a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

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Title: Impact of a low-carbohydrate versus low-fat breakfast on blood glucose control in type 2 diabetes

Research Question: Does a low-carbohydrate breakfast impact blood glucose levels in people with type 2 diabetes?

Objectives

1) To determine whether a low-carb high-fat (LCHF) breakfast, compared to a standard control low-fat (CTL) breakfast impacts haemoglobin A1c (HbA1c; the clinical marker of glucose control) in individuals with T2D;
2) To evaluate if compared to a low-fat breakfast, a low-carb high-fat breakfast influences satiety and daily caloric intake in individuals with T2D;
3) To determine whether a low-carb high-fat breakfast, compared to a standard control low-fat breakfast alters body weight in individuals with T2D;
4) To determine whether a low-carb high-fat breakfast alters glucose levels, blood lipid profile and inflammation biomarkers compared to a low-fat breakfast in individuals with T2D;
5) To verify if compared to a low-fat breakfast, a low-carb high-fat breakfast raises lutein levels and improves cognition in individuals with T2D.

Hypothesis:

a) A low-carb high-fat breakfast, compared to a standard control low-fat breakfast will reduce HbA1c levels
b) When compared to a low-fat breakfast, low-carb high-fat breakfast will improve satiety and lower daily caloric intake.
c) Compared to a low-fat breakfast, a low-carb high-fat breakfast will lower body weight in individuals with T2D;
d) A low-carb high-fat breakfast will improve glucose levels, blood lipid profile and inflammation biomarkers compared to a low-fat breakfast in individuals with T2D;
e) Compared to a low-fat breakfast, a low-carb high-fat breakfast will raise lutein levels and consequently improve cognition functions.

Background Information

Diabetes is a rapidly growing public health problem worldwide. Among adults aged 20–79 years in 2017 there was an estimated 425 million cases of diabetes. Over 90% of these have type 2 diabetes (T2D); a chronic, progressive condition that is characterized by profound insulin resistance and pancreatic beta-cell dysfunction that leads to elevated blood glucose levels [1]. Chronically elevated blood glucose

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(i.e., hyperglycemia) contributes to the devastating complications of T2D, including cardiovascular disease, retinopathy, and neuropathy [2].

More than 100 million U.S. adults are now living with diabetes or prediabetes, according to a report released by the Centers for Disease Control and Prevention (CDC) [3]. In 2015, 30.3 million Americans, or 9.4% of the population, had diabetes. Another 84.1 million have prediabetes, a condition that if not treated often leads to type 2 diabetes within five years. Diabetes was the seventh leading cause of death in the U.S. in 2015. The total estimated cost of diagnosed diabetes in 2017 is $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity [3]. Clearly, strategies to improve glucose control and reduce the burden of T2D are attractive from a quality of life and economic standpoint.
In T2D, consuming carbohydrates results in a rapid and large increase in blood glucose. Accumulating evidence indicates that these postprandial “hyperglycemic spikes” are particularly important in driving the pathophysiology of diabetes complications. Postprandial hyperglycemia is an independent risk factor for cardiovascular disease and mortality [4] and lowering postprandial glucose spikes can reduce the risk of cardiovascular disease [5]. The highest hyperglycemic spike often occurs after breakfast, leading to the largest excursion of the day and thus breakfast is a crucial barrier preventing good glycemic control [6]. Lowering post-breakfast hyperglycemia therefore represents a key treatment opportunity for people with T2D.

Although we are unaware of any long-term (i.e. weeks/months) low-carbohydrate egg-based breakfast trials, previous studies have supported possible benefits of manipulating breakfast composition in order to improve blood glucose control and other health outcomes relevant to people with, or at risk for, T2D. Pedersen et al. [7] confirmed that in T2D, excluding carbohydrate from the first meal of the day could blunt the large breakfast glucose spike. Park et al. [8] showed that a high-protein breakfast lowers postprandial glucose concentrations at this meal and does not magnify the glucose response to the second meal, suggesting that adding protein to breakfast could be a therapeutic option for T2D. Over the longer-term, consuming a “big breakfast” containing higher fat and protein that provided 33% total daily energy over 3 months led to a significant reduction in HbA1c (the main clinical marker of glucose control that reflects average blood glucose levels over the previous 90-120 days) when compared to a small breakfast providing 12.5% daily energy [9]. Thus, previous research suggests that manipulating breakfast composition can have potential benefits for people with T2D.

Targeting the meal that leads to the largest glucose spike may be a simple, feasible strategy to improve glycemic control and reduce risk for future diabetes

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complications. One strategy to eliminate this large hyperglycemic excursion is to consume an LCHF breakfast. Epidemiological studies report that the routine consumption of a LCHF breakfast could be beneficial for reducing the risk of T2D, cardiovascular disease, and other chronic diseases [10]. Recent experimental work from our lab published in the *American Journal of Clinical Nutrition* [11] shows a 74% reduction in 24-hour postprandial hyperglycemia with a LC breakfast (egg and cheese omelet) when compared to a standard low-fat breakfast (oatmeal with berries) in people with T2D. Consuming a low-carbohydrate high-fat breakfast could be a simple strategy to prevent the largest post-breakfast glucose spike and improve overall glucose control in T2D.

The potential benefits of a low-carbohydrate breakfast compliments previous research examining the impact of high-protein breakfasts. It has been demonstrated that the daily consumption of a high-protein rather than a high-carbohydrate breakfast prevented the gain in body fat, and caused reductions in daily hunger and daily food intake [9] [12] [13] [14] [15]. Indeed, in our recent study [11] we saw that consuming the LC breakfast (which was high in protein) led to lower feelings of hunger and desire to eat sweet “junk” foods later in the day.

Low-carb high protein breakfast are usually composed of eggs and bacon. Eggs contain a variety of essential nutrients that can impact human health. Egg yolks contain various antioxidant carotenoids. Among them, lutein and zeaxanthin are the only two that cross the blood-retina barrier to form macular pigment in the eye, and lutein is the dominant carotenoid in human brain tissue. In people with T2D, it is important to minimize progressive complications of the disease including cognitive impairment, macular degeneration and retinopathy. Lutein is increasingly recognized as having a role in cognitive function. The possibility of a low-carb high-fat breakfast with eggs having nutritional benefits that advance beyond regular metabolic control in T2D to influence the brain and eye is intriguing. [16] [17] [16] [17]

Taken together, our recently published work on improved glycemic control and reduced hunger with a low-carbohydrate breakfast in T2D patients [11] coupled with studies showing that high-protein breakfasts can have health benefits in T2D, provide strong rationale for a properly powered longer-term randomized controlled trial (RCT) to determine if regular consumption of a LCHF breakfast can lead to clinically important improvements in glycemic control and health markers in individuals with T2D. **We hypothesize that consuming a LCHF breakfast will improve blood glucose control, increase satiety and improve body composition, as well as cognitive function in people with T2D**. This

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information will provide high quality scientific evidence for the potential health benefits of reducing carbohydrates at breakfast as a dietary strategy for managing T2D. The proposed RCT will significantly advance the existing evidence that has shown contribution of a LCHF consumption in improving body composition in T2D [15] by strategically incorporating a low-carbohydrate high-fat breakfast to test whether it can lower HbA1c, the key clinical treatment outcome in T2D. The findings will be easy-to-implement and could help solidify LCHF as the ideal breakfast option for people with T2D.

Research Method

Eighty-two (N=82) individuals between University of British Columbia and University of Wollongong, Australia with physician diagnosed T2D (HbA1c < 8.5%), between the ages of 20-79 years, with a BMI above 25 kg/m^2 will be recruited through online social media and newspaper advertising. REACH BC and Trialfacts will assist with recruitment. REACH BC is an initiative of BC's health authorities and partner universities bridging the gap between the public and researchers. Trialfacts combines extensive marketing and advertising expertise with in-depth clinical trial experience to create effective marketing solutions. We have a partnership with the Kelowna Diabetes Program to assist recruiting from >6500 well-monitored T2D patients in our region.
Inclusion criteria will be: i) physician-diagnosed T2D of ≥1 year; ii) current HbA1c of <8.5%; iii) BMI: higher than 25kg/m^2; iv) blood pressure of <160/99 mm Hg assessed according to guidelines; v) non-smoking; vi) not on hormone replacement therapy, corticosteroids, or anti-inflammatory medications; and vii) 20–79 years old. **Exclusion criteria will include:** i) Use of exogenous insulin; ii) taking more than 2 glucose lowering medications; iii) ongoing medical treatment for diseases such as cancer, auto-immune or inflammatory disease, liver or kidney disorders; iv) allergy, intolerance or aversion to eggs or any other dietary restrictions (e.g., vegan, breakfast skipping) that will prevent them from following the standardized study diets; v) being unable to follow remote guidance by internet or smartphone; vi) being unable to follow the controlled diet instructions;.
Based on our previous studies ~55% of males and ~70% of females with T2D who volunteer will meet these eligibility criteria so we anticipate no recruitment issues. We will allow statins and anti-hypertensive medications if on a stable dose for 3 months because the majority of T2D patients are on at least one of these medications; excluding them would leave a small pool for recruitment and limit the generalizability of our findings.

A 3-month parallel-group randomized controlled trial is proposed. Eligible participants will be randomized to either the Low-carb High-fat breakfast (LCHF, n=41) or a low-fat "standard care" control breakfast (CTL, n=41), to be consumed daily for a period of 3 months.

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Due to COVID-19 breakout, this study is proposed to be done remotely since participants belong to risk group and will probably maintain in quarantine for unpredictable time. Information and guidance for the trial will be done by email, telephone calls and text messages. RedCap-UBC will be used to manage information and deliver questionnaires.
Each group will be provided with a menu of 8 LCHF breakfasts or 8 CTL breakfasts from which to choose each morning. Breakfast options (designed by Dr. Barbara Oliveira, Registered Dietitian) will be controlled in macronutrient content and calories (~400-500 kcal), but allow for personal preference and autonomy to promote adherence. Instruction will be given for digital recording of breakfast by a RedCap-UBC link sent by email. Participants will also be guided to register three 3-day food records (2 weekdays and 1 weekend day) at weeks 1, 6 and 12 of the trial using a diet logbook provided. Reminders to complete the 3-day food records and app will be given by telephone call, text messages and/or emails based on participant preference. We have used this approach successfully in several recent and ongoing trials [18] [19].

The Godin Leisure-Time Exercise Questionnaire will allow the assessment of self-reported leisure-time physical activity. The individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits at weeks 1, 6 and 12 of the trial.

Participants will complete 100 mm Visual Analog Scales (VAS) to measure self-reported hunger, fullness before each meal (breakfast, lunch and dinner) at weeks 1, 6 and 12 of the trial.
A cognition test will be performed at weeks 0, 6 and 12 by an online link provided to participant to be answered at home.
Before and after the 3-month intervention, an 8-10 hour fasting blood sample will be obtained. For the primary outcome, HbA1c participants will be asked results from a recent exam (less than 1 month old). If results are not recent, participants will be asked to go to a local laboratory for a new test. Participants with high levels of A1c (>8.5%) during screening will be notified via email and not eligible for the study. Secondary outcomes of fasting plasma glucose, insulin, blood lipid profile (triglycerides, total, HDL, and LDL cholesterol), carotenoids (lutein and zeaxanthin) and inflammation (high-sensitivity C-reactive protein [CRP] will be measured by a dried blood spot test. Dried blood spot is a form of collection where patients place blood drops on a filter card after a finger prick with a lancet. Once dry, blood spot cards are extremely stable for shipment and storage, and the dried blood format offers excellent correlation with serum tests. It offers distinct advantages because it eliminates the need for a blood draw and translocation – reducing patients burden.

A CGM device (Abbott FreeStyle Libre) will be inserted to participants' upper arm in order to collect continuous glucose readings during the first and last 14 days of the trial. CGM will serve to confirm that the LCHF meal lowers the post-breakfast

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glucose spike and will provide details on daily postprandial hyperglycemia to be used in analyses of overall glucose control (24 h average, post-meal areas under the curve [AUC], and glycemic variability).

Self-reported weight and height will be registered at the beginning and end of the study.

Study Timeline:

1. Baseline contact
2. Day 0
3. Day 1
4. Day 7
5. Day 14
6. Day 21
7. Day 42
8. Day 84 – End of study

Timeline:

Baseline Contact

Participants will be recruited by email, online recruitment (including REACH BC and Trialfacts) or telephone call. Screening will be confirmed by filling out a Health Screening form and signing an electronic Consent form through a RedCap-UBC link. The postdoctoral fellow research lead (Dr. Barbara Oliveira) will ensure that the subjects understand the details of the study and consent form. After confirmation, participants will receive a study kit at their homes containing the following:

- Study Welcoming, Instructions and Responsibilities
- 2 Dry blood spot kit (beginning and end of study)
- Recipe book
- Controlled Glucose Monitor (CGM) Reader and sensor
- Food coupons and gift card

Instructions will consist of:

- A schedule and timeline of the study with participants' responsibilities;
- Instructions on Diet Habit Survey;
- A menu and preparation of 8 LCHF breakfasts or 8 CTL breakfasts recipes from which to choose each morning;
- How to send digital recording of breakfast by RedCap link;

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- Guidance in registering three 3-day food records (2 weekdays and 1 weekend day) at weeks 1, 6 and 12 of the trial using an online diet logbook;
- How to answer questionnaires for self-reported hunger and fullness to be completed before each meal (breakfast, lunch and dinner) and a physical activity questionnaire (GODIN) at weeks 1, 6 and 12;
- How to complete the cognition test at day 0, day 42 and day 84;
- Blood collection instructions with link to explanatory video.

Day 0

- ✓ Diet Habit Survey;
- ✓ TPB questionnaire;
- ✓ Baseline Cognition test;
- ✓ HbA1c results: participants should have a recent (less than 1 month from study start) HbA1c test or head to local lab for testing.

Diet Habit Survey will be answered by a link sent to participants through RedCap-UBC.

Cognition test will be sent as a link to be answered in a quiet room. Tests will last approximately 10 minutes.

Day 1

- ✓ Blood sample collection
- ✓ Insert CGM 1

Blood drops will be collected by participants after having fasted overnight (8-10 h) and refrain from taking any medications on the morning to measure the primary outcome of HbA1c and associated secondary outcomes measures of fasting plasma glucose, insulin, blood lipid profile and inflammation. Envelope will be then sent to research team by mail.

CGM instructions will also be sent and a Zoom meeting can be scheduled to help participants with insertion of device.

Day 7

- ✓ Self-reported Hunger and Fullness Questionnaire
- ✓ GODIN Physical Activity Questionnaire
- ✓ Diet Food log

Day 14

- ✓ Remove CGM 1 and send by mail

Day 21 – Follow-up

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Research team will contact participants to follow-up on study and verify compliance to breakfast recipes as well as provide new ideas and guidance on possible issues.

Day 42

- ✓ Self-reported Hunger and Fullness Questionnaire
- ✓ GODIN Physical Activity Questionnaire
- ✓ Cognition Test
- ✓ Food log

Day 70

- ✓ Insert CGM 2

Day 84

- ✓ Self-reported Hunger and Fullness Questionnaire
- ✓ GODIN Physical Activity Questionnaire
- ✓ Cognition Test
- ✓ Food log
- ✓ TPB questionnaire
- ✓ Provide self-reported weight.
- ✓ Blood sample collection. Blood drops will be collected by participants after having fasted overnight (8-10 h) and refrain from taking any medications on the morning to measure the primary outcome of HbA1c and associated secondary outcomes measures of fasting plasma glucose, insulin, blood lipid profile and inflammation. Envelope will be then sent to research team by mail.
- ✓ Remove CGM 2 and send by mail.
- ✓ Cognition test. Cognition test will be sent as a link to be answered in a quiet room. Tests will last approximately 10 minutes.
- ✓ End of study Survey
- ✓ HbA1c results: participants should have a recent (less than 1 week from study end date) HbA1c test or head to local lab for testing.

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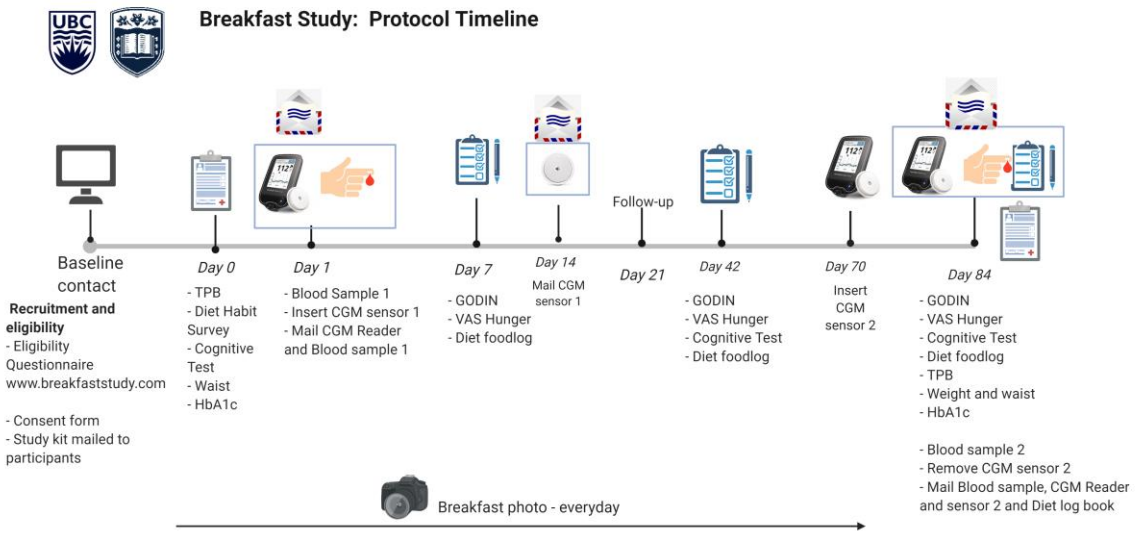

Statistical Analysis

This study will be reported according to the CONSORT 2010 statement for RCTs. Data will be analyzed on an intention-to-treat basis. Descriptive statistics (means, SD, and frequencies) will be calculated. Histograms and Q-Q plots of residuals will be used to identify any outliers and to test for normality. The primary outcome of HbA1c will be analyzed by linear mixed effects regression to assess differences between groups, with age and sex included in the model. Secondary outcomes will be analyzed similarly. Data with skewed distributions will be log-transformed prior to statistical testing or non-linear mixed effects regression will be performed. All participants will be included in the intention-to-treat analyses and missing data will not be imputed, per contemporary guidelines with use of linear mixed models.

Sample size

We used a previous breakfast intervention in T2D along with our recently published one-day egg-based LC breakfast trial to calculate sample size for this RCT. Rabinovitz et al. [9] compared a “big breakfast” containing higher fat and protein providing 33% total daily energy to a small breakfast providing 12.5% daily energy over 3 months in a similar sample of participants with T2D using a similar parallel-group design. They reported an absolute reduction in HbA1c% of 0.46%. This is similar to the magnitude of change observed in a recent study by Nichols et al. [20] who reported an average HbA1c reduction of 0.45% in response to metformin, the standard prescribed medication for people newly diagnosed with T2D. For this reason, it is reasonable to use the study published by Rabinovitz et al. to estimate a clinically relevant effect size in our sample size calculation. A medium effect size (Cohen’s d = 0.46) was calculated from the Rabinovitz study. In agreement, for our

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recent one-day study examining an egg-based LC breakfast [11], the effect size (Cohen's d) for improvements in CGM-derived glucose control variables (including AUC, iAUC, glycemic variability, and mean) ranged from d = 0.48-1.2.
Taking a conservative approach, we used an effect size of d = 0.4 in the sample size calculation. The total sample size necessary to detect a between-within interaction using repeated measures ANOVA with an effect size of d = 0.4 (which corresponds to an ANOVA effect size f = 0.2) with 90% power and 5% type 1 error with a conservative correlation among repeated measures of r=0.5 is 68 (n=34 per group, calculated using G*Power v3.1.9.2). To account for a 20% dropout rate [9] we will recruit a sample size of n=41 per group.

Significance

The results of this study will help determine whether by consuming a Low-carb High fat breakfast people with T2D will improve blood glucose control, increase satiety and improve body composition. This information will provide high quality scientific evidence for the potential health benefits of consuming a low-carbohydrate breakfast, as a dietary strategy for managing T2D.

OUTCOMES MEASUREMENTS AND METHODS

The primary outcome measure is HbA1c concentrations over the 12 week period following the LCHF breakfast or the CTL breakfast. Secondary measures will include plasma glucose, insulin, blood lipid profile (triglycerides, total, HDL, and LDL cholesterol) and inflammation (high-sensitivity C-reactive protein [CRP], tumour necrosis factor [TNF]-alpha, interleukin [IL]-6). As well as hunger/satiety levels, caloric intake and body weight/ body fat mass outcomes.

Dietary assessment

Each group will be provided with a menu and preparation instructions consisting of 8 ~400-500 kcal LCHF breakfasts (<10% carbohydrates, 65-75% fat, and 15-25% protein; e.g., omelet including low-carbohydrate additions such as cheese, meat, or non-starchy vegetables) or 8 ~400-500 kcal CTL breakfasts (45-60% carbohydrates, 20-35% fat, 15-25% protein – according to Diabetes Canada Clinical Practice Guidelines, 2018; e.g., oatmeal and berries) from which to choose each morning. Meals will be matched in calories (~400-500kcal) and protein content (15-25%). Instruction will be given for digital recording of breakfast by RedCap-UBClink. Participants will also be guided to register three 3-day food records (2 weekdays and 1 weekend day) at weeks 1, 6 and 12 of the trial using a logbook provided with instructions by the research team at initial consultation. Reminders to complete the 3-day food records will be given by telephone call, text

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messages and/or emails based on participant preference. We have used this approach successfully in several recent and ongoing trials [18] [19]. Macronutrient composition and total caloric intake will be calculated using FoodWorks (The Nutrition Company) software to determine any group differences across time.

Participants will complete 100 mm Visual Analog Scales (VAS) to measure self-reported hunger, fullness and desire for sweet and savoury foods before each meal (breakfast, lunch and dinner) at weeks 1, 6 and 12. Participants will rate each of the following 4 questions by marking vertically on a horizontal line with descriptive anchors on either side ("not at all" to "extremely"): 1) How hungry do you feel; 2) How full do you feel; 3) How satisfied do you feel; 4) How much do you think you can eat? The VAS scores will be converted to a 0–100 scale, as previously described [21]. We used this approach in our supporting preliminary study [11] showing reduced pre-dinner hunger when a LCHF breakfast was consumed by people with T2D. Questionnaire is included as attachment and will be sent as link from the RedCap platform.

The Godin Leisure-Time Exercise Questionnaire allows the assessment of self---reported leisure---time physical activity. The individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits. The leisure---time physical activity score is expressed in units and can be computed in two steps. First, weekly frequencies of strenuous, moderate, and mild activities are multiplied by nine, five, and three, respectively; these three latter values correspond to MET (metabolic equivalents) value categories of the activities listed. Then, the total weekly leisure activity score is computed in arbitrary units by summing the products of the separate components. Questionnaire is included as attachments and will be sent as link from the RedCap platform.

Cognition test
Questionnaire is included as attachments and will be sent as link from the RedCap platform.

TPB Questionnaire
Questionnaire is included as attachments and will be sent as link from the RedCap platform.

Blood samples
Blood will be collected at 2 timepoints, one at baseline and the other at the end of the trial. For the primary outcome of HbA1c, participants will be asked for results from a recent HbA1c test in 2 time points: a) less than a month from study start and b) less than one week from study end. If they a recent exam is not available, participants will be asked to go to their nearest local lab for a recent HbA1c blood test. They will receive a requisition by e-mail and will not need to pay or have a doctor's referral for the exam. Participants with high levels of A1c (>8.5%) during screening will be notified via email and not eligible for the study. For secondary

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outcomes, a dried blood spot device will be used for sampling. Dried blood spot is a form of collection where patients place blood drops on a filter card after a finger prick with a lancet. Once dry, blood spot cards are extremely stable for shipment and storage, and the dried blood format offers excellent correlation with serum tests. The same laboratory providing the blood spot will analyze primary outcome of HbA1c and associated secondary outcomes measures of fasting plasma glucose, insulin, blood lipid profile (triglycerides, total, HDL, and LDL cholesterol) and inflammation (high-sensitivity C-reactive protein [CRP]).

Continuous Glucose Monitoring (CGM)

A CGM device (Abbot FreeStyle Libre PRO) will be inserted into the subcutaneous adipose tissue of the participants' upper arm in order to collect continuous glucose readings during the first and last 2 weeks (14 days) of the trial. CGM sensor glucose readings are taken from the interstitial fluid (ISF), a thin layer of fluid that surrounds the cells of the tissues below the skin. The FreeStyle Libre PRO device is factory-calibrated so requires no finger stick calibrations (which reduces participant burden) and is indicated for detecting trends and tracking patterns of hyperglycemia and hypoglycemia. CGM will serve to confirm that the LCHF meal lowers the post-breakfast glucose spike and will provide details on daily postprandial hyperglycemia to be used in analyses of overall glucose control (24 h average, post-meal areas under the curve [AUC], and glycemic variability). The research team is experienced in CGM data collection and analyses having conducted >10 CGM-based studies in the last 8 years [11] [16][17] [22] [23].

Dr. Thomas Elliott will be the qualified investigator overseeing the continuous glucose monitoring and to whom the CGM devices will be sold as per section 83 of the Medical Devices Regulations.

Height and weight

Participants will be asked to report height and weight at the beginning and end of the trial. They will be oriented to weigh themselves on the same scale both timepoints wearing minimal clothes and at same hour of the day.

Website

As research shifts to a remote model due to COVID-19, online resources can be extremely valuable. Utilization of a website is proposed because it can be cost effective, efficient and successful in engaging individuals for initial user feedback, recruitment, follow-up and information dissemination. The website consultation and log in will not be mandatory. Participants can use it safely as no personal information will be collected by navigation. If log in is desired, participants will receive a link to create a personal account inputting a log in and password. They will then have access to documents, recipes and news. If they do not wish to create an account, they will still receive all materials by email. The only personal information sent to research team is the email.
All this information is described on the Terms of Use and Privacy Policy links (below) in the website and on Consent Form.

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Links with Private Policy and Terms of use:

https://www.ubcbreakfaststudy.com/privacy-policy

https://www.ubcbreakfaststudy.com/terms-of-use

The website was created in a Wix platform. Wix.com is a leading cloud-based development platform with millions of users worldwide. Users' and Users-of-Users' Personal Information may be stored in data centers located in the United States of America, Ireland, South Korea, Taiwan and Israel. It may use other jurisdictions as necessary for the proper delivery of Services and/or as may be required by law. More information on Privacy policy and Terms of use in link below:
https://www.wix.com/features/main

Protection of Human Subjects

All participants will be given a unique study code, with all data and information gathered connected with this code. Only the PI will have access to the master list linking the codes with participant names. Participant information and data will be either stored in a locked filing cabinet, or on an internal UBC network drive accessed only through a dedicated LAN internet connection on a password protected computer in the PIs laboratory with Salto passcard access only to the members of the research lab.
REDCap will be used as project management, storage of information, sending questionnaires and processing results. The REDCap platform is a secure web application for building and managing research data collection instruments. The platform is specifically designed to support online or offline data capture for research studies. The REDCap platform runs on server infrastructure physically located in BC, Canada, at the UBC University Data Centre (UDC).
If participants perform a HbA1c test at the Laboratory, results will be transmitted by secure fax from Laboratory to UBC (fax machine located in PI's Lab which is only accessed by lab members through Salto cards).

POTENTIAL PROBLEMS AND ALTERNATIVE STRATEGIES
Diet compliance: We will encourage accurate recording of diet by providing clear instructions and training participants on the necessary detail required. Together with the assessment of dislikes and allergies we will personalize each intervention diet and provide guidance to enhance compliance, as the recipes provided will be allow to choose from personal preference. Participants will complete a food log to record consumption of the study diets at specific timepoints (1, 6 and 12 weeks).

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Since the study involves a minor modification to diet, we do not anticipate that any adverse events due to the interventions will be seen.

Blood sampling:
Blood collection in local labs will follow all safety protocols established by laboratory and Public Health Agency of Canada (PHAC), BC-Centre for Disease Control, and Interior Health (IH). But, there is the risk of exposure to contamination by the Coronavirus. To minimize risks, participants will receive a copy of Lab's Safety information and procedures which include social distancing and face covering measures. Blood spots: when compared to traditional wet blood and plasma collection using venipuncture, capillary blood sampling is safer and easier, so much so that nearly anyone can perform the procedure, mainly type 2 diabetes patients who are used to doing finger pricks for glucose levels. However, risks associated with the process of finger-stick blood draws are minimized by usage of sterile and disposable material as well as hygiene procedures. Participants will receive their own kit with sterile material and instructions on procedure.

Protection of personal data: All participants will be given a unique study code, with all data and information gathered connected with this code. Only the PI will have access to the master list linking the codes with participant names. Participant information and data will be either stored in a locked filing cabernet, or on an internal UBC network drive accessed only through a dedicated LAN internet connection on a password protected computer in the PIs laboratory with Salto passcard access only to the members of the research lab.

If participants perform a HbA1c test at the Laboratory, results will be transmitted by secure fax from Laboratory to UBC (fax machine located in PI's Lab which is only accessed by lab members through Salto cards). Exam results will be identified only by study identification number.

If participants would like to have access to their partial results, they will opt for that on the "End of Study Survey" for an "Individual End of Study Report" that will be then sent by email. It will contain participants ID and date of birth (day/month/year) plus information from their participation such as pre and post Continuous Glucose readings and HbA1c results.

REDCap will be used as project management, storage of information, sending questionnaires and processing results. The REDCap platform is a secure web application for building and managing research data collection instruments. The platform is specifically designed to support online or offline data capture for research studies. The REDCap platform runs on server infrastructure physically located in BC, Canada, at the UBC University Data Centre (UDC).

There are no risks and it is not mandatory to visit or log in to website. Most of our services do not require any form of registration, allowing participants to visit our

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site without any identification. However, some services may require personal Information such as name and email address. This contact information will only be used for the purposes for which it is supplied to us (e.g., responding to comments or requests for information). Once consented in the study, participants have the option to log in and access study information such as recipes, forms and communicate with Research team. This can be done by creating a log in and password using the email as the only personal information. Registering in the website is not mandatory since all documents will be provided to participants via e-mail and in a printed format.

Informed consent and ethics: Prior to beginning the study Informed consent will be obtained from participants and they will be informed they can withdraw at any time. For participants already enrolled in the study, the updated version will be sent by email with new information highlighted.
Participants who completed the study will be contacted via email asking if they would like an "End of Study Report". If yes, the report will be sent by email.

References

1. Atlas, I.D., *6th edn. International Diabetes Federation 2013*. 2018.
2. Punthakee, Z., R. Goldenberg, and P. Katz, *Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome.* Canadian journal of diabetes, 2018. **42**: p. S10-S15.
3. Control, C.f.D. and Prevention, *National diabetes statistics report, 2017.* Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services, 2017.
4. Cavalot, F., et al., *Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study.* The Journal of Clinical Endocrinology & Metabolism, 2006. **91**(3): p. 813-819.
5. Chiasson, J.-L., et al., *Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial.* Jama, 2003. **290**(4): p. 486-494.
6. Ceriello, A., *Postprandial hyperglycemia and diabetes complications: is it time to treat?* Diabetes, 2005. **54**(1): p. 1-7.
7. Pedersen, E., K. Lange, and P. Clifton, *Effect of carbohydrate restriction in the first meal after an overnight fast on glycemic control in people with type 2 diabetes: a randomized trial.* The American journal of clinical nutrition, 2016. **104**(5): p. 1285-1291.
8. Park, C.H. and Y.-S. Kwak, *Analysis of energy restriction and physical activity on brain function: the role of ketone body and brain-derived neurotrophic factor.* Journal of exercise rehabilitation, 2017. **13**(4): p. 378.
9. Rabinovitz, H.R., et al., *Big breakfast rich in protein and fat improves glycemic control in type 2 diabetics.* Obesity, 2014. **22**(5): p. E46-E54.

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10. Bush, N.C., et al., *A high-fat compared with a high-carbohydrate breakfast enhances 24-hour fat oxidation in older adults.* The Journal of nutrition, 2018. **148**(2): p. 220-226.
11. Chang, C.R., M.E. Francois, and J.P. Little, *Restricting carbohydrates at breakfast is sufficient to reduce 24-hour exposure to postprandial hyperglycemia and improve glycemic variability.* The American journal of clinical nutrition, 2019. **109**(5): p. 1302-1309.
12. Bonnema, A.L., et al., *The effects of the combination of egg and fiber on appetite, glycemic response and food intake in normal weight adults–a randomized, controlled, crossover trial.* International journal of food sciences and nutrition, 2016. **67**(6): p. 723-731.
13. Fuller, N.R., et al., *The effect of a high-egg diet on cardiovascular risk factors in people with type 2 diabetes: the Diabetes and Egg (DIABEGG) study—a 3-mo randomized controlled trial.* The American journal of clinical nutrition, 2015. **101**(4): p. 705-713.
14. Jakubowicz, D., et al., *High-energy breakfast based on whey protein reduces body weight, postprandial glycemia and hba1c in type 2 diabetes.* The Journal of nutritional biochemistry, 2017. **49**: p. 1-7.
15. Njike, V.Y., et al., *Egg ingestion in adults with type 2 diabetes: effects on glycemic control, anthropometry, and diet quality—a randomized, controlled, crossover trial.* BMJ Open Diabetes Research and Care, 2016. **4**(1): p. e000281.
16. Johnson, E.J., *Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan.* Nutrition reviews, 2014. **72**(9): p. 605-612.
17. Andersen, C.J., *Bioactive egg components and inflammation.* Nutrients, 2015. **7**(9): p. 7889-7913.
18. Francois, M.E., et al., *Combined interval training and post-exercise nutrition in type 2 diabetes: a randomized control trial.* Frontiers in physiology, 2017. **8**: p. 528.
19. Myette‐Côté, É., et al., *Prior ingestion of exogenous ketone monoester attenuates the glycaemic response to an oral glucose tolerance test in healthy young individuals.* The Journal of physiology, 2018. **596**(8): p. 1385-1395.
20. Nichols, G.A., et al., *The change in HbA1c associated with initial adherence and subsequent change in adherence among diabetes patients newly initiating metformin therapy.* Journal of diabetes research, 2016. **2016**.
21. Flint, A., et al., *Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies.* International journal of obesity, 2000. **24**(1): p. 38.
22. Little, J.P., et al., *Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes.* Journal of applied physiology, 2011. **111**(6): p. 1554-1560.
23. Little, J.P., et al., *Effects of high-intensity interval exercise versus continuous moderate-intensity exercise on postprandial glycemic control assessed by continuous glucose monitoring in obese adults.* Applied physiology, nutrition, and metabolism, 2014. **39**(7): p. 835-841.