarcoma, brucellosis, leukaemia
- History of malignancy within the last 5 years or current assessment for potential malignancy
- Proliferative retinopathy or macular disease accompanied by instability or requiring treatment in the last 6 months
- A history of diabetic ketoacidosis and hyperosmolar nonketotic coma in the last 6 months
- Present history of arteriosclerosis obliterans of the lower limbs
- Severe infection or trauma within the last month
- History of $\geq$ 2 episodes of severe hypoglycaemia in recent years
- Presence of a clinically significant urinary/reproductive infection, history of complex urinary tract infection, or history of recurrent urinary tract infections in the last 6 months.
- Uncontrolled hypertension with systolic blood pressure $\geq$ 160 mmHg and/or diastolic blood pressure at screening/baseline of 100 mmHg or higher; systolic blood pressure $\leq$90 mmHg and/or diastolic blood pressure $\leq$60 mmHg
- Current presentation of thyroid dysfunction that is not steadily controlled
- A history of other serious endocrine diseases, such as multiple endocrine neoplasms
- A history of diabetic ketoacidosis and hyperosmolar nonketotic coma in the last 6 months
- A history of severe liver and kidney disease
- Suspected or confirmed history of alcohol or drug abuse
- Blood donation or blood loss $\geq$ 400 mL within the last 3 months
- Serious mental illness or language impairment; unwillingness or inability to fully understand and cooperate with the study
- Pregnancy and breastfeeding
- Known alcohol and drug abuse

- Other conditions that the investigator considers inappropriate for participation in this study

Written consent is obtained from participants after a full explanation, an information leaflet is offered, and time is allowed for consideration. The participants have the right to refuse or continue to participate in this study without giving reasons. The chief investigator ensures that participant confidentiality is respected and local data protection requirements are met.

The retention of patients is promoted by close and frequent contact with their nutritional counsellor and physician *via* telephone, email and study visits. In case of relevant issues, visits outside the study schedule are offered. Discontinuation study criteria include withdrawal of consent, subsequent occurrence of an exclusion criterion (e.g., change toward uncontrolled hypertension), lack of compliance and medical reasons for stopping the intervention.

Food records measure compliance with the intervention. For the CMNT group, there are regular additional meetings during each of the periods. These meetings have to be attended, enabling physicians and nutritional counsellors to evaluate compliance.

Interventions

Dietary intervention

During the 90-day experiment, participants will be randomized to the CMNT group or control group. The CMNT group will receive the CMNT diet for 5 consecutive days followed by 10 days of the usual diet, while the control group will receive only the usual diet for 15 days. The use of antidiabetic medications will be continued during the study. Multivitamin and mineral supplementation will be administered throughout the intervention. TCM nutritional intervention food contains a variety of oats, mulberry leaves, Poria cocos, Siraitia grosvenorii and other MFH natural raw materials or extracts.

The physician will educate each participant on the fundamentals of each dietary intervention and provide food lists. The physician will also be easily assessable to each participant for guidance and/or advice throughout the study. Ultimately, these measures should assist with participant compliance. Participants physical activity of CMNT group and control group follow the treatment guidelines for type 2 diabetes. The questionnaire also asks for information on the duration, type, and intensity of any exercise.

Medications

The process and rate of any medication reduction will be judged clinically and will depend on glycaemic control. There are clear specific recommendations for each of these medications and other classes of agents. Anti-diabetes medications, including sulfonylureas, meglitinides and insulin, are associated with hypoglycaemia, and their doses should be adjusted on days of the CMNT diet. The adjustment should take into consideration the control of the patient’s diabetes, including both fasting and postprandial glucose levels, over the preceding 2–4 weeks. Patients on an insulin pump should initially reduce their basal rate by 10%, with further adjustments based on frequent (every two hours) blood glucose testing

that continues until a stable pattern is established[25]. When the CMNT group or the control group achieves FBG or PBG ≤5 mmol/L, the physician will guide the antidiabetic medications reduction.

Adverse events

There are no major risks for patients participating in this study. We do not expect serious adverse events due to our dietary interventions. The materials or extracts in the CMNT diet are all foods in China; thus, the safety risk is under control. Patients will be asked regarding the tolerability of the interventions, and any adverse events will be recorded. Physicians will be asked to inform the research team about serious adverse events (SAEs) and adverse events (AEs). Participants will be asked at every visit about SAEs and AEs, which will be recorded at study visits and during telephone contacts with the research team.

Safety assessments

The trial is conducted in compliance with Good Clinical Practice principles (with which all investigators are confirmed to be familiar) and the applicable regulatory requirements. The study is subject to inspection and audit by the National Health and Family Planning Commission, Adherence to Good Clinical Practice in Research.

Outcomes

The endpoint will be assessed by an experienced evaluator who is blinded to both clinical data and allocation. All outcomes will be measured at baseline and at the end of the dietary intervention.

Primary outcomes

To evaluate the nutritional rehabilitation effect of the CMNT diet, our primary outcome is the withdrawal rate of antidiabetic medications after 90 days compared to baseline. Antidiabetic medications withdrawal is defined as a glycated haemoglobin (HbA1c) level of less than 7% (<53 mmol/mol) after at least 3 months off all antidiabetic medications.

Secondary outcomes

Anthropological measures, biochemical assessments and questionnaires will be evaluated.

- Glycosylated haemoglobin (HbA1c)
- Fasting blood glucose (FBG), postprandial blood glucose (PBG)
- BMI
- Systolic and diastolic blood pressure
- Total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol
- Measure of quality of life from EQ-5D-5 L

Assessments

Home assessments

During each dietary intervention, in addition to daily dietary recall, fasting blood glucose and postprandial blood glucose will be assessed.

Laboratory assessments

Anthropometry, that is, height (to the nearest centimetre) and body mass (to the nearest 100 g), will be measured using a stadiometer and electronic scale, respectively. Participants will be measured without shoes and while wearing light clothing[26]. The questionnaires employed in the project have been validated or used previously in similar settings. The EQ-5D-5 L is a validated quality of life questionnaire that measures the effects of disease and health status on perceived quality of life. It describes 5 health-related quality of life dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), all of which can take one of 3 or 5 responses depending on the level of severity[27-28].

Blood sampling and collection

After an overnight fast (minimum of 10 h), a 10-ml venous blood sample will be drawn by venous puncture from the brachial vein of the participant for the assessment of biomarkers of metabolic health. These biomarkers include HbA1c, triglycerides, LDL, HDL and total cholesterol.

Blinding

The CMNT is a diet intervention, so it is difficult to achieve double blindness. The control group only continues to maintain their usual diet and exercise habits. In the dietary intervention study, it is not possible for participants or all study personnel to be blinded to the group assignment. The study will be assessor-blinded, as the nurses who will perform the data collection (e.g., anthropometrics, doses of medications and blood pressure) and the technicians conducting laboratory work will be blinded to the intervention assignment.

Data collection and management

Data management

The Electronic Data Capture (EDC) system will be used for data management, including data entry, query, coding, security, and storage. Data will be gathered in source documents and then transferred onto paper case report forms. The data will be locally collected and transferred to the EDC system. The data will be coded and anonymised and then stored in an encrypted folder in a password protected computer. To improve the accuracy of data entry, entries will be verified for the proper format and expected range, as well as double-checked. Overall data quality will be assured by independent monitoring throughout the study.

Analysis Statistical methods

Data analysis will be performed using IBM SPSS Statistics (version 23, IBM Corporation, NY, USA). Two-tailed statistical significance will be accepted at $P < 0.05$. Continuous variables will be compared between the two groups by the independent sample t test, whereas the chi-square test will be used to compare categorical variables. Normally distributed continuous variables will be reported as the mean±SD. Multiple imputation will be used for missing data. We will adjust our final results for potential confounding factors using multivariable regression modelling.

Sample size

The primary outcome is the withdrawal rate of antidiabetic medications. An interim analysis for futility and efficacy is planned at the midpoint of the trial. At this point the sample size may also be re-assessed. Assuming a one-sided type I error of 5% and a power of 80%. A dropout rate of 15% implies that approximately 70 participants are to be recruited for this trial.

Publication policy

The study results will be disseminated by peer reviewed scientific journals, internal reports, conference presentations and publication on websites. No identifiable personal data will be published. All anthropometric and personal clinical data will be expressed as the mean/median and spread of the population in the study. All participants will be informed of the results at the conclusion of the study, and details of any publications that arise from the study will be disseminated to participants. We will comply with the official eligibility guidelines for authorship for all publications and do not intend to use professional writers.

Monitoring

Throughout the study, an independent monitoring manager monitors study documents. Four nutritional scientists/dietitians are responsible for the implementation of nutritional interventions and have frequent personal contact with study physicians. Study team and principle investigators meet every month to supervise, review and discuss study progress and all study related issues. A safety report will be submitted to the Medical Research Ethics Committee every year.

Discussion

To the best of our knowledge, no previous studies have investigated the effect of the CMNT diet in T2D. To date, this is the first study that investigates the CMNT diet nutritional rehabilitation of T2D patients. Many TCM formulations have been used as food for long-term consumption and are safe and effective. TCM has the characteristics of multiple targets, multiple links and multiple pathways in treatment[29], which can not only reduce blood glucose but also control diabetic complications and has great advantages in diabetes rehabilitation. TCM contains many active compounds that might target multiple proteins in the biological network and effectively relieve T2D [30]. Natural hypoglycaemic ingredients studied clearly in TCM at present are divided into polysaccharides, saponins, alkaloids, flavonoids, and

terpenoids by chemical structures[31]. MFH is a category of TCM, and there are food classes that can also be used as medication. In the CMNT diet, high MFH is employed for rehabilitation of T2D patients.

The meal pattern of CMNT in the diet is intermittent fasting. The advantage of intermittent fasting is that people have a major dietary adjustment for a few days every month and can thereafter return to a more normal diet. Intermittent fasting is an alternative dietary strategy for weight management and improving metabolic health. Dietary intervention studies cannot be blinded completely. Thus, expectations and observer bias cannot be ruled out. However, we will try to minimize bias by not communicating any longitudinal data during the study to patients and the study personnel who are in contact with them. Even more important, as the study research nurses who will perform the data collection (e.g., anthropometrics, drug doses and blood pressure) and the technicians measuring laboratory work will be blinded to the intervention assignment. Evaluation of the primary outcome is blinded for both clinical data and interventional allocation. Controlling and ensuring adherence to dietary interventions is rather challenging. This can only be avoided by close and frequent contact between nutrition counsellors and patients. Patients with suspected or known lack of compliance are excluded from the analysis.

There is little understanding of how the CMNT diet affects various physiological measures of T2D. The study aims to improve diabetes significantly or potentially put it into remission. Thus, our primary outcome is the withdrawal rate of antidiabetic medications after intervention compared to baseline. The CMNT diet potentially enhances the physical sustained remission to a nondiabetic state, improves quality of life and reduces the medical burden. In conclusion, the CMNT diet has the potential for nutritional rehabilitation of T2D. The study might close the gap between promising preclinical data and the lack of clinical data.

Trial status

Ongoing protocol version: 2.0; 2020-09-03: recruitment began on 2nd December 2018 and will be completed on 10th November 2020.

Abbreviations

Chinese Medical Nutrition Therapy (CMNT), Type 2 diabetes (T2D), traditional Chinese medicine (TCM), and medicine food homology (MFH)

Declarations

- **Acknowledgements**

The authors would like to express appreciation to Shizhi Mountain Community Health Service for their cooperation.

- **Authors' contributions**

DL is the Chief Investigator for the study. XY contributed to designing the study, developing the protocol, supervising the study progress and drafting the manuscript or revising it with critical input. RW managed and coordinated the performance of all aspects of the study. XK and WL contributed to the data analysis plan and prepared the data for analysis. XL and LY contributed to the data preparation and statistical analysis. All authors read and approved the final version of the manuscript.

- **Funding**

This study will be financially supported by a grant from the Hunan Science and Technology Department major project（Changsha, People's Republic of China）, the Collaborative Innovation and Achievement Transformation Project for the Prevention and Treatment of Diabetes Mellitus (2017SK1020). There is no input from the funding or sponsor organisations into the design, conduct, analysis, or reporting of the study.

- **Availability of data and material**

Data sharing is not applicable to this article, as no datasets were generated or analysed during the current study.

Ethics approval and consent to participate

The study has been approved by the Ethics Committee of the China Clinical Trial Registry (ChiECRCT20200235). All participants will sign a written informed consent form. Study protocol amendments are reviewed for approval by ethics committees when necessary. Written consent is obtained from each participant after a full explanation, an information leaflet is offered and time is allowed for consideration. The right of the participant to refuse to participate or continue participating without giving reasons and without prejudicing further treatment is respected. The Chief Investigator ensures that participant confidentiality is respected and local data protection requirements are met.

- **Consent for publication**

Not applicable.

- **Competing interests**

The authors declare that they have no competing interests.

- **Authors' information (optional)**

Xiao Yang, female, doctoral student at Hunan Agricultural University, Research direction: Functional product development and evaluation.

Author details

1 Hunan Key Laboratory of Crop Germplasm Innovation and Utilization, Hunan Agricultural University, Changsha 410128, China

2 State Key Laboratory of Subhealth Intervention Technology, Changsha 410128, China

3 Shizhi Mountain Community Health Service, Changsha 410007, China

4 Hunan Co-Innovation Center for Utilization of Botanical Functional Ingredients, Changsha 410128, China

5 Jinheyuan Outpatient Department, State Key Laboratory of Subhealth Intervention Technology Achievement Application Center, Changsha 410205, China

6 Horticulture College, Hunan Agricultural University, Changsha 410128, China

7 Nutrition and Food Catering Specialty, Changsha Commerce and Tourism College, Changsha 410116, China

References

1 Souteiro P, Belo S, Neves J S, Magalhães D, Silva R B, Oliveira S C, et al. Preoperative beta cell function is predictive of diabetes remission after bariatric surgery. Obes Surg. 2017; 27(2): 288-294.

2 Guilherme A, Virbasius J V, Puri V, Czech M P. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol. 2008; 9(5): 367-377.

3 Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg E W, et al. Mortality attributable to diabetes in 20–79 years old adults, 2019 estimates: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract. 2020; 108086.

4 Shikata K, Kodera R, Utsunomiya K, Koya D, Nishimura R, Miyamoto S, et al. Prevalence of albuminuria and renal dysfunction, and related clinical factors in Japanese patients with diabetes: The Japan Diabetes Complication and its Prevention prospective study 5. J Diabetes Invest. 2020; 11(2): 325-332.

5 Borg S, Eeg-Olofsson K, Palaszewski B, Engström M S, Gerdtham U G, Gudbjörnsdottir S. Patient-reported outcome and experience measures for diabetes: development of scale models, differences between patient groups and relationships with cardiovascular and diabetes complication risk factors, in a combined registry and survey study in Sweden. BMJ open, 2019; 9(1).

6 Tóth G, Szabó D, Sándor G L, Nagy Z Z, Karadeniz S, Limburg H, Németh J. Diabetes and blindness in people with diabetes in Hungary. Eur J ophthalmol. 2019; 29(2): 141-147.

7 Pastors J G, Warshaw H, Daly A, Franz M, Kulkarni K. The evidence for the effectiveness of medical nutrition therapy in diabetes management. Diabetes care. 2002; 25(3): 608-613.

8 Evert A B, Dennison M, Gardner C D, Garvey W T, Lau K H K, Mac Leod J. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care. 2019; 42(5): 731-754.

9 UKPDS Group. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. Metabolism. 1990; 39(9): 905-912.

10 Qian F, Liu G, Hu F B, Bhupathiraju S N, Sun Q. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA intern. Med. 2019; 179(10): 1335-1344.

11 Lean M E J, Leslie W S, Barnes A C, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The Lancet, 2018; 391(10120): 541-551.

12 Grajower M M, Horne B D. Clinical management of intermittent fasting in patients with diabetes mellitus. Nutrients. 2019; 11(4): 873.

13 Varady KA, Bhutani S, Klempel MC, Kroeger CM, Trepanowski JF, Haus JM, et al. Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial. Nutr J. 2013; 12:146.

14 Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes. 2011; 35:714–27.

15 Hutchison AT, Liu B, Wood RE, Vincent AD, Thompson CH, O'Callaghan NJ, et al. Effects of intermittent versus continuous energy intakes on insulin sensitivity and metabolic risk in women with overweight. Obesity. 2019; 27:50–8.

16 Wei M, Brandhorst S, Shelehchi M, Mirzaei H, Cheng C W, Budniak J, et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. Sci Transl Med. 2017; 9(377): eaai8700.

17 Carter S, Clifton P M, Keogh J B. Effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized non-inferiority trial. JAMA network open. 2018; 1(3): e180756-e180756.

18 Pang G M, Li F X, Yan Y, Zhang Y, Kong L L, Zhu P, et al. Herbal medicine in the treatment of patients with type 2 diabetes mellitus. Chinese Med. J. 2019; 132(1): 78.

19 Wang E, Wylie-Rosett J. Review of selected Chinese herbal medicines in the treatment of type 2 diabetes. The Diabetes Educ. 2008; 34(4): 645-654.

20 Hou Y, Jiang J G. Origin and concept of medicine food homology and its application in modern functional foods. Food Funct. 2013; 4(12): 1727-1741.

21 Tang J L, Liu B Y, Ma K W. Traditional chinese medicine. The Lancet, 2008; 372(9654): 1938-1940.

22 Wu R, Tang X, Kang X, Luo Y, Wang L, Li J, 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.

23 Wang J, Ma Q, Li Y, Li P, Wang M, Wang T, et al. Research progress on Traditional Chinese Medicine syndromes of diabetes mellitus. Biomed Pharmacother. 2020; 121: 109565.

24 De Munter J S L, Hu F B, Spiegelman D, Franz M, van Dam R M.. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. PLoS Med. 2007; 4(8): e261.

25 Grajower M M, Horne B D. Clinical management of intermittent fasting in patients with diabetes mellitus. Nutrients, 2019; 11(4): 873.

26 Perini T A, de Oliveira G L, Ornellas J D S, de Oliveira F P. Technical error of measurement in anthropometry. Rev Bras Med Esporte. 2005; 11(1), 81-85.

27 Herdman M, Gudex C, Lloyd A, Janssen M F, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011; 20(10): 1727-1736.

28 Takahara M, Katakami N, Shiraiwa T, Abe K, Ayame H, Ishimaru Y, et al. Evaluation of health utility values for diabetic complications, treatment regimens, glycemic control and other subjective symptoms in diabetic patients using the EQ-5D-5L. Acta diabetol. 2019; 56(3): 309-319.

29 Nie Q, Chen H, Hu J, Fan S, Nie S. Dietary compounds and traditional Chinese medicine ameliorate type 2 diabetes by modulating gut microbiota. Crit rev in food sci. 2019; 59(6): 848-863.

30 Gu J, Zhang H, Chen L, Xu S, Yuan G, Xu X. Drug–target network and polypharmacology studies of a Traditional Chinese Medicine for type II diabetes mellitus. Comput biol chem. 2011; 35(5): 293-297.

31 Zhang T T, Jiang J G. Active ingredients of traditional Chinese medicine in the treatment of diabetes and diabetic complications. Expert opinion on investigational drugs, 2012; 21(11): 1625-1642.

Tables

Table 1. SPIRIT figure showing the time points for enrolment, interventions and assessment.

	Study Period					
	Enrolment	Allocation	Postallocation			Closeout
Time point*	**-14 days**	**0**	**0 day**	**45 days**	**90 days**	**After completion of diet**
Enrolment:						
Eligibility screen	○					
Informed consent	○					
Allocation		○				
Interventions:						
CMNT diet			○	—	○	
Usual diet			○	—	○	
Assessments: Baseline Anthropological measures, doses of medications, biochemical assessments and questionnaires		○				
Primary Outcomes : The withdrawal rate of antidiabetic medications						○
Other Outcomes : HbA1c, blood glucose BMI,blood pressure, lipid profile,quality of life						○

Figures

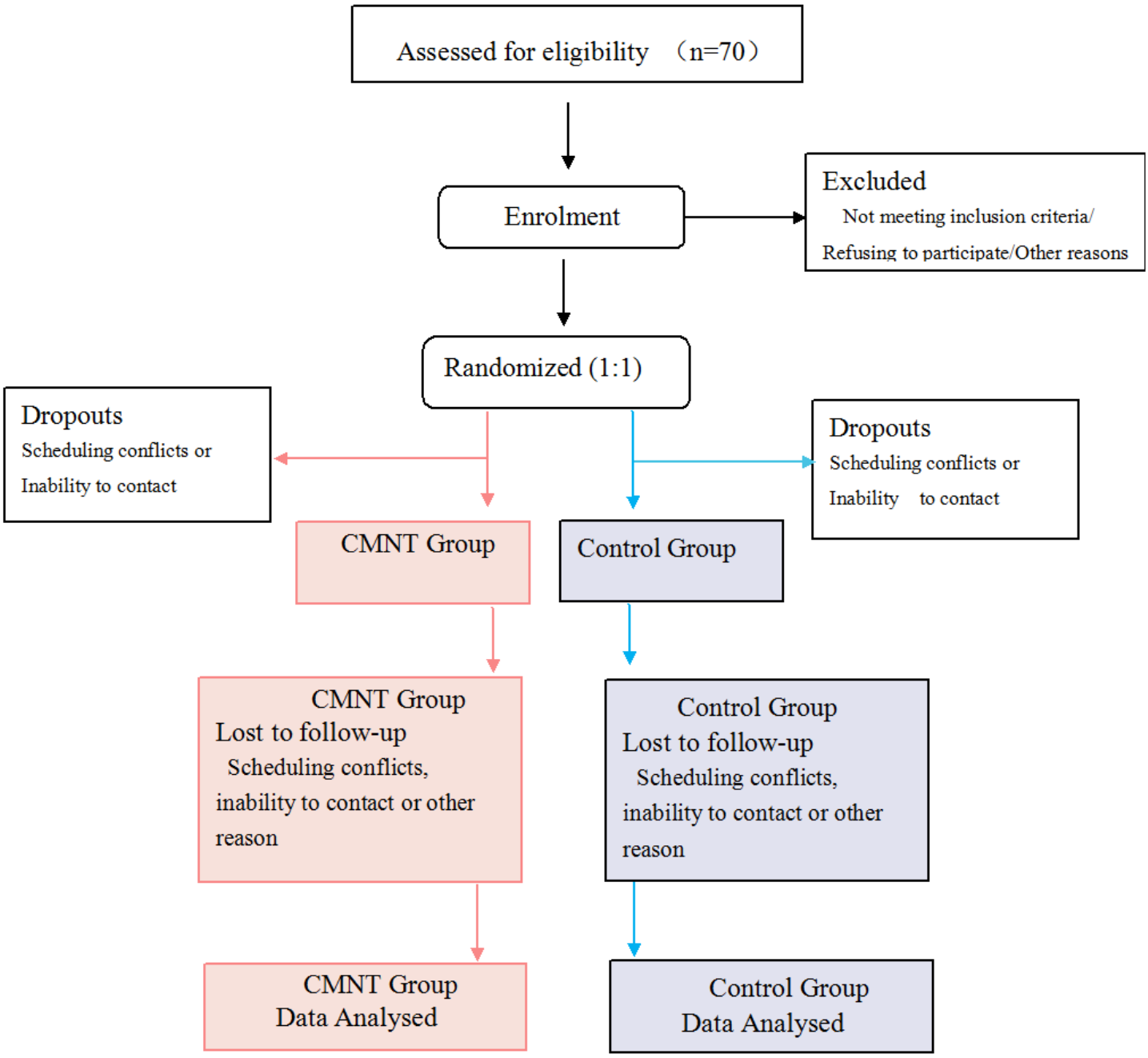

Figure 1

Diagram Showing Participants Flow through the Trial

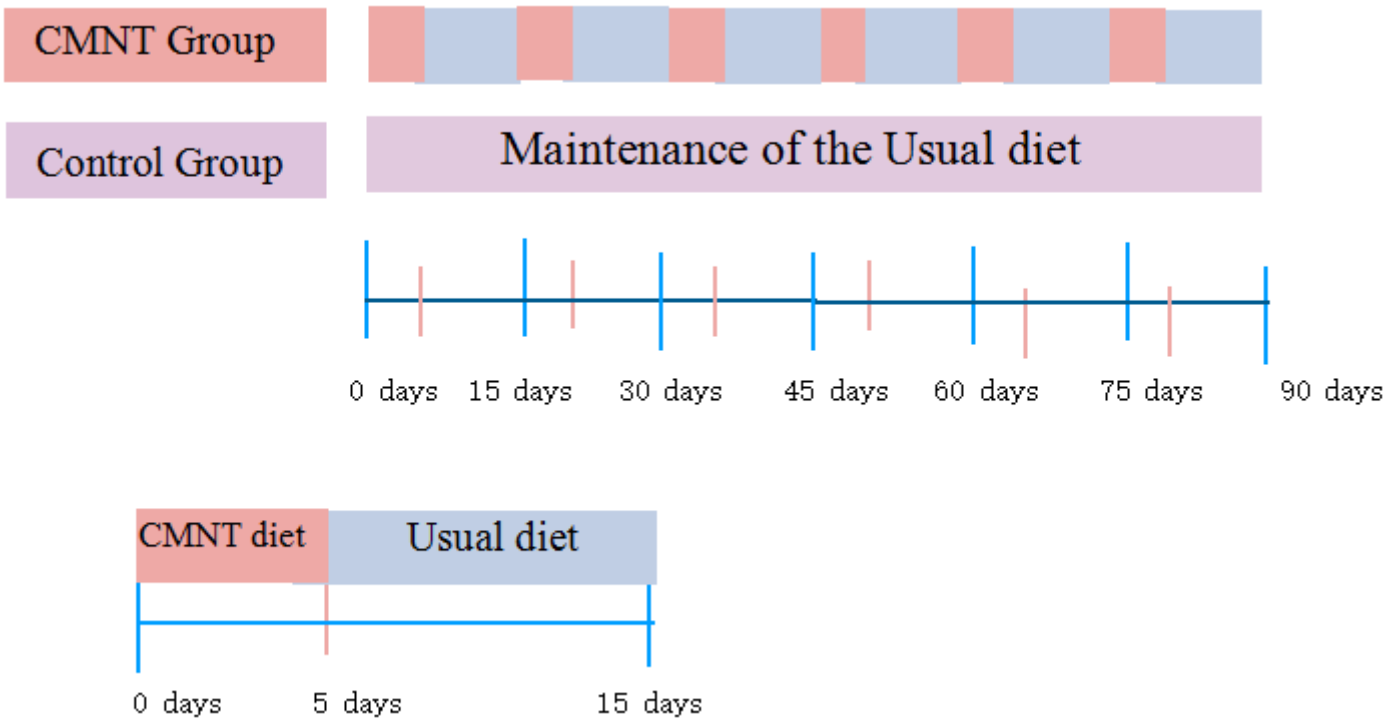

Figure 2

Scheme of the CMNT Interventions

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklist.doc