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RESEARCH ARTICLE

A PROTOCOL FOR A RANDOMIZED CONTROLLED STUDY TO DETERMINE THE EFFICACY OF INTERMITTENT FASTING AS A MANAGEMENT METHOD FOR TYPE 2 DIABETES MELLITUS

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ABSTRACT

Previous studies using intermittent energy restriction in overweight and obese people have demonstrated it to be an effective intervention in achieving weight loss, when compared to continuous energy restriction. **Objective:** We anticipate that intermittent fasting (IF) in the Malaysian population may be an effective intervention for the management of diabetes. We describe a protocol for a randomized controlled trial of intermittent fasting in Primary Care Clinics in Malaysia of 18 months' duration, comparing 3 and 5 days of IF to usual care. The objective is to determine the impact of IF on diabetes management over 18 months and to see what difference a 3 or 5 day IF makes. **Methods and analysis:** A protocol development to achieve improved clinical outcomes in a three-arm randomized controlled trial (3 and 5days IF groups and one control group) asking the question 'does intermittent fasting in adults with T2DM in primary care improve HbA1c in the Malaysian population?'. **Outcome measures:** An absolute difference in HbA1c at 18months' follow-up between the intervention arms and control arm. Our sample size (n=450) has the power to detect a difference of 0.5% in HbA1c. Secondary outcomes will measure the difference in waist circumference, BMI, blood pressure and biochemical parameters, and acceptability of the intervention between the 2 intervention arms and control arm of the study. **Eligibility:** Adults aged 18 to 70 years, diagnosed with T2DM for at least six months, and a minimum HbA1c of 7.5%.

INTRODUCTION

Metabolic disorders and type 2 diabetes mellitus (T2DM) are increasing worldwide, leading to an increased need for newer as well as easier interventions. We know that medical nutrition therapy is the first line of treatment of T2DM, and it needs to continue lifelong. Even a 5% weight loss compared to initial body weight has shown positive outcomes. And yet, lack of compliance with dietary restrictions has remained challenging.[1] One lifestyle intervention drawing interest is Intermittent Fasting (IF), which restricts all caloric intake into a few hours of each day, with a fasting period of 12 to 16 hours, with a period of normal food intake in between. Previous studies on IF in normal and overweight persons have demonstrated reductions in weight, insulin resistance and lowered risk factors for cardiovascular disease.[2] Different terms are used for regular intermittent calorie restriction. We will adopt the term Intermittent Fasting (IF) throughout this protocol. Fortunately, fasting is an accepted religious observance for most ethnic groups in Malaysia, and using it as a health related intervention may be more readily acceptable.

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Therefore, intermittent fasting may be a pragmatic approach to dietary intervention in Malaysia. New evidence shows that we should now replace the emphases on individual nutrients, total fat, and calorie counting with a more rational and sustainable strategy of simple healthy food choices.[3] Whether people can maintain intermittent fasting for years and potentially continue the benefits seen in animal models remains to be ascertained.[4] Also, adherence to most dietary regimes in the long term is a challenge [5], and increasing vegetable and fruit intake can be expensive in many settings. The reason for studying fasting based approaches is that it may be easier to sustain, and compliance may be greater. Unfortunately, long term fasting may also lead to malnutrition and lower immunity.[6]

A nutritional survey conducted in Malaysia in 2003 showed that 10.8% of respondents do not have breakfast, 11.4% of them skip lunch, and 8.0% of them do not eat dinner.[7]This paper also confirms our stand that IF will be well accepted as a dietary intervention in Malaysia. In a review paper of 27 studies, IF resulted in weight loss of 0.8% to 13.0% from baseline body weight. This weight loss occurred regardless of their caloric intake, waist circumference decreased by 3 cm to 8 cm after 4 weeks or more in all studies. The IF groups also had significantly better insulin sensitivity.[8] Short term studies have shown that intermittent fasting reduces inflammation,

reactive oxygen species, blood pressure, and cholesterol levels, some of which may occur simply due to weight loss.[9] An overview of Metabolic Syndrome showed that adherence to IF diet is as high as 83–86%.[10]

A study which looked into IF in relation to time of day, showed that unless the fasting period was earlier in the day, shorter eating durations was associated with worse metabolic outcomes. All participant groups with an earlier eating time had better metabolic outcomes unrelated to the actual fasting duration.[11] Dietary regimes that have focused on the timing of meals and the duration of fasting rather than on the type, quality or quantity of foods, have been seen to improve metabolic parameters independent of weight changes.[12] Finally, a recent systematic review was conducted where the primary outcome was the body weight change between pre and post-intervention of IF.A total of 511 participants were studied, between 18 and 65 years of age, with BMI $\geq$24 kg/m^2.There was a significant improvement in weight and body composition in the IF group, with a significant decrease in total fat mass.[13]

Most trials in the field of intermittent fasting have been for a short duration. A need for longer studies to ascertain the efficacy of fasting as an intervention has been mentioned repeatedly in most pre-existing studies. The evidence for IF to create clinical guidelines for people with diabetes is almost non-existent. More studies of a longer duration are required to create a more robust evidence base. This study will be performed on persons with diabetes mellitus in the community, who are receiving care from the primary care clinics. Justification for this research is that previous trials have been positive for improved outcomes, but only in the short term, and we are looking at the durability of the intervention over 18 months; and we also wish to clarify whether a 3 or 5-day fast is equivalent to or better than usual care and whether the intervention is suitable for the Malaysian population.

MATERIALS AND METHODS

Research Question: Does intermittent fasting for 3 or 5 days a week reduce HbA1c in persons diagnosed with type 2 Diabetes Mellitus as compared to usual care in the Malaysian population?

The aim of this study is to assess the change in HbA1c in people with T2DM after 16 hours of fasting with ad libitum eating for 8 hours, 3 or 5 days a week as compared to the change in HbA1c levels in the usual care group over an 18-month period in the management of persons with T2DM who are not on target HbA1c control.

Primary Objective: To assess the impact of a 3 or 5 days a week IF over 18 months on reducing HbA1c in people with T2DM not on target.

Secondary objectives:

- Is IF sustainable over the 18 months of this study?
- Is this approach suitable for the Malaysian population?
- Changes in parameters of Metabolic Syndrome - BMI, waist circumference, blood pressure, LDL cholesterol, triglycerides, HDL cholesterol, serum creatinine, serum uric acid, ALT, AST, urine microalbumin.
- Changes in doses of basal insulin or oral medication in the intervention group.
- Changes in DQoL (Diabetes Quality of Life)[14]

Trial Design: The trial will be designed as a multi-center, investigator blinded, randomised, controlled trial of IF on persons with T2DM whose HbA1c is above the recommended target ($\geq$7.5%). There will be three parallel arms, two of which will be intervention arms of intermittent fasting (3 and 5 days IF), and one control group of usual diabetes care. The control group would be those persons who are receiving usual care in the community which consists of 6 to 12 monthly follow-up of care without any significant dietary intervention apart from general advice on a standard diet. The primary endpoint will be change in HbA1c levels after 18 months due to the intervention, as compared to change in HbA1c with usual care of a similar duration, in persons with T2DM who are not on target.

The fasting and eating periods will be the same for all fasting participants to keep the study standardized. This protocol follows the CONSORT guidelines for research protocol development. The report will also follow CONSORT guidelines for RCTs.[15]

Training and Responsibilities: Before starting the study, the primary care doctors and all participating persons who will conduct the study will attend a training session (online, or in person) where the study is explained and they will be given details on how to implement the intervention. Basic nutritional advice will be provided to the doctor to discuss with the patient at initial contact with a reiteration at each follow-up.

All training will be performed by a suitably qualified Primary Care doctor. A research assistant will collect and manage data.

Eligibility criteria for participants:

- Diagnosed with T2DM for at least six months with a HbA1c of >7.5%
- Adults (age 18 to 70 years)
- On oral hypoglycemic agents (OHAs) and/or once a day basal insulin, or on diet and lifestyle management alone, who have remained stable (no dose adjustment) over the preceding 3 months.

Exclusion Criteria:

- On insulin therapy twice a day or more frequently
- Pregnant and lactating women
- Adults >60 years who are frail [16]
- People with immune-deficiencies or on immunosuppressive treatment
- Individuals with dementia or cognitive impairment
- Major co-morbidities (stroke, stage 3 or 4 CKD, or on dialysis)
- Individuals on antipsychotic or antiretroviral medication
- Persons who have a BMI of 23 or less
- Major hypoglycaemic episode in preceding 3 months
- Those who routinely fast for 1-2 days a week for religious or other reasons

Sample size calculation:

The NDR (National Diabetes Registry) details information about patients with diabetes managed at participating Ministry of Health clinics (klinik kesihatan or KKs). There are 57 KKs in Kedah, serving 158,193 diabetes patients.[17]

***Sample size*:** A balanced design will be planned with a sample of 150 patients being recruited to each of the 3 arms of the study (450 in total). Groups of this size are being used to achieve a power in excess of 90% in detecting a difference of 0.5% in HbA1c at the 5% level of significance as well as to account for any attrition during the study period.

Study setting: Persons with T2DM attending primary care clinics in Kedah, Malaysia.

Consent: informed consent will be obtained from every participant in writing, before any study procedures are started.

Recruitment strategy: The research assistant will recruit participants from the diabetes database of each participating clinic (KK) who meet the inclusion criteria. Invitation letters/e-mails to join the study will be sent out to the identified persons. A second letter will be sent out in 3weeks' time if the number recruited is insufficient. Practices participating in the trial will also display posters and flyers in the waiting areas with contact phone numbers. The enrollment period will extend for 3 to 4 months.

Randomisation: A convenience sampling will be used, with every participant who meets the inclusion criteria and consents to participate in the study being randomized into groups 1, 2 or 3 in sequence, at each participating clinic.

Intervention

Demographic data: Participants will fill up a demographic data form which will include their name, age, gender, place of residence, occupation, level of education, ethnicity, eating preference (vegetarian, non-vegetarian), religion, and duration of diabetes diagnosis. Each participant will be given a unique identification code (UI) for ethical reasons, and data will be stored according to the participant UI.

***Baseline data* collection to be done and repeated at 3rd, 6th, 12th and 18th month of study:**

- HbA1c
- BMI
- BP
- Waist circumference
- Fasting Blood Glucose (FBG)
- LDL cholesterol, HDL cholesterol and Triglycerides,
- Serum creatinine
- Serum uric acid
- ALT, AST
- Urine microalbumin

Apart from this data, the patient will also be reviewed for compliance to the intervention, and complete the questionnaires (adverse events, DQoL). Their SMBG (self-monitoring of blood glucose) diary (if any) will also be reviewed.

Pre-study: All participants who have consented for the study and have been randomised to the intervention or standard arm will attend an individual face-to-face diabetes education with the doctor, and a session of data collection of 60 min with the research assistant at the beginning of the study and at 6 and 12 months.

This session will be held at the patient's general practice clinic. A dietary history will be taken and recorded before each study participant starts the trial. If any change is required, the person will be counseled accordingly. A DQoL questionnaire will be recorded at baseline.

Who will perform the intervention: Primary care doctor at the clinic (KK) and a research assistant.

Intervention description

Group 1: standard care. To be given dietary advice on food choices for diabetes mellitus (pamphlet or written material).

Group 2: 16 hours fast, 5 days a week (Monday to Friday or any 5 consecutive days of their choice). Ab libitum food for 8 hours (from 11.30 am to 7.30 pm). Dietary advice on food choices for fasting and non-fasting days are the same.

Group 3: 16 hours fast, 3 days a week (Monday to Wednesday or any 3 consecutive days of their choice). Ab libitum food for 8 hours (from 11.30 am to 7.30 pm). Dietary advice on food choices for fasting and non-fasting days are the same.

Criteria for discontinuing allocated interventions

- Severe hypoglycemia
- Change in status of patient into one with any exclusion criterion
- Patient withdrawal

Criteria for modifying intervention: Festival times are Ramadan 6 weeks, Deepawali 3 weeks and Chinese New Year 3 weeks. During this period the participants may not follow the fast as described for the study, but will continue to be followed up.

Strategies to improve adherence:

- Face to face session of all participants with the doctor once at 3 months, then 6 monthly.
- Each participant will be given a phone number to call or a WhatsApp number to clear any doubts.
- Direct phone or face to face discussion on reason for non-adherence, and encouragement to continue with the intervention.
- A quality of life survey will be performed on all participants to find out how they feel about the fast and if they are having any problems of adherence (DQoL questionnaire).
- An adverse events list will be given to each participant and an adverse events questionnaire will be filled in at 3, 6, 12 and 18 months of the study. Participants will meet the researchers and dietician at the beginning of the study, and 6 monthly thereafter, for 18 months.

Safety Monitoring: Education about hypoglycemia will be given. A safety monitoring committee will be set up which will include an endocrinologist and the treating doctor. Diet will be assessed six-monthly during the trial and supplements may be prescribed if required to mitigate the risk of participants developing protein-energy or vitamin related malnutrition.

Medication Management: Management of each patient's medication will be planned by the GP in participating clinics after discussion with the study participant and any change noted during the study. For those on sulphonylurea and/or basal insulin, a management plan will be drawn up and reviewed regularly (every 3 months) by their treating team. All participants on sulphonylurea or basal insulin will be asked to test and record their fasting blood glucose levels daily, i.e. before breakfast, with the addition of 3 extra readings requested on IF days, which must include a before bedtime reading.

- If glucose is <4mmol/L, treat the hypo as per protocol, and contact the study investigator by phone or WhatsApp for advice.
- If glucose is >11mmol/L, compliance to the diet/fasting regime will be checked at their next clinic visit and if required, medication changes will be made.

Fasting blood sugar on fasting days	Sulphonylurea	Insulin (basal)
<6.5	Discontinue on fasting days	Halve basal insulin dose on fasting days
7 to 11	Continue	Adjust basal insulin dose by +2 u/2 days

Medication will be reviewed and changed as required every 3 to 6 months in accordance with weight changes and HbA1c results (Modified from [18]).

Outcome measures

Primary outcome: Treatment success will be defined as reduction in HbA1c of at least 0.5% in either or both the intervention arms as compared to the standard care arm, since based on ADA and National Institute for Health and Clinical Excellence treatment guidelines, 0.5% HbA1c is considered a clinically significant change.[19]

Secondary outcomes

- Clinical measures of BMI, waist circumference and blood pressure reduction of at least 5% from their baseline values.
- A significant reduction in medication or basal insulin dosage ($p<0.05$).
- Reduction in fasting glucose, LDL cholesterol, triglycerides, serum creatinine, serum uric acid, ALT, AST by a significant amount ($p< 0.05$) compared to their own baseline values and the standard care group. Increase or no change in HDL cholesterol.
- Change in quality of life (DQoL and Dietary and Lifestyle questionnaires done at baseline and repeated at 6 months,1 year and at end of study).

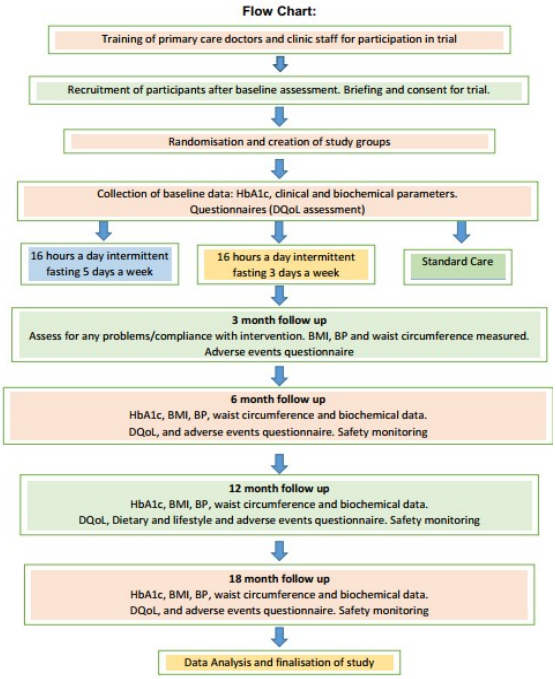
Time schedule: The study will run for a period of 18 months. It will include any festival times when the participant will follow their own cultural practices. However, they will continue to be followed up during this time. Once the festival is over, they will return to the study protocol.

Data Collection: Data will be collected by the primary care staff at the selected clinics and passed on to the research assistant for tabulation. Only the Unique Identification code (UI) number of each patient will be kept with the actual data. The patient name to UI links will be held securely at the primary care practice. Participants may withdraw from the study for any reason at any time. In case a participant drops out, they will be given the option of continuing to be followed up for the duration of the study to assess any legacy effect of the intervention.

Data Management:

Data entry will be initially on paper. All data will be transferred to an excel sheet by the research assistant weekly, and stored electronically on a secure server which will be password protected. Only anonymised data will leave participating practices. Any hard copies of participant files are to be stored in numerical order and in a secure place, accessible to only specified members of the research team. All data will be saved until 3 years after the trial is published. Anonymised data will be saved for longer for any secondary analysis at a later date.

Statistical method: Analyses will be performed using SPSS V25.0. A minimum reduction of 0.4% in HbA1C will be considered as statistically significant (as noted in primary outcome). The analysis will be based on an intention to treat. For the secondary outcome measures, a p-value of < 0.05 will be considered statistically significant. For the quality of life, dietary and lifestyle assessment and adverse events measures: The comparisons of change between each intervention group and the control group will be assessed using 2-sample t-tests. Comparisons between group demographics e.g. age, gender, etc. will be performed using appropriate independent sample tests (t-test, chi-square test) and if very significant differences are found, analyses of the main study outcome variables may be changed to allow for this.



RESULTS AND DISCUSSION

Humans, like most living organisms, have evolved to have an in-built circadian (24 hour) rhythm during which metabolic functions cycle through the 24 hours depending on changes in daylight, ambient temperature, and nutrition availability. When activity, food intake and sleep occur according to our optimal circadian rhythms, our organ functions and health are optimised. In humans, eating earlier in the day is associated with better glucose tolerance and improved thermic effect of food. [20] In a country like Malaysia, where 3 major ethnic groups (and many smaller ethnicities as well as foreign workers) co-exist, each with their own cultural and dietary differences, giving standardized dietary advice is difficult. Using an approach like IF, where no major change may be required, except for avoidance of pure sugars and processed foods can be the major advantage of this intervention. Another advantage is that this population is not naïve to fasting and IF may prove to be more acceptable. We are therefore developing a pragmatic, 18-month, three arm RCT protocol which is designed to study the effect of early intermittent fasting (IF) on long term blood sugar control in persons with diabetes mellitus, as well as check secondary outcome measures related to cardiovascular health. The study is also attempting to assess the safety of 3 or 5 days of intermittent fasting as well as establish the duration of intermittent fasting needed before cardiovascular benefits occur. Our study can provide important and robust evidence regarding this lifestyle approach in the delivery of diabetes self-management among the increasing numbers of persons with diabetes mellitus in Malaysia and may help to re-shape clinical approaches to T2DM in this region and around the world. These results may produce a direct impact on the health and healthcare costs of managing patients with T2DM.

Research Ethics Approval: This will be obtained from the ethics regulatory authority prior to the study implementation.

Conflict of interests: None.

Author Contribution: The author is the sole developer of the protocol and has also written the manuscript.

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Appendices

- Patient demographics and Consent form
- Diabetes quality of life Questionnaire
- Adverse events Questionnaire

APPENDIX 1: Patient Demographics and Consent form

Project Title: FAST-DM

Project title: A protocol for a randomized controlled study to determine the efficacy of intermittent fasting as a management method for Type 2 Diabetes Mellitus.

Project summary: Intermittent fasting (IF) is the practice of alternating periods of eating and fasting. Previous studies in humans have shown that IF can reduce weight, blood pressure and blood sugar in people with diabetes. The purpose of this study is to assess if 16-hours of fasting (at night and early morning) with 8-hours of eating (3 days or 5 days) where you will not be restricted as to food choices will be easy to follow and will help with your diabetes treatment. There will be one group of persons undergoing usual care in the management of persons with T2DM. You will be given a booklet with the study details and what you need to do during the trial, as well as four sessions over 18 months where everything will be explained in person, and queries addressed.

Study Design: There will be three parallel groups; two groups will be undergoing Intermittent Fasting (3 or 5 days), and one control group will receive standard diabetes care. You may be allocated for the time of the study to any of the 3 groups. Fasting for 16 hours, and all meals to be eaten within 8 hours of the day, for 3 days a week. Drinking water or sugar free drinks is allowed at any time. You continue your usual eating schedule for the other 4 days. Fasting for 16 hours, and all meals to be eaten within 8 hours of the day, for 5 days a week. Drinking water or sugar free drinks is allowed at any time. You continue your usual eating schedule for the other 2 days. This group will continue their usual diabetes care and will be seen by the research team at 3, 6, 12 and 18 months for blood and urine tests. The primary endpoint will be your HbA1c levels after 18 months of the trial as compared to normal care of a similar duration.

You will be asked to fill in three questionnaires about your lifestyle, quality of life and be asked to keep a track of any problems throughout the study. During the study, you may list any adverse events you face. You can withdraw from the study at any time if you so desire (details in patient information booklet). You will meet the doctor or research assistant at the beginning of the study, and after 3, 6, 12 months and 18th month of the study, where the doctor will explain the study to you and will explain that you may require a change in your medicines as the study progresses. You will also be cautioned about watching out for any episodes of hypoglycaemia and what you should do if that happens. You will also come in for blood and urine tests, for checking your weight and blood pressure, as well as to clarify any doubts. You will need to repeat the questionnaires regarding any adverse events and any reduction or improvement in your quality of life during these meetings.

You will be provided with a WhatsApp number if you have any questions during the trial, at any time.

You may continue to visit your regular doctor during the trial, and the research doctors will be informing your regular doctor of your test results, and any changes in medication you have required during the trial.

Demographic Data: **Date:**

Name:	
Age:	**Gender: M/F**
Place of residence (state and district):	
Occupation:	
Married or Single:	
Family Members you live with at home:	
Level of Education (tick one): a)Primary school or less b)Secondary School c)College d)University	**Ethnicity (tick one):** a)Bumiputra (non-Malay) b)Malay c)Chinese d)Indian e)Punjabi f)Other (please specify)
Eating habit: a)Vegan b)Vegetarian c)Non-vegetarian	**Religion:** **How long have you been diagnosed with Diabetes Mellitus, in years?**

CONSENT FORM: Please tick box on the right

1.	I confirm that I have read the research information sheet dated..... for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that the study involves dietary changes on my part, as well as blood and urine tests periodically	
3.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	
4.	I understand that the information collected about me will only be used to supportthe research.	
5.	I have been assured that no identifying details will be used and all data will remain anonymised for the research.	
6.	All my questions have been answered satisfactorily and I agree to take part in the above study.	

Date Signature

Identifying Number:

Appendix 3:

DQoL (DIABETES QUALITY OF LIFE QUESTIONNAIRE) FAST-DM

Name(initials only):

Identifying number:

Please tick on the box where on a scale of 1 to 5, how will you rate your satisfaction regarding the following items on your life?
1 = very satisfied; 2 = moderately satisfied; 3 = neither; 4 = moderately dissatisfied; 5 = very dissatisfied)

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Appendix 4

ADVERSE EVENTS QUESTIONNAIRE FAST-DM

Name (initials only):
Identifying number:

Please indicate if you have suffered from any of the following problems during this trial, and how you would rate the severity of your problem (mild, moderate or intolerable) by putting a tick in the box.

SN	Symptom	Mild	Moderate	Intolerable
1.	Abdominal discomfort			
2.	Upper abdominal pain			
3.	Constipation			
4.	Fatigue/tiredness			
5.	Dizziness			
6.	Headache			
7.	Irritability			
8.	Hunger			
9.	Others (please list):			

Date:

****