Precision Diets for Diabetes Prevention

NCT03919877

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1. PURPOSE OF THE STUDY

a. Brief Summary

With this study we want to understand the physiological differences for people developing pre-diabetes and diabetes. We Hypothesize that different individuals go through different paths in the development of the disease. By understanding the personal mechanism for developing disease, we will find a personalized approach to prevent that development. We are also hoping to be able to find a biomarker that will pinpoint to the particular defect and thus, diagnose the problem at an earlier stage and have the information to give personalized diet recommendations to prevent the development of diabetes more effectively.

b. Objectives

With more than 1/3 of the US population developing prediabetes, it is imperative that we get a better understanding of the reasons why individuals develop this disorder. at present these individuals are lumped together as a single entity, but almost certainly they represent a mix of different gene-environment interactions that lead to one of four dominant physiologic mechanisms underlying their dysglycemia. 1- liver insulin resistance, 2- muscle insulin resistance, 3- impaired insulin secretion, 4- impaired incretin hormone secretion. Gaps that we are addressing here are extremely important – first, we will define a composite biomarker to identify different subphenotypes of prediabetes based on the four known physiologic mechanisms that contribute differentially in each individual to glucose elevations, which we hypothesize will also be reflected in their "glucotype". Importantly, because both continuous glucose monitor and administration of standardized meal testing and metabolic tests are not practical in the clinic, the development of a composite biomarker comprised of select multi-omics measures and clinical variables will enable clinicians and possibly patients (without clinician) to easily identify the specific diet that will yield optimal health results. What we learn from this study can be scaled to the entire worldwide population. Also, sleeping patterns are very much involved with glucose regulation. To investigate so we will ask participants to complete the Alliance Sleep Questionnaire (ASQ) at baseline to figure out participants' sleeping patterns. After, we will ask to wear a portable polysomnography system for 1 or 2 nights to detect EEG (brain activity), EMG (muscle movement), EOG (eye movement), etc.

c. Rationale for Research in Humans

We would like to understand the pathophysiology of insulin resistance in humans. In vitro or animal studies would not give us the answers we are seeking.

2. STUDY PROCEDURES

a. Procedures

Screening:
We will review their medical history, have their height, and weight measured, and have their blood pressure and heart rate taken and a lab test to check their fasting glucose level. This visit will occur at Stanford University Medical Center in the Clinical Translational Research Unit CTRU. To allow for an easier flow, some participants will have the opportunity to choose to consent through our e-consent system on Redcap.

We will enroll 3 types of participants cohorts:
- people with pre-diabetes
- people with type 2 diabetes
- healthy control.

If they qualify, participants will be scheduled for the following procedures:

3 METABOLIC TESTS (all cohorts)

1) The Oral Glucose Tolerance Test. This test is approximately 3-4 hours in length. The subject drinks a standard amount of glucose (75gr) and blood sugars will be measured at 15,30,60,90,120,150,180 min after drinking the solution. Subjects will also be given 1 gram of acetaminophen to consume along with the glucose. The acetaminophen given at baseline is given as it is a surrogate and safe way of testing gastric emptying. Before the test, the subject will meet with the study dietitian who will show them how to use a continuous glucose monitor. The subjects will be advised to use this device for 7 to 10 days. During this time, the subject will be instructed to keep track of food eaten. The subject will wear the CGM while undergoing the OGTT + will be asked to repeat the test at home (drinking 75g of a solution of water and glucose as first thing in the morning and waiting for 2-3h before eating anything else). This at-home OGTT will be done twice (3 times if one of the first 2 times will not produce high enough quality data).Participants will then use the Dexcom continuous glucose monitor and will keep track of their foods using the "cronometer" app.

2) The Insulin Sensitivity Test (SSPG: Steady State Plasma Glucose): This test is approximately 6-7 hours in length. Participants will be asked to fast for 12 hours. The insulin sensitivity test is designed to measure how well your cells remove glucose from your blood in response to insulin. This test will involve the infusion of sugar (glucose), insulin, and octreotide by vein for three to four hours. During this test participants will have two small catheters (tubing) placed in their veins (I.V. lines). One of these will be used for blood drawing and the other for giving the infusion of glucose, insulin, and octreotide. Blood samples will be taken every 30 min until 90 min into the study, then every 10 min at 100, 110, and 120 min. The glucose infusion will then be changed and samples will be taken every 30 min until 210 min, then every 10 min at 220, 230, and 240 min. The total amount of blood that will be drawn during this test will be 140 mL of blood (approximately 9.5 tablespoons). Insulin is a natural hormone, and octreotide (a

synthetic hormone) is a drug that temporarily blocks the secretion of insulin from your pancreas.

3) The Isoglycemic Intravenous Glucose Infusion (IIGI): This test will be approximately 4-5 hours in length. Participants will be asked to fast for 12 hours. This test is designed to measure the effect of glucose in the blood independent of the effect it has when ingested orally by way of the intestinal tract. Participants will have two catheters placed in their veins: one for a glucose infusion in one arm and the other for taking small blood measurements to adjust the glucose infusion. Small amounts of blood will be taken from that catheter during the testing to analyze for insulin and c-peptide measurement (product of insulin synthesis). The total amount of blood that will be drawn during this test will be 60 mL of blood (approximately 4 tablespoons).

The order of these tests will be determined by participants' preference and availability at the CTRU. Each test requires a separate visit, and they will have to be done 7 days or more apart from each other.

DIET CYCLES (for pre-diabetic and healthy controls, optional for the diabetic participants):

Diet cycle 1, 10 days.
During this first diet cycle, participants will be asked to follow their normal diet, plus consume the special meals described below.
In order to better compare individual responses to various different types of carbohydrates, we will provide them with 3-4 different foods or “meals” to consume at home. These will be different types of carbohydrates such as: rice, potatoes, and bread. Each portion will contain 50g of total carbohydrates. We will ask them to consume these special meals for breakfast.

Diet cycle 2, 10 days.
During the second diet cycle, participants will be provided additional portion of rice and asked to consume this 6 more times with provided supplemental fiber (two times), cream (two times), and egg whites (two times) to see if fiber, fat, and/or protein can attenuate the glucose response.

Right after the test meals, participants will be asked to not eat any food for 3h after the consumption of the provided meals for diet cycles 1 and 2. They will work with a dietitian who will help them follow these different diets.

During the time participants are using the CGM monitor, we will ask them to keep detailed logs of their food intake, including the time they ate, and the portions of all food consumed using the ronometer” app. This is to help us link the food they’ve consumed with their corresponding glucose values on the monitor. We will send them a link to use the research food logging app and they will have an opportunity to consent to send us their food logs.

Glucose data will be analyzed to determine which foods caused a pronounced peak ("bad") versus those that did cause a high glucose response ("good").

Participants will be also asked to complete some questionnaires related to physical activity, stress (STRAIN questionnaire), and sleeping pattern (ASQ questionnaire).

Lastly, we will ask participants to collect blood microsampling during the 2 diet cycles. Specifically, we will provide them with 20 devices and ask them to use the kits during 4-time points:

- One time during cycle 1 (rice);
- Three times during cycle 2 (rice+fiber, rice+fat, and rice+protein). For every time point, they will be asked to collect the samples 5 times: right before eating, 30 min, 1h, 2h, and 3h after finishing the provided meal. The total of microsampling collected is 20 (4 timepoints * 5 kits).

To do so, they will be given a Tasso arm-prick microsample kit, containing all the supplies and instructions. They will return the collected samples to the research team by the end of the 2 cycles.

STUDY UPDATE AFTER COVID19 PANDEMIC:
Unfortunately, our study was heavily affected by the COVID19 Pandemic and the mandatory shelter in place (SIP), starting March 2020. We are now authorized to retrieve research activities at the CTRU. The the research team is facing 2 issues: 1- Funds are running low, and this study is very expensive 2- Some data collected from participants right before March 2020 can't be used anymore, as the metabolic profiles of our research participants are most likely not the same after 1 year of SIP and stressful events such as COVID19 pandemic.

Due to these factors, the research team decided to modify this protocol in the following way:

1- We want to repeat the OGTT test at the CTRU for participants who already completed it. Adding to that, we want to perform 2 OGTTs "at home", about 1 week apart. We will also have them wear the CGM Dexcom G6 during both OGTTs. Each time they will wear the CGM monitor for 10 days total. During each time, participants will be asked to complete a daily food log using the Cronometer app and might be asked to check thier blood sugar with the glucose meter and fingerprick. That will allow the study team to interpret the CGM readings.

2- For participants who signed up right before March 2020, who could do no test or only part of them, we would like to just do a smaller version of the above protocol. We will STILL perform all metabolic tests. For those who have done 1 or 2 out of the 3 metabolic tests, we will repeat the test(s) that were already done again. After the 3 metabolic tests will be completed, we will do the
following:
i- One visit at the CTRU for a blood draw, urine, stool, and swab collection.
ii- Two diet cycles (instead of 3) while wearing the CGM G6 Dexcom monitor (10 days each time). For cycle 1 we will test 3-4 meals (instead of 7) and for cycle 2 we will test

rice for everyone (instead of the worst carb as previously done). During each diet cycle, participants will be asked to complete a daily food log using the Cronometer app. That will allow the study team to interpret the CGM readings.

Participants will also be asked to complete the study-related surveys.

b. Procedure Risks

All procedures have been performed before and those doing the procedures are highly skilled and safety measures are in place for all procedures. SSPG has no alternative besides euglycemic clamp, which is not less risky.

c. Use of Deception in the Study

No deception will be used.

d. Use of Audio and Video Recordings

No audio or video recording will occur.

e. Alternative Procedures or Courses of Treatment

There are no alternative treatments other than not participating in the study. The advantages to the subjects are that they will have the opportunity to see how their blood sugars vary through the day and how they react to different foods. They will learn what meals work best for them.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

During the course of the study they might learn of a personalized diet that works best for their health and they will be able to follow that if they choose. Participants with diabetes will know if the monitor is helpful for them to better control blood sugars and they can then discuss this option with their physicians.

g. Study Endpoint(s)

The only treatments in this study are trying different diets to find the optimal one for each subject. The design of the study is to personalize the diets and we do not have one placebo and one treatment group- each person will be their own control. The study will not be terminated before the projected total participant population has been enrolled and completed the study.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Most studies measuring blood sugars continuously, have been done in people with diabetes. One of the few studies done on healthy individuals was led by Eran Segal and Eran Elinav of the Weizmann Institute of Science, were they studied 800 people in their responses to different meals. They found that individuals react differently to the same meals.They report that post prandial glucose responses (PPRGR) were associated with

several risk factors, including BMI, HbA1c%, and fasting glucose.They also found several associations between microbiome features and variability in PPGRs across people. In some cases, such as for Actinobacteria, Proteobacteria, and Enterobacteriaceae, the direction of their associations are consistent with previous associations reported between these taxa and higher-level phenotypes such as dietary habits, obesity and overall glycemic control. In our study, we want to look for patterns from glucose levels that are measured in a continuous fashion in order to predict long-term outcomes. We are looking specifically for insulin resistance role in the pathophysiology of this disorder and we are hoping we can develop clinical guidelines to diagnose individuals with higher risk
at a much earlier stage.

b. Findings from Past Animal Experiments

There have been some animal studies on glucose response to meals, but these don't translate well to human responses.

4. Devices Used in the Study

N/A

5. Drugs, Biologics, Reagents, or Chemicals Used In The Study

a. Investigational Drugs, Biologics, Reagents, or Chemicals

N/A

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Ocreotide/Sandostatin
Dosage:	25 micrograms and 0.27 micrograms
Administration Route	First dose is given over 5 minutes. Second is given over 3 hours by IV infusion.
New and different use? (Y/N)	No
Commercial Product 2	
Name:	Regular insulin
Dosage:	6 mU/m2/min and 32 mU/m2/min
Administration Route	Intravenous
New and different use? (Y/N)	No
Commercial Product 3	
Name:	Acetaminophen
Dosage:	1000 mg
Administration Route	Oral
New and different use? (Y/N)	Yes

6. Participant Population

a. Planned Enrollment

i) we expect to enroll 130 participants:
- people with pre-diabetes 40
- people with type 2 diabetes 30
- healthy control 60

ii) no other sites, this study will be done at Stanford only
iii) we will accept individuals with normal blood sugars, prediabetes or diet-controlled type 2 diabetes. These can be students, staff, people from our community, or anyone willing to come to Stanford to do the study.

b. Age, Gender, and Ethnic Background

The participants must be 18 years of age or older. There is no limitation on gender, or ethnic background for the participant population being recruited.

c. Vulnerable Populations

We will not enroll potentially vulnerable subjects in our study.

d. Rationale for Exclusion of Certain Populations

We are not enrolling children as we expect this would put a high burden for any healthy child.

e. Stanford Populations

Any personnel or employee that qualifies for the study will be treated exactly the same as outside participants. They will receive the same consent to sign and given the same high quality care we will give all our subjects.

f. Healthy Volunteers

We are studying the response to different foods in people with the full range of glucose regulation: normal, prediabetes and diabetes. There is no greater than minimal risk for any volunteers due to the design of our study.

g. Recruitment Details

Recruitment methods include:

1- Advertise on social media platforms, such as Facebook, Instagram, Nextdoor, LinkedIn, etc. (please see section 16 for the attached script we will plan to post).

2- We may place flyers (attached in section 16) in public spaces with appropriate permission from the owner of the space, for example, a flyer in a hospital department or staff meeting room.

3- Primary care physicians, nurses, and other healthcare workers may, if they agree, tell patients/colleagues about this study.

4- Participants who enrolled in other studies in the Snyder's Lab and McLaughlin's Lab or other Stanford collaborating labs and consented to be contacted for future research opportunities.

5- We will use the Stanford Diabetes Research Center (SDRC) Registry as a method of recruitment. Flyer/email (attached in section 16) will be sent to people who have signed up through the SDRC website to be contacted for research studies relating to diabetes. The list of potential participants will be obtained directly from the SDRC.

6- Established research registries, email listservs, and newsletters with appropriate permission from the moderator of those registries/listservs/newsletters, including non-profit organizations that operate in the field.

7- Snowball recruitment through word of mouth (for example a study investigator may share the study or lab website with their friends, who may, in turn, choose to pass on that information to their family/friends).

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h. Eligibility Criteria

i. Inclusion Criteria

Persons eligible for this study must:
- Be 18 years of age or older;
- Not be pregnant, if female;
- Can be prediabetic or normal blood sugar control

For the Diabetic cohort (type 2), people will be eligible for the study if they are:

- Between 30 and 69 yrs of age;
- Have diet-controlled type 2 diabetes defined as:
i) fasting blood glucose ≥ 126-150 mg/dL or A1c ≥ 6.5% or OGTT 2 hour glucose ≥ 200 mg/dL;

ii) Plasma or Finger-Stick Blood Glucose <150 mg/dl and A1c between 6.0% and 7.9% off antidiabetic medications

iii) Metformin-treated patients with A1c <7.0% may undergo a 2-week washout with permission from their physician and will be eligible if post-washout fasting plasma or FSBG glucose is <150 mg/dL.
BMI 23-42 kg/m2

ii. Exclusion Criteria

A person may not participate in this study if any of the following applies to him/her:
They have major organ disease, hypertension defined as >160/100, pregnant/lactating, diabetogenic medications, malabsorptive disorders like celiac sprue, others, heavy alcohol use, use of weight loss medications or specific diets, weight change > 2 kg in the last three weeks, history of bariatric surgery.
Any medical condition that physicians believe would interfere with study participation or evaluation of results.
Mental incapacity and/or cognitive impairment on the part of the patient that would preclude adequate understanding of, or cooperation with, the study protocol.

For the diabetic cohort, the following exclusion criteria will apply:
- Active (symptomatic or uncontrolled) cardiovascular disease,
- active cancer,
- other major organ disease (liver, pulmonary, or kidney failure),
- unstable body weight defined as self-reported weight change >2 kg over the past 6-8 weeks,
- unstable hypertension (defined as BP >160/100 mm Hg),
- hematocrit < 33%,
- use of medications known to alter blood glucose,
- insulin sensitivity, or inflammation.
- Pregnancy, lactation
- prior bariatric surgery,
- active eating disorder,
- current substance abuse,
- untreated psychiatric disease

i. Screening Procedures

Subjects will be contacted from our database of past participants who agreed to be contacted. If they agree to be screened for this study, we will use our screening protocol (protocol # 35935) to do a telephone screening call to review current medical history.

j. Participation in Multiple Protocols

The study consent specifically asks the question - Are you participating in other studies and Yes or No has to be checked.

k. Payments to Participants

Participants will receive no payment.

l. Costs to Participants

Other than time to participate in the study and travel costs there are no direct study costs.

m. Planned Duration of the Study

The total duration of this study will be 4 years.

The screening time for the participant will be up to 1 hour, active participation in the study for each participant will be 5-6 months.

Analysis of participant data will take approximately 12 months after the final subject completes the study.

7. RISKS

a. Potential Risks

i. Investigational devices

No investigational devices will be used.

ii. Investigational drugs

No investigational drugs will be used.

iii. Commercially available drugs, biologics, reagents or chemicals

Potential risks to healthy volunteers:
Risks involving the insulin sensitivity test: Using glucose, insulin
Hypoglycemia- Blood sugars monitoring is done at regular intervals per the study and more frequently if needed. The procedure for monitoring blood sugars is described below.
Blood glucose levels are measured every 30 min for the first 2 &1/2 hrs and more frequently if needed. In the last 1/2 hr they are measured every ten minutes.
The test will be terminated early if the blood glucose is < 60 mg/dL and or a patient becomes symptomatic with a glucose < then 70 mg/dL.
20% Dextrose will be administered at 75 ml/hr after completion of the test if the blood glucose is < 120 mg/dL and the participant will be served lunch immediately.
Blood glucose levels are checked 30 and 60 minutes upon completion of the meal and the level must be at or above 100 mg/dL before the individual can be discharged.
Participants also receive a snack to take home with them consisting of juice and graham crackers to be eaten several hours after the test with written instructions regarding signs and symptoms of hypoglycemia.
Octreotide -Transitory side effects can be- metallic taste and nausea (5-10% of our study population), rare side effect 5-10% or our study population- abdominal cramping and diarrhea after discharge. This is explained to participants during consenting and during the procedure.
Possible effects of the continuous glucose measurement CGM sensor include redness, bleeding, pain, tenderness, irritation, or inflammation at the insertion site. There is also a possibility of infection at the insertion site. We will educate subjects on the early symptoms of infection and have them contact us if they see these.

Acetaminophen: besides possible sensitivity to the medication in general it is well tolerated.
Hepatic side effects including severe and sometimes fatal dose dependent hepatitis have been reported. In general occurs at doses of 4GM and chronic use. In this study the participants will receive 1GM once.
Gastrointestinal side effects have included nausea (34%) and vomiting (15%).
Renal
Renal side effects are rare and have included acute renal failure, acute tubular necrosis, and interstitial nephritis.
Hypersensitivity side effects including anaphylaxis and fixed drug eruptions have been reported rarely in association with acetaminophen use.
Hematologic side effects including rare cases of thrombocytopenia associated with acetaminophen have been reported.
Dermatologic
Dermatologic side effects including erythematous skin rashes associated with acetaminophen have been reported, but are rare.

Respiratory
Respiratory side effects have included dyspnea and a case of acetaminophen-induced eosinophilic pneumonia.
Cardiovascular
Two cases hypotension have been reported following the administration of acetaminophen.
Cardiovascular side effects including hypertension and hypotension have been reported following the administration of acetaminophen.

Dr. McLaughlin's associates are present and monitoring the results along with with nursing staff of the CTRU. Participants are told they can call one of the associates if there is any problems when they are discharged.

iv. Procedures

Risks from taking blood from the participants' arm is minimal, which may involve a little pain, a bruise or local infection at the site. There is no risk of taking nasal, tongue and skin swabs or for saliva, urine and stool collection, except of minor and temporary discomfort. Reversibility of potential risks of procedures to be performed does not apply for blood draws or saliva/urine/stool collections.

Risks of using continuous glucose monitor are minimal. Very few participants have reported slight redness and swelling. If this happens, participants might feel discomfort in the area the sensor is inserted.

Microsampling: risks of micro-sampling using the microlet lancet are minimal. There may be minor discomfort and slight redness or swelling at the site of lancing.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

Potential risk of procedures is minimal. Risks to physical well being would be discomfort during the insulin resistance test. The use of the continuous monitor might incur the discomfort of having the adhesive on the skin and carrying the monitor with them most of the time.

Microsampling may cause slight discomfort but are not harmful in nature.

vii. Psychological well-being

N/A

viii. Economic well-being

N/A

ix. Social well-being

N/A

x. Overall evaluation of risk

Low

b. International Research Risk Procedures

N/A

c. Procedures to Minimize Risk

1. IVs are started by qualified nurses in the CTRU who have been doing this for over 10 years. This minimizes the risk of bruising or infection.
2. For insulin, glucose levels are monitored throughout the study, guidelines for stopping are as follows:
-for glucose readings in the 60s, if patients are symptomatic, the test is stopped
-for glucose readings in the 50s, the test is automatically stopped
-in both of these instances 20% dextrose is run at 75mL per hour and the patient is given food immediately
-blood sugars are then checked at 30 and 60 min after completing their meal before patients are allowed to go home; blood sugars have to be minimally between 95 and 100 ml/dL before patient is discharged
-patients are also given a snack
3. There are no major side effects for octreotide. Participants are informed of minor side effects of abdominal cramping, nausea and diarrhea. They are consented before the study and before the test is administered.

These tests have been part of our research for well-over 20 years and we have had no adverse events.

All patient information is kept in books not shared with anyone else which is in a locked room. Some information may also resides on an encrypted computer. Everyone in the McLaughlin research group is HIPPA certified and follow confidentiality rules.

d. Study Conclusion

The study is of very short duration and it involves only monitoring with no intervention, thus we do not plan on terminating the study early.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

Monitoring will include any expected side effects such as hypoglycemia resulting from SSPG or IVGTT tests. If these are of a serious nature (e.g. more than expected resulting in clinical deterioration or requiring medical assistance) they will be reported as adverse events, and then graded as to severity and likelihood of being related to study procedures/drug. Unexpected adverse events (eg. hospitalization or death) will be reported within 24 hours to the Stanford IRB.

ii. Person(s) responsible for Data and Safety Monitoring

The protocol director will fill this role. He is in close communication with the study physician, Dr. Tracey McLaughlin who oversees the clinical aspects of the study.

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

This is a short term study and unless something totally unexpected occurs, this study will not be terminated early.

We do not anticipate any unusual events based on are previous experience and the short term nature of the study. If there is an unexpected adverse event, i.e. hospitalization or death we would re- evaluate regarding stopping the study early.

Unintended identity leakage of the participants will lead to further investigation.

v. DSMB Reporting

When a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem, the investigator will submit the adverse event(s) to the IRB with a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

NO

f. Risks to Special Populations

N/A

8. BENEFITS

They will learn if they are insulin sensitive or insulin resistant, they will learn more about their risks for type 2 diabetes. If they have diabetes or prediabetes, they will learn about dietary measures to better control blood sugars. Participants will learn about their body's response to different meals and which (if any) would be healthier for them.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children’s Health.