Cover letter:

Official project title:
Effectiveness of Low-Calorie MIND-HK Diet and Very Low-Calorie Diet on Glycemic Control and Cardiovascular Outcomes in Adults With Type 2 Diabetes: A 12-Week Randomized Controlled Trial

Funding source: HKMU R&D Fund

NCT number: HE–OT2025/25

Document updated date: 03/02/2026

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Abstract:
Type 2 diabetes mellitus (T2DM) represents a significant global health concern, especially among adults. This research aims to assess the effectiveness of a low-calorie and very low-calorie Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND-HK) diet in improving glycaemic control and cardiovascular outcomes in adults with T2DM. A total of 180 participants aged 40 to 70, diagnosed with T2DM, will be recruited and randomized into three groups: intervention 1 following the low-calorie MIND-HK diet, intervention 2 following the very low-calorie diet, and an attention control group. The two intervention groups will attend four in-person nutrition counselling sessions (one per week, 60 minutes per session, followed by a 30-minute Q&A) at a community centre and will use KetoMetrics Breath Ketone System and dietary mobile app, to track diet and monitor daily ketone levels for early signs of ketosis that may lead to diabetic ketoacidosis (DKA). The attention control group will receive an equal amount of attention through four in-person infectious disease counselling sessions. The primary outcome will be HbA1c levels. Secondary outcomes include fasting blood glucose, lipid profile, blood pressure, body mass index, waist circumference, breath ketone, scores from the Summary Diabetes Self-Care Activities (SDSCA) Questionnaire, and MIND diet scores. This study will contribute to the growing body of evidence on dietary interventions for managing T2DM in adults.

Project team:

	Full Name	Post	Unit/School
Principal Investigator:	Dr. Queenie Pui Sze Law	Associate Dean (Learning & Teaching)	N&HS
Co-Investigator(s):	Prof. Rick Kwan	Professor & Associate Dean	TWC
	Ms Jess Lau	Senior Lecturer	N&HS
	Dr Terry Ho-yan Ting	Assistant Professor	PolyU
	Ms Sandra Chan	Senior Lecturer	N&HS
	Dr Kenny Kung	Specialist	Premier Healthcare

Project objective:

1. To determine the effectiveness of the low-calorie MIND-HK diet and the very low-calorie diet in improving HbA1c levels in adults with T2DM over a 12-week period.
2. To assess the impact of these diets on secondary health outcomes, including fasting blood glucose, lipid profile, body mass index, waist circumference, blood pressure, and self-reported diabetes self-care activities and MIND-diet scores.

Introduction

Type 2 diabetes mellitus (T2DM) is a long-term metabolic condition marked by elevated blood sugar levels due to the body's inability to effectively use or produce insulin. It is a significant contributor to complications such as cardiovascular disease, kidney dysfunction, and other health issues, particularly in adults. The prevalence of T2DM continues to rise globally, largely driven by increasing rates of obesity and sedentary lifestyles. Managing T2DM effectively is crucial to minimizing these risks and improving patients' overall well-being. Among various management strategies, dietary interventions, particularly low-calorie and very low-calorie diets, have shown promise in improving blood sugar control and even achieving remission in some cases.

Obesity is a well-recognized risk factor for T2DM, accounting for nearly half of all cases worldwide. Research has consistently demonstrated that weight loss plays a critical role in both preventing and reversing T2DM, as well as reducing the burden of related health conditions. Even modest weight reductions have been associated with significant improvements in glycemic control, with studies showing that losing just 1 kg of body weight can lead to a 0.1% (1.1 mmol/mol) reduction in glycated hemoglobin (HbA1c). A personalized approach to weight management, which may include dietary changes, increased physical activity, behavioral support, medication, or surgical interventions, is often recommended based on individual needs and the severity of obesity (10).

Very low-calorie diets (VLCDs) have emerged as an effective tool for achieving rapid weight loss and improving blood sugar levels. Several clinical trials have demonstrated their potential to induce significant weight loss and, in some cases, remission of T2DM. For example, studies such as the DiRECT trial in the UK and the DIADEM-1 trial in Qatar have reported substantial weight reductions and remission rates ranging from 45% to 60% after one year. (8, 9). The DiRECT study further reported a remission rate of 35% at 24 months. Similarly, the South Asian Diabetes Remission Feasibility Trial (STANDby), a smaller RCT involving 25 South Asians in the UK, reported a weight loss of 7.2% and a T2DM remission rate of 38% at four months (7, 11). In a non-randomized, open-label primary care study from Australia (DiRECT-Aus), VLCDs achieved a weight loss of 11.2% and a T2DM remission rate of 55% among 155 participants at one year (12).

However, maintaining T2DM remission over the long term remains a challenge, as evidenced by the five-year DiRECT extension study, which reported an overall remission rate of only 13% at five years. The relationship between the amount of weight lost and the likelihood of remission is particularly noteworthy. For instance, individuals who lost between 5–10 kg achieved remission rates of approximately 30%–35%, while those who lost more than 15 kg experienced remission rates as high as 86% after one year. These findings underscore the importance of sustained weight loss in achieving long-term improvements in glycemic control. (7).

Given the growing evidence supporting the role of dietary interventions in managing T2DM, this study aims to explore the impact of the low-calorie MIND-HK diet and the very low-calorie MIND-HK diet on blood sugar control and cardiovascular health in adults with T2DM.

Study hypotheses:
This study hypothesizes that low-calorie MIND-HK diet and very low-calorie diet will lead to greater improvements in glycaemic control, as measured by HbA1c levels, in adults with T2DM compared to usual care. It also expects positive changes in secondary outcomes, including fasting blood glucose, lipid profile, blood pressure, weight circumference, body mass index, MIND diet scores and diabetes self-care activities.

Methodology

The proposed study will adopt a Randomized Controlled Trial (RCT) design. Participants will be screened for eligibility through local community centres. Those who meet the inclusion criteria will be invited to participate in the study and sign the consent forms. At baseline, demographic information, medical history, and clinical measurements—including HbA1c, fasting blood glucose, lipid profile, blood pressure, weight circumference, and body mass index—will be collected for all participants.

Interventions:

1. **Low-calorie MIND-HK diet group**

The low-calorie MIND-HK diet intervention utilized in this study is based on the MIND diet originally developed by Morris and colleagues in 2015 (1, 2) and adapted from the Arjmand group's 3-month MIND diet intervention (5). Patients with T2DM will be encouraged to adopt a structured 1,000-calorie MIND-HK diet tailored to their individual nutritional needs and health goals (3 .4). This carefully designed dietary plan aims to optimize glycemic control, promote weight management, and support overall cardiovascular health, while adhering to the principles of the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND-HK) diet.

By providing clear guidance and practical strategies, the intervention seeks to empower patients to make sustainable dietary changes that align with evidence-based recommendations for effective diabetes management. To support this, a 7-day sample menu meeting the required daily servings will be provided as a reference. Additionally, visual aids, such as posters highlighting the 14 key food items of the low-calorie MIND-HK diet, will be displayed in kitchens and dining areas to reinforce participants' memory and serve as reminders for both participants and their caregivers.

Adherence to the low-calorie MIND-HK diet will be assessed using a predefined scoring system (1, 2), based on 14 components—nine healthy and five unhealthy food groups (excluding wine). Each group is scored 0.0, 0.5, or 1.0, with higher scores reflecting healthier

intake, for a total score ranging from 0 to 14. Participants can connect the breath ketone device to the diet app via Bluetooth, which auto-logs ketone levels, nutrients, and calories over time.

2. **Very Low-calorie diet group**

A structured, intensive dietary intervention for individuals with type 2 diabetes mellitus (T2DM) involves a very low-calorie diet plan, providing approximately 800 kilocalories per day with strict carbohydrate restriction, limited to no more than 50 grams per day. Typically implemented over a 12-week period, this intervention is designed to achieve significant weight loss and improve glycemic control. The primary objectives of this approach include reducing insulin resistance, lowering hepatic and pancreatic fat, and minimizing the need for glucose-lowering medications.

The dietary composition consists of approximately 25% carbohydrates, 30–40% protein (60–80 grams per day), and 35–45% fat (35–45 grams per day), with protein intake adjusted to meet individual clinical needs. Meals are structured into three low-calorie servings per day, such as 200 kilocalories for breakfast and 300 kilocalories for both lunch and dinner, while ensuring carbohydrate intake remains below 50 grams daily. Recommended foods include lean proteins, non-starchy vegetables, healthy fats, and limited quantities of low-sugar fruits, such as berries. Beverages should primarily consist of water, black coffee, and unsweetened herbal teas.

Both intervention groups will follow a 12-week nutrition program consisting of four in-person nutrition counseling sessions held weekly during the first month. Each session will last 60 minutes, followed by an additional 30-minute question-and-answer segment. These sessions will be conducted in activity rooms at participating community centers. After the initial 4-week in-person sessions, participants will continue to receive support through WhatsApp groups for the remaining 8 weeks of the intervention. These groups will serve as platforms for appointment reminders, personalized health tips, educational materials, and fostering self-management practices. The study will assess whether the involvement, support, and encouragement provided during the intervention predict participants' adherence to the low-calorie MIND-HK diet and very low-calorie diet, as well as their subsequent health outcomes. All intervention sessions will be led by a registered nutritionist, who will guide participants on how to modify their diets to align with the guidelines of the low-calorie and very low-calorie diets.

Throughout the 12-week intervention, participants in the intervention groups will monitor and report their daily ketone levels using the KetoMetrics Breath Ketone System. Adherence to the low-calorie MIND-HK diet and very low-calorie diet will be encouraged and supported through weekly check-ins and the use of dietary logs. The attention control group will continue their regular diet without ketone monitoring.

At the end of the 12-week period, all baseline assessments will be repeated to evaluate changes in cardiovascular health and self-care practices. This structured approach allows for the comparison of outcomes between the interventions and the attention control groups to assess the effectiveness of the low-calorie MIND-HK diet and very low-calorie diet.

To further incentivize adherence, participants will receive a HK$100 supermarket coupon upon completing the study. To monitor the potential development of ketosis and mitigate the risk of diabetic ketoacidosis (DKA), participants in the intervention groups will be provided with the KetoMetrics Breath Ketone System and its accompanying mobile app, generously donated by AusMed Global. The app will enable participants to track and log their daily dietary intake.

The research team will conduct weekly follow-ups via phone or WhatsApp to ensure dietary adherence and address any concerns. The control group will continue with their usual dietary habits throughout the study.

Control group

An attention control group will receive the same amount of attention in four in-person infectious disease counselling sessions (6).

Primary and secondary outcomes:

The primary outcome of the study will be HbA1c levels.

Secondary outcomes will include changes in fasting blood glucose, breath ketone, lipid profile, body mass index, waist circumference, and blood pressure, as well as scores from the Diabetes Self-Care Activities Questionnaire and MIND diet scores.

Subjects:

Inclusion criteria:

1. aged 40 to 70 years old;
2. diagnosed with Type II DM; and
3. Chinese ethnicity and able to speak and understand Cantonese.

Exclusion Criteria:

1. patients on dialysis;
2. patients with insulin use;
3. allergic to more than one type of food in the Low-calorie MIND-HK diet and very Low-calorie MIND-HK diet (e.g. nuts, berries, olive oil, or fish); and
4. participation in any dietary programme within the past 3 months.

Data collection

Data collection will occur at two time points: baseline (before the intervention begins) and at the end of the 12-week intervention. Prior to the start of the study, all participants will be recruited and informed consent will be obtained. At baseline, participants in both the interventions and control groups will undergo assessments, including measurements of HbA1c, fasting blood glucose, lipid profile, body mass index, waist circumference, blood pressure, breath ketone administration of the Summary Diabetes Self-Care Activities (SDSCA) Questionnaire, and MIND diet scores.

Throughout the 12-week period, participants in the intervention groups will monitor their ketone levels daily using the KetoMetrics Breath Ketone System. The research team will conduct weekly check-ins with the intervention groups via phone or WhatsApp to ensure adherence and provide support as needed. All collected data will be securely recorded and stored for analysis.

Safety Protocol for Ketone Monitoring:

Participants in the intervention groups will receive training on how to properly use the KetoMetrics Breath Ketone System for daily monitoring of ketone levels. The protocol is as follows:

- < 5 ppm: Normal
- 5 to 20 ppm: Is slightly high – test again in 2 hours
- 21 to 40 ppm: You're at risk of DKA and should contact research team
- > 40 ppm: Is high and means you may have DKA and should call 999 right away

Participants will be trained on using the ketone monitoring device, interpreting results, and recognizing DKA symptoms. They will be instructed to contact the research team if ketone levels are elevated or if they experience DKA symptoms. Clinical safety protocols will be followed.

Data processing and analysis:
All collected data will be checked for completeness and accuracy before analysis. Descriptive statistics will be used to summarize baseline characteristics of the participants. Statistical analyses will be performed using SPSS (version 26, SPSS Inc., Chicago). The alpha level will be set at 0.05 for two-tailed tests. Chi-square tests and analyses of variance will be used to compare the groups at baseline. The treatment effect size will be estimated by calculating Cohen's d using the pooled standard deviation of the adjusted means when the group difference is statistically significant. Intention-to-treat analyses will be performed to compare the intervention and control groups.

Missing Data:
Missing data will be addressed using multiple imputation assuming data is missing at random (MAR). For minimal missing data, complete case analysis may be used. Sensitivity analyses will be conducted to assess the impact of missing data on the study outcomes.

Ethical considerations:
The proposed study will be reviewed by the Research Ethics Committee of HKMU. All participants will receive an information sheet and an informed consent form before the study begins, and will be informed that withdrawal at any time will not result in any adverse health consequences. The completed consent form will be collected during the briefing session.

Participants will undergo blood tests through a finger prick, causing minimal discomfort. Tests will be conducted using Point-of-Care Testing (POCT) by trained personnel. To protect

personal information, all data collected will be kept electronically under password encryption. Only the PI and her collaborators will have access to the encrypted data. The data will be destroyed 5 years after the completion of the study.

Project duration:
36 months

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