MONASH University

EXPLANATORY STATEMENT

Project: Elucidating the Effects of Tocotrienol rich Vitamin E in a Prediabetes Population of Different Ethnicities in Malaysia.

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You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate. Your participation in this study is purely voluntary, and you may withdraw from it at any time. If you would like further information regarding any aspect of this project, you are encouraged to contact the researchers via the phone numbers or email addresses listed above.

Why were you chosen for this research?

Prediabetes is a stage where your blood glucose levels are slightly higher than normal but not high enough to be called diabetes. You are invited to participate in this research study because you may have the risk of developing type 2 diabetes mellitus (pre-diabetes) and we assume that the supplementation of tocotrienol-rich vitamin E from palm oil will be able to help prevent the progression of the disease.

What is the purpose of the study?

The purpose of this study is to determine the benefits of tocotrienol-rich Vitamin E in prediabetes and whether it will improve the function of insulin and pancreas gland in your body that plays an important role in maintaining a healthy blood sugar level. This research is important because at this early stage, the progression of developing into diabetes can be delayed or prevented.

Previous studies have also shown that the low levels of Vitamin E in our body does play a role in diabetes disease progression. Hence, we aim to reduce the risk of the progression by the supplementation of tocotrienol-rich Vitamin E, and consequently for an improvement in the Vitamin E levels.

Currently, the treatment for prediabetes is by maintaining a healthy weight, regular exercise and keeping a good eating habit. However, even with these measures there is still some chance for individuals with prediabetes to progress towards diabetes. We believe, by supplementing tocotrienol-rich Vitamin E to prediabetes this might help glucose metabolism and delay or prevent diabetes.

Furthermore, this study is important as it is the first study in identifying the benefits of tocotrienol rich Vitamin E in prediabetes.

What does the research involve?

Firstly, if you agree, by using a screening tool (FINDRISC questionnaire) and a blood test, it will help us identify whether (or not) you have a higher risk of developing type 2 diabetes. Depending on your diabetes risk score; you will be invited to participate in this study. This study will consist of multiple (four) clinical visits, physical examinations, and some blood tests.

Timeline of Study

- Your participation will be a total of approximately 6 months that includes 3 month of study period and 3 months for post study visits.
- There will be four visits and each visit will take approximately 2 hours each.

Outline of the Study

This is a randomized, multi-centred, double-blinded, placebo-controlled study involving participants with prediabetes. During the randomisation, we will divide participants into either the active group (tocotrienol-rich Vitamin E) or the control group (placebo). This means that you will be randomly assigned into two groups. Double-blinded means both you and the doctors/researchers will not know whether you are assigned to the active group or the control group. The drugs will be labelled as "study drug A" or "study drug B". Both drugs will look identical, and the identity will not be known by the investigator or the participant until the end of the study (double blinded).

1) **Pre-Screening (Before Visit 1)**

If you decide to take part in the research project, you will be given a set of questionnaires (FINDRISC) to help identify whether you have the potential risk of developing diabetes. It will take 5 minutes for you to complete this form. If you have any issues completing the FINDRISC form – you are encouraged to seek for assistance from the research team.

Based on your FINDRISC score, your doctor will explain further about your condition – whether you are at risk of prediabetes and diabetes mellitus.

If the screening questionnaire shows that you meet the requirements then , a total of 20 ml blood (1 ½ tablespoon) and urine sample will be obtained . These samples are used to measure baseline safety tests that includes blood glucose level (HbA1c and fasting blood glucose), Renal Function Test (RFT), Urine FEME, Liver Function Test (LFT), lipid profile, full blood count and ECG. An electrocardiogram (ECG) is a test which measures the electrical activity of your heart to show whether or not it is working normally. You will be asked to lie down and small electrode patches will be put on the skin of your chest, arms and legs. It is a non-invasive and painless procedure. All of these results will be used for comparison over time to look for changes and then afterwards to see if the treatment had an effect. Vitamin E levels will also be measured. If the blood tests results shows that you meet the requirements, then you are able to start the research project. Conversely, if the screening questionnaire and the blood test results does not meet the requirements you will not able to join the study and the research coordinator will discuss other options with you.

If you have any one of the criteria below you are not eligible for the study: -

1. Fluctuating blood sugar level
2. High blood pressure
3. Pregnancy
4. Breastfeeding mothers
5. Protein in the urine.
6. Urinary tract infection
7. Kidney stone
8. Acute or severe chronic illness such as acute coronary syndrome, active tuberculosis, and previous or current history of cancer, liver, or inflammatory disease, etc
9. Taking other vitamins such as Vitamin C or A for the past 1 month
10. Abnormal liver enzyme
11. Abnormal kidney function
12. Participants that are below 40 years old and above 75 years old

If the screening test shows you cannot be in the study, the research coordinator will discuss other options with you.

What You Should Do Before Coming for Each Visit

Before coming to all the visits, you are required to:

1. Fast for at least 8 hours (only plain water allowed)
2. Take usual dose of blood pressure medication or other medications
3. Bring study drug
4. Bring all new medications and supplements
5. Laboratory/Diagnostic Test Results
6. Bring all investigative test results for review.
7. Inform us if you are having your period so that we can arrange for another suitable appointment [females only]
8. Inform us if you are unable to come for the appointment date so that we can arrange for another suitable appointment.

2) **Initial Study Visit (Visit 1)**

If you consent to participate and are eligible based on pre-screening, we will invite you to an initial study visit where we'll take your medical history including an interview questionnaire to gather your personal information such as age, gender, race, education background and occupation. Physical examination which involves measuring your blood pressure, weight, height, and waist circumference will also be conducted. This physical examination will also be routinely carried out at every visit. Written informed consent will be obtained from each eligible participant upon agreement to participate in this study and prior to pre-screening and any tests being conducted/samples being taken. Your blood pressure, weight, height, and waist circumference will be routinely carried out in every visit.

We will divide you into either the active group (tocotrienol-rich Vitamin E) or the control group (placebo containing cooking palm oil) labelled as “study drug A” or “study drug B”. Both drugs will look similar, and the identity will not be known either by you or your doctor. This is to prevent any bias in the study. The randomisation process will be done manually according to your age, gender and HbA1c levels. You will receive 1 bottle of the study drug containing 60 capsules each for 30 days of supply. You will need to take 2 capsules once daily after a meal.

A total of 20 ml of blood (1 ½ tablespoon) and urine samples will be obtained. These samples are used to measure the Vitamin E levels, fasting blood glucose level (FBG), HbA1c, lipid profile and protein levels such as Insulin, Adiponectin, Resistin and Glut-4 which will serve as biomarkers for diabetes. Female participants with potential of childbearing will be given urine pregnancy test kits throughout the study period (3 month). Follow-up on the pregnancy status will be done monthly. These results will also ensure you remain eligible to participate in this study.

3) **Follow up Visit (Visit 2 (1st Month)**

During these visits, you will receive 2 bottles of the study drug containing 60 capsules per bottle. Each bottle will contain 30 days of supply as you will need to take 2 capsules per day after a meal. A total of 20 ml blood samples (1 ½ tablespoon) and urine samples will be obtained at each visit and will be processed on the same working day. These samples are used to measure the Vitamin E levels, lipid profile, fasting blood glucose level (FBG), and HbA1c level. During these visits, the doctors will ask you for any adverse events such as nausea and headache upon taking the study drugs within the 60 days period. Apart from nausea and vomiting there are no known adverse side effects for Vitamin E. Study drugs compliance will be monitored by capsule counting and returning of study drugs bottles.

4) **End of Treatment Visit (Visit 3(3rd Month))**

A total of 20 ml of blood samples (1 ½ tablespoon) and urine samples will be obtained and processed on the same working day. These samples are used to measure the Vitamin E levels, lipid profile fasting blood glucose level (FBG), HbA1c, and protein levels serves as indicator for the diabetes. Baseline tests such as Renal Function Test (RFT), urine FEME, Liver Function Test (LFT), full blood count and ECG will also be done to study the effects at 0 month – 3-month (start-end) period. Study drugs compliance will be monitored by capsule counting and returning of study drugs bottles.

5) **Post treatment Visit (Visit 4 (6th Month)**

During this visit, investigators will continue to monitor for any side effects after the treatment period. Your blood pressure, weight, height and waist circumference, and urine dipstick test will be carried out in this final visit. Blood samples will be taken for HbA1c level, fasting blood glucose level, vitamin E level, lipid profile, and measurements of protein levels. These test are repeated to ensure participant 's baselines are within the normal range and remain stable after the study.

Consenting to participate in the project and withdrawing from the research

The details of the study are described in this document. It is important that you understand why the study is being done and what it will involve. When you are satisfied with the explanation of this study, and you wish to participate, you will be requested to sign two informed consent forms; one is for you to keep and the other must be returned to the investigator.

Your participation in this study is voluntary. You do not have to be in this study if you do not want to. You may withdraw from it at any time. You may also refuse to answer any questions that you do not wish to answer. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

If you withdraw from the study, any data collected from you up to your withdrawal will still be used for the study and you will need to attend one last follow-up visit (discontinuation visit). During this visit, you will need to return the study drugs supplied. The investigating team will also take your history, perform a physical examination, and conduct several safety tests such as, lipid profile, full blood count and ECG to ensure that you are healthy.

If you were found to have abnormal findings from the tests, you will be referred directly for consultation to the chief investigator, Dr Badariah Ahmad, or other designated co-investigators. If necessary, arrangements for referral to your primary carers will be done.

Possible benefits to participants

There may or may not be any benefits to you. Nevertheless, the information obtained from this study may help to improve the treatment or management of other people with pre-diabetes.

Possible risks to participants

- **Vitamin E Supplementation**

There are no known side effects of Vitamin E (active drug) or inactive drug (placebo containing cooking palm oil). According to the Drug Control Authority of Malaysia, Vitamin E is approved as a health supplement safe for consumption. Nevertheless, you will be monitored for any side effects during the monthly follow-ups. If you have any concerns, you can contact the investigators, by phone call or email. If a side effect occurs, the investigator may choose to withdraw you from the study based on his/her discretion. Participants who are withdrawn will be followed up with a discontinuation visit as mentioned previously. The duration of follow-up of adverse events will be based on the investigator and study team's discretion.

- **Pregnancy**

The effect of the study product on an unborn child is not known. You should also avoid becoming pregnant or fathering a child while in this study. Women of childbearing age will be given a pregnancy test to confirm they are not pregnant. It is important that you use highly effective birth control methods consistently and correctly; the study doctor will discuss these methods with you. Notify your study doctor immediately if you think that you or your partner has become pregnant during the study. If you or your partner is pregnant, the study therapy will be discontinued immediately, and you will be removed from the study. However, we would like to follow your pregnancy until term to ensure the health of you and your newborn baby.

- **Blood Test**

The main risks of blood tests are discomfort and bruising at the site where the needle goes in. These complications usually are minor and go away shortly after the tests are done.

- **ECG (Electrodiagram)**

Risks associated with ECG are minimal and rare. You will not feel anything during the ECG, but it may be uncomfortable when the sticky electrodes are taken off. Some people may experience a skin rash where electrodes were placed, but this usually goes away without treatment

- **Privacy**

During randomization, your participant identification number will be used to identify you instead of your name, therefore there is very minimal risk of disclosure of your personal information to the public. We will also inform you in a timely manner about any new findings or changes about the study product which may affect your health or willingness to continue in this study. Where necessary, you may be asked to re-consent to participate.

Research involving diagnostic testing or possible incidental findings

We will usually ask our participants if they wished to be informed of i) any diagnostic findings, ii) incidental findings (e.g., high blood pressure, overweight, abnormal ECG findings), and/or (iii) only those adverse findings that would usually lead directly to treatment. You will also be asked whether you would like any of these findings to be discussed by your family doctor, another doctor of your choice, or by a member of the research team.

If you have consented to any of the above, the research team will inform you accordingly throughout the trial. You will, however, not be informed if you are taking the active drug or inactive drug as it will affect the results of the study. If you were found to have abnormal findings you will be referred to your primary carers for further management.

Payment

You will be reimbursed RM *30* per visit for your travel expenses to our Clinical Research Centre, even if you choose to undertake only part of the requirements or withdraw from the research early.

Confidentiality

The nature of this study requires personal information to be collected from you through history-taking, physical examination, and tests. However, only information pertaining to your eligibility for recruitment will be obtained. Once recruited, you will only be identified by a participant identification number that has no relation to your personal information or personal identifiers. Each participant number is unique and accessible only by investigators. The master list which contains your particulars will only be made accessible to the Chief Investigator. Data collection on data sheets and subsequent analysis will utilize only your participant identification number. The master list of study participants will be destroyed once findings for this study are published.

All your information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, your identity will not be revealed without your expressed consent. Investigators of this study, qualified monitors or auditors, study sponsor or its affiliates and governmental or regulatory authorities may inspect and copy your medical records, where appropriate and necessary. Data from the study will be archived and may be transmitted outside the country for the purpose of analysis, but your identity will not be revealed at any time.

Storage of test samples and data

Data gathered for this study will be stored in a file kept in a locked cabinet in a locked room in our clinical research facility in Monash University Campus. Upon completion of the study, all data will be stored and handled by Monash University Malaysia for a minimum of 15 years after the study has ended.

Your blood serum and plasma samples will be kept for future testing of other biomarkers (other proteins that were not measured in this study) once funds are available upon your consent. No genetic testing will be conducted on your biospecimen. Your biospecimen will be coded and any information that can identify you will be removed. Only your study doctor and study staff will be able

to link the code with you. You can withdraw your consent and your biospecimen will be destroyed but any information previously obtained from your biospecimen can be used for this research study.

Use of data for other purposes

Data gathered for this study will not be used for any future study without prior approval from relevant regulatory bodies and/or ethical committee(s) and participant consent. Please be assured that only aggregate re-identified data may be used for other projects where ethics approval has been granted.

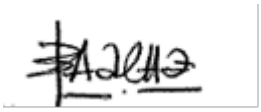
Results

The results of the trial will be made available within a year after the study has been completed. If you wish to access your test results during the study, you may contact your study doctor or the investigating team by phone, email or at the Clinical Research Centre. A full individual report will be made available upon participant request.

Funding
This study is funded by a Government Matching Grant R&D (Tocotrienol) between Monash University and Malaysian Palm Oil Board (MPOB). The matching grant number is :

Complaints
Should you have any concerns or complaints about the conduct of the project, you are welcome to contact:

Research Management
Monash University Malaysia
Jalan Lagoon Selatan
46150 Bandar Sunway
Selangor Darul Ehsan, Malaysia
Tel: +6035514 6000 Ext:46053
Thank you,



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Dr Badariah Ahmad