Impact of a Low-Carbohydrate Diet on Glycemic Control and Lipids in Pediatric Type 1 Diabetes

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Impact of a Low-Carbohydrate Diet on Glycemic Control and Lipids in Pediatric Type 1 Diabetes

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1.0 Background

Chronic hyperglycemia worsens both microvascular and macrovascular complications for patients with T1DM[1,2]. After acute diabetes complications, cardiovascular disease (CVD) is the leading cause of death for adult T1DM patients[3], making the prevention of chronic hyperglycemia critically important. Carbohydrate quantity and type affect post-prandial glycemia more than any other dietary factor in non-diabetic populations[4,5]. Additionally, consuming larger meals is associated with underestimation of carbohydrate quantity and mealtime insulin dose, leading to increased glucose variability[5]. These findings serve as the theoretical basis for implementing a carbohydrate restricted diet to improve HbA1c and decrease glycemic variability. Current dietary recommendations from the ADA for patients with T1DM[6] align with guidelines from the Institute of Medicine for healthful eating in the general population[7]. While the ADA recommends individualization of dietary plans for patients with T1DM, most recent guidelines state that "evidence is inconclusive for an ideal amount of carbohydrate intake for people with diabetes"[6].

While LCDs have been associated with improved HbA1c in adults with T1DM, no randomized, prospective studies have evaluated the effect of a LCD on outcomes in the pediatric T1DM population. Cross sectional and prospective studies in adults with T1DM have demonstrated improvement in HbA1c after a LCD[8-11], but these studies have significant limitations including small sample size[9] and methodologic flaws such as using HbA1c as both a dietary adherence marker and outcome measure[10]. Large observational[12] and survey studies[13] have revealed associations between lower carbohydrate intake and lower HbA1c in pediatric patients with T1DM. However, existing studies have major limitations, including significant selection bias and methodologic concerns, such as recruiting highly motivated participants from a social media group and using self-reported HbA1c as the primary outcome[13]. No study to date has prospectively investigated the impact of a LCD intervention on glycemic control in children with T1DM in a randomized controlled design. To fill this knowledge gap, in Aim 1 we will test the hypothesis that a LCD intervention will improve HbA1c compared to a SCD in pediatric patients with type 1 diabetes.

Carbohydrate quantity and type affect post-prandial glycemia while also influencing low-density lipoprotein cholesterol (LDL-C)[14]. Epidemiologic evidence suggests that LDL-C above 100 mg/dL is associated with increased cardiovascular disease (CVD) risk in patients with T1DM[15]. One study surveyed a social media group of pediatric T1DM patients who consumed a very low-carbohydrate diet (VLCD) and found glycemic control was excellent (HbA1c = 5.7%), but total cholesterol and LDL-C were elevated[13]. These findings contrast with larger studies showing that LCD reduced LCL-C in adult populations of both non-diabetic and diabetic patients[16]. Further, experts have noted that directly measuring the number and size of LDL particles (LCL-P) using nuclear magnetic resonance (NMR) may better capture CVD risk[17] as suggested by multiple cross sectional[18] and prospective studies [19-22]. In one prospective, parallel isocaloric nutrition study in overweight men, the percent dietary carbohydrate consumption was directly proportional to smaller (i.e. worse) LDL-P size[23]. No study has yet prospectively investigated the influence of a LCD on lipid profiles in

children with T1DM. In Aim 2, we will use NMR spectroscopy to comprehensively quantitate the atherogenic lipoprotein load by measuring lipoprotein particle number and size in addition to lipoprotein cholesterol concentrations.

Dietary intake influences several life domains that may affect QOL, including social interactions, personal satiety, economic, physical, and psychological domains[24]. Significant challenges in prospective dietary intervention trials include high rates of attrition and difficulty maintaining participant compliance[25], both of which are ultimately linked to the impact of the diet on QOL. While improved QOL with LCD interventions has been demonstrated in patient populations including obese adults[24] and children with epilepsy[26], findings are often confounded by improvements in the underlying disease process such as weight loss or improvement in seizure frequency, respectively. No study has prospectively evaluated the impact of a LCD intervention on QOL outcomes in pediatric T1DM, which will be investigated in aim 3.

2.0 Rationale and Specific Aims

We hypothesize that pediatric patients with T1DM who consume a LCD will have improved HbA1c compared with T1DM patients who consume a standard-carbohydrate diet (SCD). We further hypothesize that differences in lipidemia and quality of life (QOL) between the groups will be minimal. To test our hypotheses, we will employ a pragmatic nutrition education intervention. The study will randomize adolescent patients (ages 13-21 years) to one of three groups (n = 15 per group). We will instruct participants to consume a LCD (group 1) or a SCD (group 2), or provide no specific recommendations regarding diet (group 3). We will prescribe isocaloric diets for groups 1 and 2 equaling the estimated energy requirements of the Institute of Medicine[7]. Participants on the SCD intervention will consume 45-65% of total daily caloric intake from carbohydrates, 25-35% from fat and 10-30% from protein. Participants on the LCD intervention will consume 25-35% of total daily intake from carbohydrates, 45-65% from fat and 10-30% from protein. Group 3 will serve as a control that receives the same number of education sessions as groups 1 and 2 to teach general diabetes management but without specific dietary recommendations. This study design will allow for discrimination of the effect of the composition of the diet versus the effect of receiving any nutritional prescription.

Nutrition interventions are effective in producing dietary behavior change among adolescents[27], particularly when information and communication technologies (ICT) are incorporated[28]. Previous brief nutrition interventions teaching LCD or low glycemic index diets in T1DM patients have resulted in appropriate dietary adherence[29,30]. We will provide both traditional and ICT-based education and monitor dietary adherence with a smart-phone based nutritional tracking tool.

<u>Aim</u> 1 will provide preliminary estimates of improvement HbA1c after a nutrition intervention that teaches a LCD versus education reinforcing a SCD to families of pediatric T1DM patients. To determine the primary outcome—change in HbA1c—we will obtain HbA1c at baseline and at 12 weeks after the nutrition intervention. Additionally, we will quantify glycemic variability using continuous glucose monitoring (CGM) as a secondary outcome. Low rates of severe hypoglycemia, diabetic

ketoacidosis and growth attenuation have been reported in pediatric T1DM patients on a VLCD[13], therefore, we anticipate low rates of these adverse events with the LCD intervention.

Aim 2 will provide preliminary estimates of the change in the atherogenic lipoprotein profile in patients on a LCD versus SCD. The primary outcome measure will be change in total LDL-P from baseline to 12 weeks after the nutrition intervention. As secondary outcomes, we will measure the change in other contributors to atherogenic lipoprotein load, such as high-density lipoprotein particle (HDL-P) number, small LDL-P number, and LDL size.

Aim 3 will provide preliminary estimates of the change in QOL in patients on a LCD versus SCD. Participants will complete the PedsQL, a validated QOL measure in T1DM patients, and Problem Areas in Diabetes-Teen (PAID-T), a validated measure of diabetes-specific distress, at baseline (week 0) and at 12 weeks after the nutrition intervention[31,32]. Additionally, parents of participants will complete the WHO-5 Well-Being Index, a questionnaire for assessing subjective psychological well-being[33], and Problem Areas in Diabetes-Parent Revised version (PAID-PR), a validated measure of perceived parental burden associated with caring for a child with diabetes.[34]

We will perform an independent samples t-test to compare outcomes between groups, in addition to multilinear regression analysis to account for potentially confounding covariates, such as total daily dose of insulin, weight change, glycemic variability as measured by continuous glucose monitoring (CGM), and age.

This proposed research will be the first prospective study to determine the effect of a LCD intervention on key diabetes outcomes in a pediatric T1DM population. This study will also provide a basis of training for a new pediatric investigator in the conduct of clinical trials under the mentorship of a highly successful mentorship team including Dr. Kevin Niswender and Dr. Justin Gregory.

3.0 Animal Studies and Previous Human Studies

3.1 Previous Human Studies – Adult T1DM Population

A recent systematic review described eight studies that investigated the effect of a low-carbohydrate diet on glycemic control using HbA1c as the primary outcome. Of these studies, four reported non-significant changes in HbA1c with a LCD while three reported statistically significant reductions[8].

3.2 Previous Human Studies – Pediatric T1DM Population

Published studies focused on the effects of a low carbohydrate diet on outcomes in pediatric T1DM have been limited to observational and survey studies.

One study surveyed an online social media group of pediatric T1DM patients who consumed a very low-carbohydrate diet (VLCD) with an average carbohydrate intake goal of 36 +/- 15 grams of carbohydrates per day and found glycemic control was excellent with a reported mean

HbA1c of 5.7%[13]. There were low rages of adverse events, including episodes of diabetic ketoacidosis (1%), hypoglycemia with seizure or coma (2%), hypoglycemia requiring assistance from others (12%), and hypoglycemia requiring glucagon (4%)[13].

A large cross-sectional observational study in 46,010 patients with T1DM aged 1 – 18 years in Germany and Austria found that lower carbohydrate intake was associated with lower HbA1c ($p < 0.001$) with the average HbA1c being 0.2% lower in the lowest quartile of carbohydrate intake than in the highest quartile[12].

4.0 Inclusion/Exclusion Criteria

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Currently receive care at the Eskind Diabetes Clinic at Vanderbilt University Medical Center • Diagnosed with T1DM for at least 12 months • Age 13 to 21 years • Total daily dose of insulin 0.5 to 1.5 units/kg/day • Current use of an insulin pump and CGM • Participant or parent of participant use of smart phone • Able to read and speak English • HbA1c between 7% and 10%	• Any episode of diabetic ketoacidosis (DKA) in the last 12 months • Any episode of severe hypoglycemia (defined as requiring assistance from another person, including coma, seizures, or episodes requiring glucagon, IV dextrose or oral carbohydrate administered by another person[1]) in the last 12 months • Any prior abnormal fasting lipid panel (LDL > 130) • Additional dietary restrictions • Following a weight-loss or otherwise restrictive diet • Use of medication or supplements other than insulin to control blood glucose • Use of medication or other supplements to lower lipids • Pregnancy or breast feeding • History of hemoglobinopathy

5.0 Enrollment/Randomization

5.1 Recruitment

5.1.1 Recruitment Resources

We will use multiple tools to identify prospective study participants. The PI will contact intramural and extramural endocrinology colleagues at Vanderbilt and in the region to discuss this study and ask them to refer potential subjects. The

Vanderbilt Eskind Diabetes Clinic is a large academic center that sees approximately 2,700 patients with T1DM annually. The study team will also use additional research tools including Research match, Subject locator, and My Research at Vanderbilt. We will post flyers and send an institution-wide mass email through the Research Notifications Distribution List. In addition, we will post our research flyer on social media platforms (e.g. Facebook and Twitter) to target further potential T1DM and control group participants. For example, the Middle TN JDRF Chapter Facebook page has a large number of followers across the state of Tennessee many of whom may participate in our research.

Participants will also be recruited from the Vanderbilt Children's Endocrinology Franklin [redacted] IRB-approved flyers will be posted in the clinic (both provider workroom and in patient care areas). I will also ask my endocrinology colleagues at Vanderbilt who see patients at the Franklin clinic to refer potential subjects.

5.1.2 Initial Contact with Potential Participants

Once the research team becomes aware of a potential subject, we will either telephone the participant (or parents in the case of potential pediatric participants) or visit with them in person during an endocrinology clinic visit. The initial discussion will aim to make a preliminary assessment of whether the subject might be eligible to participate in the study. Study personnel will ask the potential subject to share his or her:

- Diagnosis of T1DM
- Age
- Weight
- Height
- Most recent HbA1c
- Diabetes duration
- Medications
- History of severe hypoglycemia in the past 12 months
- History of any episodes of DKA in the past 12 months
- Food preferences and restrictions
- Level of physical activity
- Use of insulin pump and CGM
- Ability to read and speak English

Inclusion and exclusion criteria are listed in table 1. We will invite eligible subjects to participate in the initial screening visit. The initial screening visit will occur in the Vanderbilt Eskind Diabetes Center or Vanderbilt Children's Endocrinology Franklin clinic. The participant will receive an electronic or paper copy of the informed consent document to review prior to the initial screening visit.

5.2 Enrollment

A member of the study team (i.e. key study personnel, KSP) will obtain written, informed consent or adolescent ascent with parental consent at the beginning of the screening visit as detailed in section 6.1.1.1. Once consent/assent is obtained, the participant will be enrolled in the study. A detailed description of special protection for adolescents as research subjects follows in section 7.2 below.

The Vanderbilt Eskind Diabetes Center [redacted].

The Vanderbilt Children's Endocrinology Franklin [redacted] The performance site at the Vanderbilt Children's Endocrinology Franklin clinic is not engaged in research. KSP from this study would utilize the clinic space to meet with participants for study visits. Phlebotomists at this location would be utilized to obtain blood work, which would then be handled by KSP.

5.3 Randomization

Random permuted blocks with a fixed size of 3 will be used for randomization into treatment groups. We will stratify participants based on open vs. closed loop insulin pump use and age prior to randomization.

5.4 Participant Compensation

Research subjects will be compensated for their time and inconvenience in the study in the form money in the amounts specified below. Following study completion, participants will be mailed a check equal to the dollar amount below.

- Visit 1 (Screening visit): the initial screening visit will last approximately 2-3 hours. Subjects who complete their screening visit will be compensated $25.
- Visit 2 (Week 1 visit): this visit will last approximately 2-3 hours. Subjects who complete this week 1 visit will be compensated $25.
- Visit 3 (Week 12 visit): this visit will last approximately 1-2 hours. Subjects who complete this week 12 visit will be compensated $25.

- Telephone visits (weeks 2, 4, 8): these visits will last approximately 30-60 minutes. Subjects who complete these visits will be compensated $10 per visit.

- Participants will receive full compensation for study visits and telephone visits only if they have completed all pre-visit tasks, which will be outlined in both the consent documentation and included in the written instructions participants are given in the preceding visit.

6.0 Study Procedures

6.1 Research visits

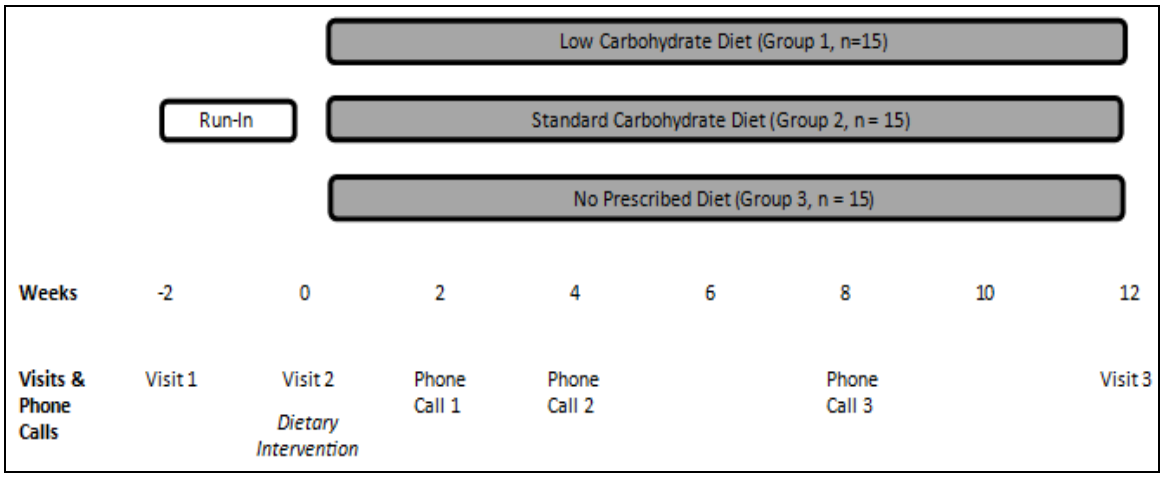


Figure 1: Study Timeline

6.1.1 Study Visit 1, Initial Screening Visit (Week -2)

Screening visits will take place in a room designated for research in the Eskind Diabetes Center or the Vanderbilt Children's Endocrinology Franklin Clinic.

The purpose of the screening visit is to:

- obtain informed, written consent/assent,
- conduct a history and physical exam,
- confirm each participant is able to properly use their insulin pump and continuous glucose monitor (CGM),
- calculate the estimated energy requirement to be consumed before during the study period,
- show participants how to log their food intake on their digital device.

The screening visit will consist of the following:

6.1.1.1 Consent/Ascent

The PI or designated KSP will obtain consent/assent from all participants. Consent/assent will be obtained in a private room in the Eskind Diabetes Center or Vanderbilt Children's Endocrinology Franklin clinic prior to beginning study procedures. The consent and assent form will be provided to the subject and family (if applicable) for review prior to the visit. The PI or designated Key Study Personnel will review the consent/assent forms with the family in detail and

provide time for discussing any questions. The study team will provide a copy of the consent/assent form to the participant and parents if applicable.

6.1.1.2 History and Physical Exam

The PI or designee will review each subject's clinical history, perform a physical exam, and take anthropometric measurements.

6.1.1.3 Nutritional Tracking App Instructions

The study team will use a nutritional tracking smartphone application, such as Nutrihand, MyFitnessPal, or FatSecret, on which participants will log their daily caloric intake using the software's web-based or Smartphone app interfaces. Participants will be asked to intermittent track intake using this smartphone app throughout the study.

Participants may be asked to use their personal email to send a CSV file containing data files from the smartphone app to the study team. This CSV file does not contain any PHI. The file will be directly uploaded into REDCap, then the email will be permanent deleted.

6.1.1.4 Continuous Glucose Monitor Instructions

The study team will instruct T1DM participants in the use of a continuous glucose monitor (CGM) such as Dexcom G6 or Medtronic Guardian for the monitoring of glycemia during the study. The team will then show T1DM participants how to upload CGM data into a HIPAA and FDA-compliant cloud-based, data-integration platform such as Dexcom Clarity or Tidepool. The team will show the control participants how to use the CGM device during this time.

Participants in group 3 will also be asked to keep a manual blood glucose log intermittently throughout the study.

6.1.1.5 Insulin Pump Instructions

The study team will instruct T1DM participants in the use of an insulin pump such as Medtronic Minimed 670G, Tandem T-Slim, or Omnipod Insulim Management System for the adminsitration of insulin during the study. Instructions will include administering all insulin via insulin pump and recording all carbohydrates consumed into the insulin pump. The

team will then show T1DM participants how to upload insulin pump data into a HIPAA and FDA-compliant cloud-based, data-integration platform such as Medtronic Careline or Tidepool. The team will show the control participants how to use the insulin pump device during this time.

6.1.1.6 Randomization

We will then randomize patients to 1 of 3 groups: group 1 is low carbohydrate diet, group 2 is standard carbohydrate diet, group 3 is general diabetes education without dietary recommendation. Each group will contain 15 participants. Random permuted blocks with a fixed size of 3 will be used for randomization into treatment groups.

6.1.2 Run In Period (Weeks -2 to 0)

Participants will log all dietary intake in the smartphone nutritional tracking app, which will serve as a baseline of dietary habits. They will also be instructed to consistently wear the CGM and to administer insulin boluses using their pump's bolus calculator.

Participants in groups 1 and 2 will be asked to complete nutritional tracking in the smartphone app during this time. Participants in group 3 will be asked to complete a blood sugar and exercise log.

6.1.3 Study Visit 2 (Week 0)

This visit will correspond with the participant's routine diabetes follow up at the Eskind Diabetes Center or Vanderbilt Children's Endocrinology Franklin clinic with their primary endocrinologist. Each T1DM participant's endocrinologist will manage his or her glycemic control and insulin doses throughout the study. The study team will review data from the nutrition log, CGM, and insulin pump. Participants will be excluded for any of the following:

- Tracking < 2 meals per day in the nutritional tracking app
- Entering carbohydrates from < 2 meals per day in their insulin pump
- Wearing CGM < 80% of run-in period.

6.1.3.1 History and Physical Exam

The PI or designee will review each subject's clinical history, perform a physical exam, and take anthropometric measurements. They will ensure the patient has an up to date intramuscular glucagon kit for treatment of hypoglycemia as needed.

6.1.3.2 Blood draw

Blood will be drawn from each participant and the following labs obtained:
- HbA1c
- Beta hydroxybutyrate
- NMR spectroscopy lipoprofile.

6.1.3.3 Continuous glucose monitor and insulin pump data collection

Continuous glucose monitor and insulin pump will be downloaded into a HIPAA and FDA-compliant cloud-based, data-integration platform such as Dexcom Clarity, Medtronic Carelink, or Tidepool.

Information that will be collected from the continuous glucose monitor download will include (but not be limited to):
- Percent of time spent above the glycemic target of 140 mg/dL
- Percent of time spent in the glycemic target of 70 – 140 mg/dL
- Percent of time spent below the glycemic target of 70 mg/dL
- Percent of time spent in hypoglycemia below 50 mg/dL
- Average blood glucose
- Blood glucose standard variation

Information that will be collected from the insulin pump download will include (but not be limited to):
- Average total daily dose of insulin
- Average bolus amount of insulin per day
- Average basal amount of insulin per day

6.1.3.4 Nutritional tracking smartphone application data collection

Information that will be collected from the smartphone app will include (but not be limited to):

- Total number of calories consumed
- Average grams of carbohydrates consumed per day
- Average grams of fat consumed per day
- Average grams of protein consumed per day
- Additional macronutrient data

Participants will also be asked to photograph all food consumed in the 24 hours prior to the study visit. At the study visit, they will complete a 24 hour dietary recall.

6.1.3.5 Quality of life survey

Participants will complete the PedsQL, a validated QOL measure in T1DM patients, and Problem Areas in Diabetes-Teen (PAID-T), a validated measure of diabetes-specific distress[31,32]. They will also

complete the Self-Care Inventory, a validated measure of adherence with diabetes self-care behaviors[35]. All surveys will be scored by a member of the research team.

Additionally, parents of participants will complete the WHO-5 Well-Being Index, a questionnaire for assessing subjective psychological well-being[34], and Problem Areas in Diabetes-Parent Revised version (PAID-PR), a validated measure of perceived parental burden associated with caring for a child with diabetes[33]. All surveys will be scored by a member of the research team.

6.1.3.6 Diet Instructions

From weeks 0 to 12, research participants in groups 1 and 2 will consume a weight-maintaining diet designed by the Vanderbilt Diet, Body Composition, and Human Metabolism Core and the research team.

The research team will discuss food preferences with each participant to design diet plan with standard macronutrient contents. The Institute of Medicine formula[7] or similar formula will be used to calculate the estimated energy requirement (EER).

EER for males (kcal/day) = 662 – (9.53 × age [y]) + PA × (15.91 × weight [kg] + 539.6 × height [m]).

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)

PA = 1.11 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)

PA = 1.25 if PAL is estimated to be ≥ 1.6 < 1.9 (active)

PA = 1.48 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

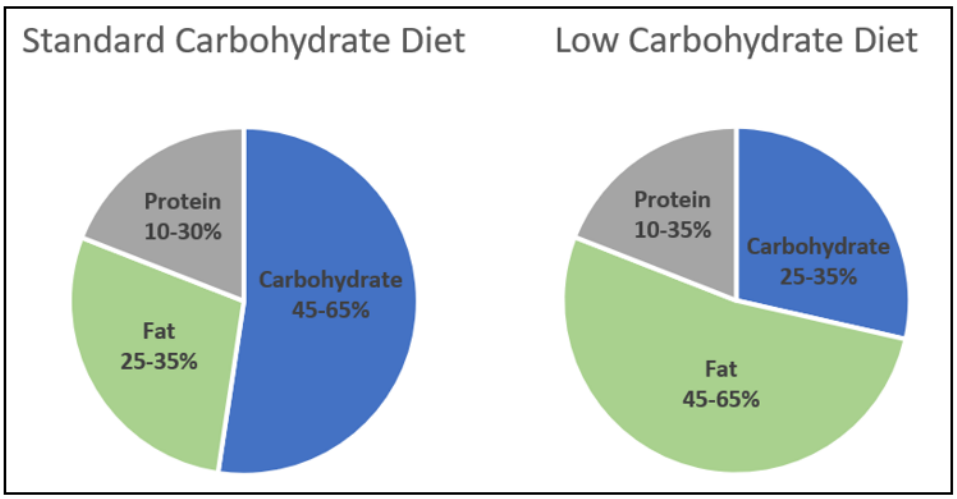
EER for females (kcal/day) = 354 – (6.91 × age [y]) + PA × (9.36 × weight [kg] + 726 × height [m])

Where PA is the physical activity coefficient:

PA = 1.00 if PAL is estimated to be ≥ 1.0 < 1.4 (sedentary)

PA = 1.12 if PAL is estimated to be ≥ 1.4 < 1.6 (low active)

PA = 1.27 if PAL is estimated to be ≥ 1.6 < 1.9 (active)



PA = 1.45 if PAL is estimated to be ≥ 1.9 < 2.5 (very active)

Figure 2: Macronutrient Content of SCD and LCD

The study team will devise two isocaloric diet plans for each participant in groups 1 and 2. One plan, the standard carbohydrate diet (SCD), will reflect the acceptable macronutrient distribution range of the Institute of Medicine's Recommendations for Nutrition: carbohydrate (45%–65% of energy), protein (10%–30% of energy), and fat (25%–35% of energy) (figure 2).[7] The other plan, the low carbohydrate diet (LCD), will reduce the percent caloric intake from carbohydrates and replace that amount with calories from dietary fat. Thus with the LCD, 45%–65% of energy will come from fat, 10-30% of energy will come from protein, and 25%–35% of energy will come from carbohydrates (figure 2).

Group 3 will serve as a control that receives the same number of education sessions as groups 1 and 2 to teach general diabetes management but without specific dietary recommendations. This study design will allow for discrimination of the effect of the composition of the diet versus the effect of receiving any nutritional prescription.

6.1.3.7 Quality Assurance of Interventions

In order to ensure consistency in the education provided to each group, we will audio record 20% of study visit 2 in each group. Key study personnel who did not perform the educational intervention will review the audio recording and score for fidelity. These audio recordings will be strictly used to ensure consistency of the intervention, will not be used to collect data. Audio files will be contained within REDCap.

6.1.4 Management between study visit 2 and 3

Each T1DM participant's will manage his or her glycemic control before and between study visits using insulin as prescribed by their primary endocrinologist. Participants will be instructed to contact the research team and will be removed from the research protocol in the event of any of the following: weight loss more than 10% from baseline or any episode of DKA or severe hypoglycemia.

6.1.4.1 Adherence monitoring

The study team will monitor adherence by reviewing each participant's dietary log, CGM data, and insulin pump data in an ongoing fashion. Should the research team detect suboptimal adherence a member of the team will contact the participant to help troubleshoot the reason for the suboptimal adherence.

6.1.4.2 Text Messaging

Participants will receive text messages 2 to 4 times per week[36] that will provide reminders regarding key components of the dietary intervention, encouragement regarding diabetes management, and general positive quotes. The study team will create a bank of 50 text messages for each dietary intervention (LCD and SCD), and participants will receive 2 to 4 of these text messages per week. Examples of message content include: "Try a breakfast high in protein! An omelet with a side of bacon would be a great choice" and "The only way of finding limits of the possible is by going beyond them and into the impossible – Arthur C. Clarke." The text message will be sent using the text messaging feature in RedCap with the Twilio messaging service and will contain no protected health information. Text messaging will continue until participants have completed study visit 3.

6.1.5 Telephone Visits (Weeks 2, 4, and 8)

The study team will monitor adherence by reviewing each participant's dietary log, CGM data, and insulin pump data. The team will conduct a 30 to 60-minute telephone session (either via Facetime, Skype, or phone call) with the participant. The study team will review with the participants their nutritional intake and reinforce key concepts from the diet to which they are assigned (LCD or SCD). If the CGM is being worn less than 80% of the time or insulin pump is not being used to record more than 2 meals per day, the study team will troubleshoot the reason for suboptimal adherence with the participant.

Participants in groups 1 and 2 will be asked to complete nutritional tracking in the smartphone app during this time. Participants in group 3 will be asked to complete a blood sugar and exercise log.

In the event that study visit 3 occurs more than 14 weeks after study visit 2, we will conduct an additional telephone visit at week 12. We will

continue to conduct a telephone visit every 4 weeks after week 12 until the participant has completed study visit 3.

6.1.6 Study Visit 3 (Week 12)

This visit will again correspond with the participant's routine diabetes follow up at the Eskind Diabetes Center or Vanderbilt Children's Endocrinology Franklin clinic with their primary endocrinologist.

6.1.6.1 History and Physical Exam

The PI or designee will review each subject's clinical history, perform a physical exam, and take anthropometric measurements.

6.1.6.2 Blood draw

Blood will be drawn from each participant and the following labs obtained:

- HbA1c
- Beta hydroxybutyrate
- NMR spectroscopy lipoprofile.

6.1.6.3 Continuous glucose monitor and insulin pump data collection

Continuous glucose monitor and insulin pump will be downloaded into a HIPAA and FDA-compliant cloud-based, data-integration platform such as Dexcom Clarity, Medtronic Carelink, or Tidepool.

Information that will be collected from the continuous glucose monitor download will include (but not be limited to):

- Percent of time spent above the glycemic target of 140 mg/dL
- Percent of time spent in the glycemic target of 70 – 140 mg/dL
- Percent of time spent below the glycemic target of 70 mg/dL
- Percent of time spent in hypoglycemia below 50 mg/dL
- Average blood glucose
- Blood glucose standard variation

Information that will be collected from the insulin pump download will include (but not be limited to):

- Average total daily dose of insulin
- Average bolus amount of insulin per day
- Average basal amount of insulin per day

6.1.6.4 Nutritional tracking smartphone application data collection

Participants in groups 1 and 2 will be asked to complete nutritional tracking in the smartphone app during this time.

Participants in group 3 will be asked to complete a blood sugar and exercise log.

Information that will be collected from the smartphone app will include (but not be limited to):

- Total number of calories consumed
- Average grams of carbohydrates consumed per day
- Average grams of fat consumed per day
- Average grams of protein consumed per day
- Additional macronutrient data

Participants will also be asked to photograph all food consumed in the 24 hours prior to the study visit. At the study visit, they will complete a 24 hour dietary recall.

6.1.6.5 Quality of life survey

Participants will complete the PedsQL, a validated QOL measure in T1DM patients and Problem Areas in Diabetes-Teen (PAID-T), a validated measure of diabetes-specific distress[31,32]. PedsQL will be scored by a member of the research team.

Additionally, parents of participants will complete the WHO-5 Well-Being Index, a questionnaire for assessing subjective psychological well-being[34], and Problem Areas in Diabetes-Parent Revised version (PAID-PR), a validated measure of perceived parental burden associated with caring for a child with diabetes[33]. All surveys will be scored by a member of the research team.

7.0 Risks

7.1 The following risks associated with participation are considered:

7.1.1 Suboptimal growth

Adherence to a low carbohydrate diet has the potential to result in a low total caloric intake and lead to suboptimal growth. One small case series describes outcomes in 6 pediatric patients who consumed between 22 – 75 grams of carbohydrates per day, including poor linear growth velocity[13]. However, both diet plans will be designed to maintain weight by using the Institute of Medicine or similar formula to calculate each participant's individual estimated energy requirement and will provide a significantly larger number of grams of carbohydrates per day than the previously described case series. Anthropomorphic measures will be taken at each study visit and participants will be removed from the study if they experience weight loss more than 10% from baseline.

7.1.2 Hypoglycemia

Hypoglycemia is encountered intermittently by patients with T1DM as part of the natural consequence of diabetes management with exogenous insulin administration, and we do not anticipate that this risk will be increased by consuming a low carbohydrate diet.

One study surveyed an online social media group of pediatric T1DM patients who consumed a very low-carbohydrate diet (VLCD) with an average carbohydrate intake goal of 36 grams per day and found low rages of adverse events, including hypoglycemia with seizure or coma (2%), hypoglycemia requiring assistance from others (12%), and hypoglycemia requiring glucagon (4%)[13]. We anticipate that the rates of these events will be considerably lower in the current study given that the carbohydrate intake in both the low-carbohydrate and standard-carbohydrate groups will be substantially higher than in the previously mentioned study.

We will use the following safety provisions to minimize risk of hypoglycemia: Participants will wear a continuous glucose monitor throughout the study period and will be instructed to contact the study team for any episode of hypoglycemia (blood glucose <70). If hypoglycemia occurred, the study team would instruct the patient to be treated orally (administer 15 grams of carbohydrates in liquid form or with glucose tablets) if the patient is responsive and able to consume the treatment orally. If the patient is unresponsive, the study team would instruct the participant's caretaker to administer intramuscular glucagon. The study team will ensure that the participants have an up to date glucagon kit at time of enrollment.

7.1.3 Diabetic Ketoacidosis

During very low carbohydrate intake, the transition to utilizing fatty acids as a fuel source leads to production of ketone bodies in state known as dietary ketosis[37]. In severely uncontrolled T1DM (ie when exogenous insulin is not adequately supplied), ketone bodies are produced in supranormal quantities and cause ketoacidosis[37]. In the T1DM population, consuming a low carbohydrate diet could potentially lead to dietary ketosis. However, the low carbohydrate diet that we are utilizing in this study is not intended to induce ketosis. Participants will continue to consume enough carbohydrates at each meal to necessitate insulin administration, which suppresses ketosis.

However, we anticipate that rates of ketoacidosis will be low given low observed rates of DKA in a population of adolescent T1DM patients on a very low carbohydrate diet (about 1%)[13]. Carbohydrate intake was significantly restricted in the very low carbohydrate study to less than half of the amount that we propose in the current study. Therefore, we anticipate that rates of DKA will be equivalent to that typically experienced by patients with T1DM.

To monitor for ketosis, we will measure beta hydroxybutyrate levels at study visits 2 and 3. Participants will additionally be instructed to contact the study team if they have any clinical signs of developing ketoacidosis, including abdominal pain, vomiting, and presence of urine ketones at home.

7.2 Special Protections for Adolescents as Research Subjects

Because the study includes adolescent T1DM subjects between ages 15-18, special consideration has been given to provisions designed to protect children as outlined in 45 CFR 46, Subpart D.

7.2.1 Justification and rationale for inclusion of adolescent subjects with T1DM

Chronic hyperglycemia worsens both microvascular and macrovascular complications for patients with T1DM[1,2]. After acute diabetes complications, cardiovascular disease (CVD) is the leading cause of death for adult T1DM patients[3], and it is clear that the mechanisms that contribute to macrovascular disease are present early in the natural history of T1DM[38]. The atherosclerotic changes of macrovascular disease in T1DM appear to begin in childhood and adolescence[39,40]. Therefore, identifying strategies for the prevention of chronic hyperglycemia to prevent micro- and macrovascular complications is critically important in the childhood and adolescent T1DM population.

Carbohydrate quantity and type affect post-prandial glycemia more than any other dietary factor in non-diabetic populations[4,5]. Additionally, consuming larger meals is associated with underestimation of carbohydrate quantity and mealtime insulin dose, leading to increased glucose variability[5]. These findings serve as the theoretical basis for implementing a carbohydrate restricted diet to improve HbA1c and decrease glycemic variability with the ultimate goal to prevent CVD.

7.3 Assessment of risk to adolescent participants relative to 45 CFR part 46, subpart D

It is our impression that T1DM subjects would fall under 45 CFR 46.406, as outlined in Vanderbilt's Human Research Protections Program Policy Number IX.A, section II.C. The proposed research is likely to yield generalizable knowledge about these adolescents' condition. Specifically,

7.3.1 The risk represents a minor increase over minimal risk.

7.3.2 The procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical situation.

7.3.3 The procedure is likely to yield generalizable knowledge about the participants' disorder or condition, which is of vital importance for the understanding or amelioration of the participants' disorder or condition.

7.3.4 Adequate provisions are made for soliciting assent of the children and permission of their parents or legal guardians as detailed in the present IRB application.

7.4 Discussion of Risks as Part of the Consent Process

The study team will discuss all procedures, risks, and benefits with potential study participants, as part of the consent process. An IRB approved written informed consent document will be required for participation in this study. It is understood that consent is a process and not a discrete event. A participant's decision to withdraw consent will be respected throughout the duration of each subject's participation in this study. It is also understood that there may be as-yet unknown or unanticipated adverse effects of this study. The study team will continually monitor for these effects and consider altering the protocol as needed to ensure patient safety. Changes in the procedures of the study, as well as any change(s) in the risks and/or benefits will be presented to and discussed with the subjects upon approval from the IRB for implementation of such revision(s), and any IRB revised written consent will be signed, as appropriate.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

8.1 Serious Adverse Events

8.1.1 Defining Serious Adverse Events

Consistent with FDA guidelines, serious adverse events (SAEs) will be defined as any untoward medical occurrence that:

- requires inpatient hospitalization
- results in persistent or significant disability
- is suspected to cause a congenital anomaly or birth defect in a subject's unborn child
- is life-threatening
- results in death
- is considered to be an important medical event based on appropriate medical judgement (e.g. bronchospasms requiring emergency department referral, seizures that might not result in hospitalization).

8.2 Assessing relationship between a SAE and relationship to study procedures

An SAE's relationship to the study procedures will be assessed and graded as either: not related, unlikely, possible, probable, or definite.

8.3 Assessing whether an AE is an anticipated problem

Any AE will be assessed for whether or not it was an anticipated problem. In accordance with Department of Health and Human Services guidance and consistent with 45 CFR part 46, an "unanticipated problem" will

include any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given
    a. the research procedures that are described in the protocol-related documents, including the IRB-approved research protocol and informed consent document; and
    b. the characteristics of the subject population being studied; related or possibly related to participation in the research; and
2. suggests that the research places subjects or others at a greater risk of harm.
3. related or possibly related to participation in the research;
4. suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

8.4 Unanticipated, non-serious AEs

All unanticipated, non-serious AEs and the study team's response to the non-serious AE will be included in a report at the time of annual continuing review. The PI will review the AEs and notify the Data Safety Monitor (DSM) and the IRB of any changes needed to the protocol. If needed, appropriate changes will be made to the consent form.

8.5 Unanticipated SAEs

In accordance with IRB policy, any unanticipated SAE that is considered possibly related to participation in the study will be reported within 7 calendar days of the PI's notification of the event to the IRB and DSM. The study team will continue to follow or obtain documentation of the resolution of any SAE.

8.6 Adverse Event Reporting

The annual summary of all unanticipated adverse events and any audit reports will be sent to the IRB at the time of continuing review. A copy of this report will also be sent to the NIH who currently funds the PI on a T32 grant.

Data and safety monitoring activities for this study will continue until all subjects have completed their participation and until a sufficient amount of time has passed beyond which any study-related AEs are unlikely.

This protocol will be reviewed annually (at a minimum) by the Vanderbilt IRB. The goal of this process is to determine the risks and benefits of the study in the actual experience of subjects and that measures taken to minimize risks are adequate

9.0 Study Withdrawal/Discontinuation

Subjects will be free to withdraw from the study at any time, which will be made clear at enrollment. Subjects will be withdrawn from the study if:

- Pregnancy is detected

- The PI's (or designated MD, NP, or PA KSP) medical judgement is that participation places the subject at risk for harm

10.0 Statistical Considerations

10.1 Recruitment and Sample Size Justification

We have targeted an accrual of 40 participants in this pilot study to achieve two goals. First, we require a sufficient number of participants to estimate the effect size and variance of the LCD as a means to reduce HbA1c in T1DM in a future definitive trial. We utilized the method of Whitehead et al. to estimate our pilot study's optimum accrual, which proposes stepped increases in sample size based on the anticipated standard difference, d, between interventions[41,42]. We defined the minimum important difference (MID) in ΔHbA1c between LCD and SCD interventions as 0.3% and estimated a pooled SD of 0.8% based on our literature review[9]. If d=MID/SDpooled=0.3%/0.8%=0.38, a sample size of 20 participants per arm will optimize future sample size calculations for the definitive study, while allowing for up to 40% dropout. Second, this sample size allows for up to 4 degrees of freedom in multivariable linear regression analysis.

10.2 Statistical Analysis

Statistical analysis will be performed using an independent samples t-test to compare change from baseline to 3 months post-intervention values from each aim (ΔHbA1c, ΔLDL-P, and ΔQOL score) between the two groups. We will also perform a series of multivariable linear regression analyses with change in primary outcomes from each aim (ΔHbA1c, ΔLDL-P, and ΔQOL score) from baseline to 12 weeks post-intervention as the dependent variable. Explanatory variables in the multivariable linear regression modeling will include mean total daily dose of insulin normalized for body mass, weight change, coefficient of variation of glucose as measured by CGM, and age.

11.0 Privacy/Confidentiality Issues

A database will be designed for this study using REDCap (Research Electronic Data Capture) tools. REDCap is a secure, web-based application designed to support data capture for research studies, providing validated data entry, audit trails, seamless data downloads to common statistical packages, and mechanisms for importing data from external sources. It will reside on a secure server with access provided exclusively to the research personnel. Subjects will be identified with a study identification number. A key to the subject identification number will be kept in a separate locked file drawer to which only the Principal Investigator and research coordinators have access. Reports will thereby be generated without Protected Health Information (PHI) data, and access will be restricted so that statisticians, etc. don't have access to all data.

Risk of leakage of PHI is minimized by keeping paper records in a locked cabinet and maintaining computerized records in the password protected REDCap data base. The principal investigator and the research staff are trained in HIPAA privacy regulations. The participant's identification is concealed, and a number is used as the identifier instead of the subject's name. Only the principal investigator or members of the research team will have the list of study patient's names as the correlate with the study number.

12.0 Follow-up and Record Retention

The study is anticipated to last for up to three years. The study results will be maintained indefinitely for research purposes.

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