Research Protocol

1. Title

Glycaemic variability in Indigenous and Non-indigenous Australians with prediabetes and type 2 diabetes.

2. Investigator Details and Qualifications

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3. Purpose and Aims of the Study and Hypothesis

Indigenous and non-indigenous Australians with prediabetes and T2D will demonstrate increased Glycaemic Variability (GV), and both variability and excursion duration will change across an individual's pay cycle and be worse among those with food insecurity. The aim of this study is to compare glycemic variability (GV), both cumulative excursions outside of homeostatic range, and excursion duration across an individual's pay cycle, in Indigenous and Non-Indigenous Australians with prediabetes and T2D with and without food insecurity.

4. Background and scientific rationale of proposed project

Despite greater attention and resource allocation over the last two decades, the improvements in diabetes- related morbidity and mortality in Indigenous Australians have lagged the trends in the rest of the country. In particular, the social determinants impacting management of chronic diseases like T2D have not been evaluated adequately in Indigenous and Non-indigenous Australians. Many Australians experience financial, and food, insecurity, but the impact of such experiences on glycaemic control and variability has not been assessed. Reliance on 'standard management' advice for T2D, such as dietary modification, has been largely ineffective in this community, as it fails to appreciate that it may not be possible for an Indigenous person with T2D to make an optimal dietary choice (such as complex carbohydrates, vegetables, and fruits) due to economic constraints. High Glycaemic Variability (GV) is strongly associated with renal disease, CVD, and mortality, independently of HbA1c. For example, GV predicts mortality from acute myocardial infarction, and is associated with markers of cardiovascular damage and endothelial dysfunction, in T2D. Advances in diabetes related technologies such as the Continuous Glucose Monitoring (CGM) technology, which provides 24-hour data over extended periods, and easily measures glycaemic variability represents a major advance on the traditional single point measure of glycated haemoglobin. Our study, will for the first time, evaluate the GV around pay cycles in prediabetes and T2D Indigenous and Non-indigenous Australians with and without food insecurity using CGM. If our hypotheses prove correct, confirmation with a larger sample size will be required and, if so, will have the potential to impact both clinical practice and health policy substantially e.g., clinicians will need to be educated regarding social determinants of chronic diseases (financial stress, food insecurity etc) and actively screen Indigenous patients for its presence.

The stark disparity of the burden of T2D and its complications on Indigenous Australians compared with their non-Indigenous counterparts despite increased governmental attention and resource allocation in recent decades, is a compelling argument for fresh, alternative and original approaches to diabetes management tailored to the specific requirements of the community. Our proposal will utilise the latest diabetes-related technology (continuous glucose monitors or CGM) to explore our hypothesis that food insecurity and its subsequent coping strategies have a major adverse impact on postprandial glycaemic control. Few studies have previously assessed the relationship of food insecurity and glycaemic control in T2D world-wide, but none has used CGM technology, which provides 24-hour data over extended periods, representing a major advance on the traditional single point measure of glycated haemoglobin or HbA1c.

However, this study should be regarded as a feasibility trial. While the findings of the current study are not expected to have immediate and direct benefits to the participants, they will stimulate research on the different coping strategies adopted by food insecure households and

their impact on glycaemic excursions. On the health policy front, the findings may encourage trialling food security programs and their impact on glycaemic patterns. The impact of national strategies to ameliorate food insecurity on glycaemic control in Indigenous and Non-indigenous Australians with T2D would be of major relevance to health and chronic disease more broadly.

5. Participants

Participant selection criteria

Selection criteria:

Aboriginal and/or Torres Strait Islander and and Non-Indigenous people aged 18 to 80 years with and without T2D (HbA1c ≥6.5%) and prediabetes (5.7 to <6.5%) diagnosed as per WHO criteria with or without food insecurity as per USDA (HFSSM) questionnaire, residing in South Australia who are registered with an Aboriginal health clinic and who receive payment (for salaried work or as unemployment benefits) on a fortnightly basis.

Exclusion criteria:

Individuals not residing in South Australia, unable to provide informed consent, refusal, or inability to have a CGM sensor applied to the back of the upper arm, or unwillingness to provide informed consent, pregnancy, or receipt of dialysis.

6. Study Plan and Design

This study will be conducted by the Centre of Research Excellence in Translating Nutritional Science to Good Health based at The University of Adelaide in collaboration with Wardliparingga Aboriginal Health Equity at SAHMRI. Participants will be recruited from Aboriginal Health Centres, Hospital Liaison Units, and through word of mouth and advertisement. The study will be performed predominantly in Adelaide's Biomedical Precinct. The study team will include endocrinologists (Marathe and Horowitz), PhD student Md Kamruzzaman, the Implementation Science team at Wardliparingga Aboriginal Health Equity (including leading Aboriginal Health academic Brown, social epidemiologist Howard, and Aboriginal PhD student, Brodie) and nutrition scientist Wycherley. Principal investigator (PI) Marathe will take primary responsibility for supervising the studies and for driving the research project.

We will study a) 30 male and female Aboriginal South Australians 18-80 years with T2D or prediabetes with food insecurity ("IAFI") and b) 30 male and female Aboriginal South Australians 18-80 years with T2D or prediabetes without food insecurity ("IAFS"), c) 15 male and female Non-Aboriginal South Australians 18-80 years with T2D or prediabetes with food insecurity ("IAFI"), d)) 15 male and female Non-Aboriginal South Australians 18-80 years with T2D or prediabetes without food insecurity

("IAFI"). Food insecurity will be measured by the United States Department of Agriculture (USDA) Household Food Security Survey Module (HFSSM) questionnaire and ≥1 affirmative response will be taken as evidence of food insecurity.

Screening visit: Participants arriving on the day of screening will be furnished with a plain language statement of the study and explained by the study nurse. Prospective participants that express their interest in participating and meet the criteria will be provided with an informed consent form. Upon executing the form, participants will be assisted in completing the study questionnaires, namely sociodemographics and medical history questionnaires (including evidence of retinopathy and microalbuminuria). Participants will then undergo a basic clinical assessment, which will include 1) Anthropometric measurements: Waist circumference, height and weight and Mid Upper Arm Circumference (MUAC), 2) blood pressure, heart rate and cardiac autonomic reflex tests (CAN), bioelectrical impedance tests 3) baseline blood tests (full blood count, electrolytes, liver function and lipid profile) and point of care HbA1c. 4) Questionnaires: Participants will be requested to complete validated questionnaires assessing dietary intake (The Dietary Questionnaire for Epidemiological Studies or DQES v3.2), diabetes distress, anxiety and depression. Continuous glucose monitoring: Once informed consent has been obtained, participants will be asked to wear the CGM sensor (applied by the study nurse) for the entire period of the study. The date of next payment day will be noted (a pay cycle is defined as the interval between 2 consecutive payment days and will last for 14 days). The participants will be asked to come back for three subsequent visits, 10 days apart, to replace the CGM sensor. This will be performed by the study nurses. At the end of the study the participants will be offered diabetes and dietary education, if they are willing by trained clinical staff.

7. Outcomes

The primary outcome will be the relationship among food insecurity, diabetes distress, gastrointestinal symptoms and dietary habits with glycemic variability (GV). The secondary outcome will be the relationship among glycaemic variability, diabetes distress, gastrointestinal symptoms and food insecurity and dietary habits with autonomic nerve function (CAN).

8. Ethical considerations

This study does not involve medical intervention or radiation exposure and the ethical risks are considered 'minimal'. An information sheet will be provided, and each participant will be given the opportunity to discuss the study with friends or family prior to involvement if they wish to do so. Each volunteer will give written, informed consent, in accordance with the attached form, and the participants will be free to withdraw from the study at any time. Each participating volunteer will be provided a study code number and their personal information will not be made public, unless legally required. This study will be performed in accordance

with the Declaration of Helsinki and the NHMRC National Statement on Ethical Conduct in Human Research (2007), a document written to protect the rights of participants in research trials.

9. Storage, access and analysis of Data

All records will be kept for a minimum of 15 years at the Faculty of Health and Medical Science (FHMS) of The Adelaide University, in accordance with the University of Adelaide protocol and the anonymity of the participants will be maintained, as per university protocol. The study data will only be accessible to the investigators of the study and the data will be owned and maintained by the principal investigator Dr. Chinmay Marathe. The de-identified data will be freely available in the public domain in the form of scientific abstracts, peer-reviewed manuscripts, and power-point presentations made by the research team upon completion of the study.

Participant Information Sheet

Study Title: Glycaemic variability in Indigenous Australians with type 2 diabetes.

YOUR PARTICIPATION IS VOLUNTARY

You are invited to take part in a research study conducted by Dr Chinmay Marathe, Prof Alex Brown, Prof Michael Horowitz, Md Kamruzzaman, Dr. Natasha Howard, Dr Thomas Wycherley, Prof. Karen Jones and Ms Tina Brodie. Your participation in this research is voluntary and you are free to withdraw from the study at any time.

WHAT IS THE PURPOSE OF THE TRIAL?

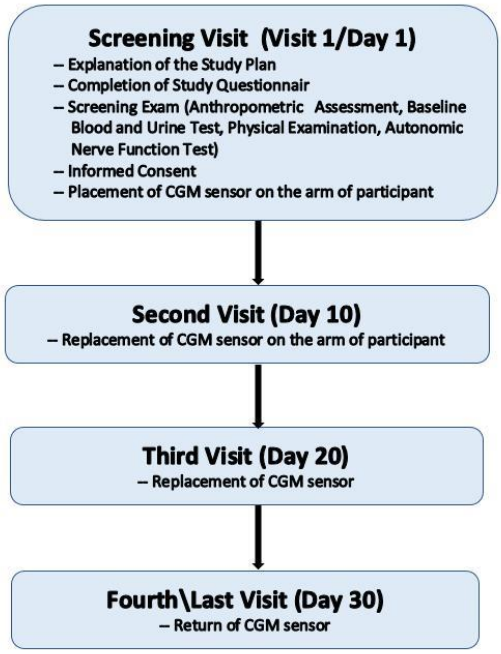
The incidence of type 2 diabetes in the Aboriginal community is particularly high, about three times greater and up to five times in the age group of 35-44 years compared with Caucasians. The consequences of this are grave and studies have suggested there is a 17-year gap in life expectancy between Indigenous and Caucasians in Australia for which diabetes is a major contributor. A number of a patient related factors such as social economic situation, food habits, physical exercise and mental health affect diabetes control. The latest diabetes related technology such as continuous glucose monitors provide a convenient and minimally invasive way of measuring blood sugar for 24 hours and provide a more complete picture and is a significant advance over a single blood test reading. This study is designed to evaluate, how these social, psychological and economic factors contribute to the control of diabetes using the technology of continuous glucose monitoring.

WHAT WILL YOU HAVE TO DO?

You will be required to visit the research centre on four separate occasions. The study period will be 30 days. On your first visit the study nurse will carefully go through the study plan with you. You will be asked a series of questions relating to diabetes control, food habits etc. You will also undergo a clinical diabetes examination which includes a blood test, urine sample and diabetes nerve testing. We will proceed with the study only if you're willing and have signed the informed consent form. Before you

leave the study, nurse will apply a glucose sensor to your arm. You will be required to keep the sensor on your arm at all times for the duration of the study. The sensor lasts about 10 days. You will therefore be asked to come back three more times 10 days apart to replace the sensor. This has been explained clearly in the floor chart attached.

We estimate that the total time you will spend with the research team over the course of the study will be approximately 5-6 hours. Payment for your participation is by way of honorarium at the rate of $18/hr for the time spent with the research team. Travel expense to and from the laboratory will be covered, if required.



WHAT IS CONTINUOUS GLUCOSE MONITORING?

Continuous Glucose Monitoring (CGM) is a means of measuring glucose levels continuously in order to gain insight into patterns and trends in glucose levels throughout the day and night. It removes the need to prick your finger to obtain blood glucose level. A Continuous Glucose Monitoring System sensor is inserted under the skin,and measures the level of glucose in the interstitial fluid (fluid in the tissue). The sensor is disposable and changed according to manufacturer recommendations. Continuous glucose monitoring is a user-friendly way to discreetly obtain glucose readings and provides 24 hours glucose data.

WHAT IS AN AUTONOMIC REFLEX TEST?

These tests simply measure how your heart rate and blood pressure respond during exercises such as deep breathing, sitting and standing and sustained hand grip. High blood sugar can cause damage to the nerves controlling your heart rate and breathing and an abnormal reflex test is an indicator of early nerve damage.

WHAT PROBLEMS MIGHT OCCUR DURING THE STUDY PERIOD?

This study does not involve frequent blood sampling or radiation exposure and therefore the risk associated are expected to be minimal. However, we will take a blood sample on the screening visit. Taking blood from a vein is associated with a small amount of pain and may cause bruising, localized bleeding, faintness and in rare cases infection. You may experience slight bruising as a result of insertion of the needle used for blood sampling. Infection or inflammation near the vein can also sometimes occur and there is a rare chance of blood clots (thrombosis) in the vein.

The CGM sensor is applied on the arm, and this is minimally invasive procedure. Generally, we do not anticipate any injury due to the presence of sensor on your arm. It is however possible that some people may experience mild itchiness, inflammation or skin irritation from continuously wearing the sensor for 30 days. The research team will be in regular contact with you for the whole period of study.

Please do not hesitate to contact us if you have any concerns during and after the study. We will arrange for appropriate medical assessment and treatment within the public health system, according to the nature of the emergency. For example, if it is an acute medical emergency, you will be first

transferred to the emergency department at the Royal Adelaide Hospital. On the other hand, if an incidental abnormality of subacute or chronic nature is found, we will liaise with your GP/ACCHO to provide a plan of further management. You will have access to contact the chief investigator, who is a registered medical practitioner and endocrinologist, at any time.

IS THERE ANYTHING TO GAIN FROM PARTICIPATING?

You will not derive direct benefit from participating in this study. The study findings will help us understand, how diabetes impacts people in the day-to-day living. A comprehensive 24-hour glucose report for the entire study period will be printed and provided to you and you will be encouraged to take this report to your GP/ACCHO. As our research team comprises of dietician, diabetologist, and diabetes nurse, we will offer an opportunity to provide comprehensive diabetes management advice before you leave.

CONFIDENTIALITY

Your personal information will be kept strictly confidential and only be available to the study investigators. Once you have been enrolled in our study you will be given a study participant code, and this identified data will be analysed further. The information we gather from this study will be published in a way that does not personally identify you in any way.

NHMRC NATIONAL STATEMENT ON ETHICAL CONDUCT IN HUMAN RESEARCH (2007)

This research study will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research (2007).

ETHICS COMMITTEE APPROVAL

This study has been approved by the Research Ethics Committee of the Royal Adelaide Hospital and the Aboriginal Health Research Ethics Committee.

CONSULTATION WITH ABORIGINAL COMMUNITY

This study has been presented to and has received in principle support from Nunyara Aboriginal health service, Whyalla.

AMES AND CONTACT NUMBERS OF INVESTIGATORS

Should you have any questions or concerns before, during or after the study, please contact the chief investigator, Dr Chinmay Marathe (Ph: 8313 6497, email: chinmay.marathe@adelaide.edu.au).

INDEPENDENT CONTACT

If you would like to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also contact the Chairman, Aboriginal Health Council of South Australia Ltd on (08) 8273 7200 during office hours or email at ahcsa@ahcsa.org.au.

Consent Form

Study Title: Glycaemic variability in Indigenous Australians with type 2 diabetes.

Investigators: Dr Chinmay Marathe, Prof Alex Brown, Prof Michael Horowitz, Md Kamruzzaman, Dr.

Natasha Howard, Dr Thomas Wycherley, Ms Tina Brodie and Prof. Karen Jones.

1. The nature and purpose of the research project have been explained to me. I understand it, and agree to take part.
2. I understand that I will not directly benefit from taking part in this trial.
3. I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
4. I understand that I can withdraw from the study at any stage, and that this will not affect my medical care, now or in the future.
5. I have had the opportunity to discuss taking part in this investigation with a family member or friend.

Name of Participant: .....

Signed: .....

Dated: .....

I certify that I have explained the study to the volunteer and consider that he/she understands what is involved.

Signed: .....

(Investigator)