OREGON HEALTH & SCIENCE UNIVERSITY
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EFFECT OF AEROBIC EXERCISE VERSUS RESISTANCE TRAINING ON ENERGY BALANCE AND GLUCOSE CONTROL IN PATIENTS WITH T1D

By

Amanda Wittenberg

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CERTIFICATE OF APPROVAL

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This is to certify that the Master's thesis of

Amanda S. Wittenberg

Has been approved

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Dr. Melanie Gillingham, PhD, RD, LD

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Dr. Peter Jacobs, PhD

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Dr. Jessica Castle, MD

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Chapter 1: Specific Aims

Inaccurately estimating carbohydrate intake and therapeutic insulin dosage, in conjunction with physical exercise, can lead to an increased risk of hypoglycemic events in patients with type 1 diabetes (T1D), which can cause confusion, blurred vision, seizures, or even loss of consciousness. In fact, hypoglycemia is reported as the primary barrier to exercise in those with T1D. In the general population, insulin secretion is suppressed during exercise to allow for glucose and lipid production to meet the energy requirements of the working muscles. For patients with T1D, therapeutic insulin inhibits gluconeogenesis and glucose release into circulation during exercise, which increases their risk of hypoglycemia.

Despite the risks of hypoglycemia, exercise is encouraged for patients with T1D. Regular exercise is known to reduce the risk of many chronic diseases in the general population. Additionally, it is well established that exercise is beneficial in those with type 2 diabetes (T2D), since it produces improvements in insulin sensitivity and glycemic control. Different types of exercise, exercise duration, and exercise intensity impact glycaemia to varying degrees. For example, aerobic exercise results in a greater decrease in blood glucose levels in comparison to resistance training. Some experts have suggested that resistance training might protect those with T1D from hypoglycemic events. For either aerobic or resistance exercise, accurate estimation of carbohydrate intake, pre-exercise glucose levels, therapeutic insulin, and the type of activity to be undertaken all need to be considered in maintaining glycemic control in those with T1D.

The impact of exercise on glycemic control and the ability of patients to adjust energy and carbohydrate intake to avoid hypoglycemia has not been fully described among subjects with T1D. While exercise is encouraged for cardiovascular health, lowered insulin needs, increased lean body mass, and improved self-esteem, it is unknown which type of exercise, duration, and level of intensity is optimal in this population. Additionally, questions remain as to how well those with T1D estimate their carbohydrate and energy intake to accurately adjust their therapeutic insulin and safely take part in exercise. Moreover, some concern exists as to whether subjects with T1D who do exercise overconsume carbohydrates out of fear of hypoglycemia, which could ultimately hinder the benefits of exercise due to the resulting increased need for insulin and potential weight gain. More research on how those with T1D adjust energy and carbohydrate intake for exercise and how an acute bout of exercise affects glycemic control is needed to address these uncertainties around glycemic control, and dietary intake with varying types of exercise.

In this randomized, three-armed crossover study, we will look at the relationship between carbohydrate and energy intake, and glycemic control, with differing types of exercise in subjects with T1D. Participants will be observed for three weeks, with each week focusing on a different exercise intervention: 1) aerobic exercise, 2) resistance training, and 3) no explicit exercise. During the aerobic exercise and resistance training weeks, the actual exercise intervention will occur on two nonconsecutive days. Participants will photograph each of their meals on a smartphone, which will be analyzed to quantify energy and macronutrient intake on

the day of and the day after exercise. Glycemic control will be collected via a continuous glucose monitoring system. This study will allow us to:

Specific Aim 1: To determine changes in carbohydrate and total energy intake following aerobic exercise, resistance training, or no exercise in subjects with T1D. **Hypothesis**: An acute bout of aerobic exercise will increase carbohydrate and kilocalorie intake more than an acute bout of resistance training in subjects with T1D.

Specific Aim 2: To identify if accurately estimating carbohydrate intake maintains euglycemia in subjects with T1D. **Hypothesis**: Subjects with T1D who more accurately estimate carbohydrate intake will experience more time in euglycemia.

Chapter 2: Background & Review of Literature

Exercise Benefits

The Physical Activity Guidelines for Americans recommends adults incorporate 150 minutes of moderate-intensity or 75 minutes of vigorous aerobic activity, and at least two days of resistance training, per week[1]. This recommendation of regular physical exercise is associated with a reduced risk of cardiovascular disease, T2D, metabolic syndrome, some cancers, improvements in bone and muscle strength, mental health, weight status, as well as longevity[2-5]. The American Diabetes Association's physical activity recommendations for those with diabetes are the same as for those in healthy adults[6]. In addition to the previously noted benefits of physical exercise, it is also associated with a greater health related quality of life,

specifically social functioning and vitality, for those with T1D[7]. Many studies indicate regular exercise decreases therapeutic insulin requirements[7-10]. On the other hand, while insulin needs may decrease, the impact on Hemoglobin A1c (HbA1c), a measure of average blood glucose control over 2 to 3 months, is mixed[8,10-12]. While there are clear benefits to exercise, it is estimated that less than 40 percent of people with T1D meet the recommendations for physical exercise[13,14].

Those with T1D have additional barriers to exercise beyond those often noted by healthy adults. One primary concern is the increased risk of hypoglycemia associated with exercise[15]. Fear of hypoglycemia is the number one reported barrier to physical exercise in T1D[16]. Taking part in exercise for someone with T1D requires a delicate balance between insulin therapy, carbohydrate intake, and type of exercise performed to prevent large swings in blood glucose[17].

Glucose Regulation

Exercise increases the body's need for energy, and in non-diabetic individuals, metabolic and hormonal changes occur to maintain blood glucose levels. It is well-established that exercise causes a hormonal adaptation including a decrease in insulin and a corresponding increase in glucagon, stimulating the body to release more glucose into the blood as the working muscles increase glucose utilization[18]. In those with T1D, this hormonal adaptation to exercise is lost due to insulin deficiency or the complete inability to synthesize insulin. Insulin changes are independent of exercise or other metabolic changes in this population[19]. If there is too little insulin in the blood, overcompensation with counter-regulatory hormones can cause

hyperglycemia. On the other hand, too much therapeutic insulin can cause hypoglycemia during exercise because even if exercise lowers glucose levels, insulin remains unchanged[17]. The American Diabetic Association provides guidelines to help this population manage blood glucose during exercise: 1) avoid activity if fasting glucose is >250 mg/dL and ketotic, or >300 mg/dL without ketosis; and 2) consume added carbohydrate when glucose levels are <100 mg/dL. Less specific guidelines by the ADA recommend making changes to insulin and carbohydrate intake as necessary based on the learned glycemic response to specific activities and foods[17]. This balance to maintain euglycemic proves to be an ongoing challenge for this population, as they must consider their current blood glucose concentration, type and timing of carbohydrate intake, type and length of physical activity, and the appropriate dose of insulin therapy[20].

Exercise Type and Glycemic Control

Aerobic exercise increases the need for glucose production to maintain euglycemia as glucose uptake by the working muscles increases. In those with T1D, the rate of glucose production may inadequately compensate for glucose uptake, increasing the risk for hypoglycemia during exercise[21]. Sustained aerobic exercise usually results in an increase in insulin sensitivity not only during exercise, but for up to 48 hours after[22-24]. Muscle glycogen depletion through prolonged moderate intensity exercise increases post-exercise glucose uptake for glycogen repletion via increased glycogen synthase I activity[23,24]. It is reasonable that this increase in insulin sensitivity and glucose uptake further predisposes those with T1D to post-exercise hypoglycemia.

Sandoval et al. looked specifically at the metabolic responses to post-exercise hypoglycemia in 12 individuals with T1D. The study randomized the participants to 4 different groups of either a a) 2 hour hyperinsulinemic eugylcemic clamp, b) 2 hour hypoglycemic (50 mg/dl) clamp, c) 90 minutes of moderate-intensity exercise (50% VO_{2max}), or d) 2 hours of resting with basal insulin infusion. After the various interventions, each participant was then studied during an additional 2 hour hyperinsulinemic hypoglycemic clamp. They found that the groups exposed to either the initial hypoglycemic clamp (b) or the moderate-intensity exercise (c) had blunted metabolic responses to the hyperinsulinemic hypoglycemic clamp, specifically a decrease in epinephrine, which would assist in raising blood glucose. Additionally, those that exercised (c) had significantly lower glucose production, corresponding with higher exogenous glucose infusion rates required to maintain the target glucose concentration (~50 mg/dL or 2.9mmol/L) during the post-intervention clamp period. Glucose uptake in the exercise group remained high during the hyperinsulinemic hypoglycemic clamp, while it decreased in the hypoglycemic group (b). The results suggest that those experiencing a bout of hypoglycemia (b) or moderate-intensity exercise (c) experience less metabolic protection from further hypoglycemia, and those that exercised have the highest risk due to an increased glucose uptake and decreased glucose synthesis as compared to those maintaining euglycemia (a & d) prior to the hypoglycemic clamp[15].

To further illustrate the challenges of controlling glycaemia and aerobic exercise in those with T1D, post-exercise hyperglycemic responses are documented. Yardley et al. completed an observational study where the participants performed 45 minutes of either running or cycling

at 60% VO_{2max} 1 hour after decreasing their basal insulin by 10-50%. Blood glucose dropped as expected during exercise, with 42% of the 19 participants needing glucose tabs to prevent hypoglycemia. After exercise was completed, blood glucose began to rise, with 37% of the participants experiencing hyperglycemia within 3 to 4.5 hours after exercise, which not surprisingly corresponded with their ad libitum dinner meal. Nocturnal hypoglycemia occurred in 21% of the participants[25]. While this study only controlled for the exercise type and intensity, and recommendations on reducing basal insulin prior to exercise, it demonstrates the challenging balance of physical activity, therapeutic insulin, and food intake this population endures to attempt to maintain euglycemia, often unsuccessfully. This could also provide further reasoning for why little positive changes are seen in HbA1c with aerobic exercise[26].

Existing research on the impact of resistance training on short- and long-term glycemic control is much less established as compared to aerobic exercise. It does appear that resistance training has a different impact on glycaemia as compared to moderate-intensity aerobic exercise. During exercise blood glucose drops less dramatically during resistance training as compared to aerobic exercise[27]. Hypoglycemia is much less prevalent during resistance training, as documentation of no or minimal occurrences of hypoglycemic events in existing studies appears consistent[27-29]. Jimenez et al studied the impact of resistance training on insulin sensitivity in 14 people with T1D. The participants were randomized to either an exercise group, who performed strength training consisting of 5 sets of 6 repetitions at 80% of their 1-repetition max for both hamstrings and quadriceps exercises, or to a control group who performed normal activities of daily living. The participants were observed for 5 days, with the

exercise or activities of daily living interventions occurring on day 3. All of the participants' diets were controlled to 55% carbohydrates, 30% fats, and 15% proteins. To quantify insulin sensitivity, a euglycemic hyperinsulinemic clamp was used. The study observed no acute impact on insulin sensitivity for up to 36 hours after resistance training[29]. This observed minimal impact of resistance training on insulin sensitivity could explain the reduction in hypoglycemic events in this study as compared to aerobic exercise. While resistance training may have a lower impact on blood glucose acutely, some studies have noted a decrease in HbA1c associated with resistance training programs[11,12]. Though, the impact on HbA1c is controversial as some have shown minimal or no impact at all[8,10].

Diet

Another primary factor of blood glucose control is diet. Carbohydrates in particular have a profound impact on blood glucose levels[30]. Because of this, bolus insulin therapy is based on carbohydrate intake as a way for regulating blood glucose. To determine the amount of insulin to dose during a meal, those with T1D need to know how much carbohydrate they are consuming. This method of carbohydrate counting is the primary medical nutrition therapy utilized for those with T1D to control diabetes-related complications[31]. Interestingly, the effectiveness of carbohydrate counting has shown to be variable[32-35]. G. Scavone et al. showed the effectiveness of carbohydrate counting by randomizing 256 people with T1D to either a group that went through carbohydrate counting education or were not educated at all. Over 4 weeks, the group that went through the education were taught about the nutritional value of food, the impact macronutrients have on blood glucose, estimating the amount of

carbohydrate in foods, appropriate amounts of carbohydrate per meal, the importance of meal spacing, and how to dose insulin based on carbohydrate content. Both groups were then followed for 9 months and were assessed every 3 months for glycemic control. The group that went through the education program and implemented carbohydrate counting achieved an overall significant decrease in HbA1c, demonstrating the efficacy of this medical nutrition therapy protocol[32].

It is known that there are other dietary factors than just carbohydrate that impact blood glucose. While carbohydrate is seemingly the primary component to post-prandial blood glucose increases, fat also has an impact[36-38]. Specifically, Wolpert et al. utilized a randomized crossover study design to compare insulin needs from a high-fat meal versus a low-fat meal where all other macronutrients were held consistent. The average amount of insulin needed to prevent postprandial hyperglycemia was 42% higher for the high-fat meals as compared to the low-fat meals[37]. Lodefalk et al. also utilized a similar method as Wolpert to demonstrate the impact of fats on glycemia. The study also validated the impact fat has on gastric emptying – a decreased rate – which correlated with the changes in blood glucose concentrations post-prandially. Eating fat with meals slows the initial glycemic response, postponing the peak of post-prandial blood glucose, further complicating insulin dosing based on food intake[39].

Balancing Exercise, Diet, and Insulin Therapy

It is clear that the type and duration of exercise, diet, and insulin dosing are critical components to glycemic control. Decreasing rapid-acting insulin typically injected with a meal prior to a

bout of exercise is understandably related to fewer hypoglycemic events during exercise[40]. In addition to reduced insulin administration, West et al. demonstrated that consuming a low-glycemic index carbohydrate meal 30 minutes prior to exercise can improve glycemic control during and after exercise[41]. Additionally, carbohydrate supplementation during extended exercise reduces hypoglycemic occurrences. Another study by West et al. compares the impact of glycemic index of foods on blood glucose during and after exercise. The participants consumed either a low-glycemic index carbohydrate or a high-glycemic carbohydrate 2 hours prior to 45 minutes of running at 80% VO_{2max}. The low glycemic carbohydrate peaked blood glucose at 120 minutes, while the high glycemic carbohydrate peaked at 90 minutes. Overall, both groups experienced similar drops in blood glucose during exercise; however, post-exercise, blood glucose concentrations in the low glycemic carbohydrate group were similar to resting conditions and less than the high glycemic carbohydrate group. In the 3 hours after exercise that the participants were monitored, blood glucose concentrations in the low glycemic index group were consistently lower than those in the high glycemic carbohydrate group and maintained euglycemia. Despite the differences in post-exercise blood glucose concentrations, subjects in both groups experienced a hypoglycemic event suggesting low glycemic index carbohydrates do not prevent post-exercise hypoglycemic events[42].

Carbohydrate intake during exercise may prevent exercise-induced hypoglycemia. Geat et al. demonstrates that glucose oxidation during a 3-hour moderate intensity aerobic exercise protocol was not significantly different between metabolically normal people and those with T1D. However, those with T1D required carbohydrate supplementation to avoid hypoglycemia

throughout the exercise intervention[43]. Riddell et al. completed a similar study in which participants with T1D completed 60 minutes of moderate-intensity cycling, where 1 group drank water and the other drank a 6-8% glucose solution based on their specific carbohydrate expenditure from indirect calorimetry. Those that were in the group that replaced carbohydrate expenditure with carbohydrate intake experienced significantly less hypoglycemic events[44]. Because exercise, particularly aerobic exercise, lowers blood glucose, making sure to not only properly dose insulin, but also incorporate adequate carbohydrate around and during exercise is critical to avoiding dramatic swings in blood glucose.

Few studies are available analyzing the relationship between energy intake, energy expenditure through exercise, and glycemic control. Dubè et al. evaluated 35 participants with T1D, all of which were accustomed to carbohydrate counting and insulin dosing. Each participant completed a detailed 3-day activity log detailing in 15 minute increments what they were doing and level of exertion on a number scale with 1 (sleeping or resting) to 9 (high energy expenditure, i.e. running). They additionally completed a 3-day food log where a registered dietitian trained the participants to document food type and quantity. Based on the energy expenditure calculated from the recorded activity log, and the energy intake based on the food logs, participants who reported higher frequency of higher energy expenditure activities also had higher HbA1c values and relied more on carbohydrates and less on lipids as their energy source as compared to those who expended less energy[45].

Food Intake Documentation and Reporting

The reliability of self-reported energy intake is an ongoing debate, as it is generally recognized as imperfect. Some even feel that self-reported energy intake is so inaccurate that they should not be relied upon for drawing conclusions related to diet[46]. Subar et al. assessed self-reported energy intake error associated with both food frequency questionnaires and 24-hour dietary recalls. Two unbiased dietary biomarkers – doubly labeled water and urinary nitrogen – were used to analyze the accuracy of dietary intake. They found that men and women underreported both energy and protein intake, which is a consistent finding with many other studies. Men underreported energy intake by 12-14% with a 24-hour dietary recall, and 31-36% on a food frequency questionnaire, while women underreported by 16-20% and 34-38% respectively. In terms of protein intake, men underreported intake by 11-12% with a 24-hour dietary recall, and 34-38% on a food frequency questionnaire, while women underreported by 11-15% and 27-32% respectively[47]. While the 24-hour dietary recall was more reliable than the food frequency questionnaire, an error ranging from 11-15% was still present. In addition, there are biases – athletes, obesity status – that correlate with increased underreporting of energy intake[48]. While there is inherent error in self-reported energy intake, it does not mean that this data is valueless or insignificant. Subar et al. recommends continuing the collection of self-reported dietary data, but it is important to also recognize the limitations, and analyze the data appropriately.

Digital Photography for Measuring Food Intake

Creative methods to improve the accuracy of self-reported energy intake are in development. As technology becomes an integral part of everyday life, utilizing smartphones to collect dietary data as a form of a food log is up-and-coming[49]. The addition of photography, while still experiencing limitations and imperfections, can improve the accuracy of dietary recalls[50].

Williamson et al. showed that using digital photography is a valid method for determining portion sizes of food served and consumed. He used test meals to compare the amount and type of food served and wasted using pre- and post-weights of the foods, direct visual estimation, and digital photography. He found that estimates of the types of food, and the food served and wasted using digital photography and visual estimation were highly correlated with the actual weights of the foods. However, this was in a cafeteria setting and focused on plate waste[51].

Lassen et al. took food photography a step further by training analysts to estimate the nutrient composition of photographed meals that were separated on the plate by various meal components (i.e. meat, fruit and vegetables, starches, etc.). Additionally, a ruler was provided in the photo for assistance with determining the size of the portions. To test the accuracy of the nutrient estimations, the participants kept a notebook recording the recipes and weights of the ingredients. The analysts underestimated the weight and total calories of all of the food categories by approximately 11%. However, the energy density and macronutrient distribution of the meals were not significantly different between the estimation from the photo analysis

and the actual weight of the food[52]. Other studies have found similar results to Lassen et al. with registered dietitians' underestimating energy (~4.7-13% underestimation) intake of participants based on photographs of the participants' meals as compared to the actual weight of the meals[53,54].

Some studies have not found significant differences in average energy intake amongst various dietary recall methods. Delisle et al. compared food photography analysis to a 24-hour recall and doubly labelled water. There was no statistical difference in the average energy intake between the three methods[55]. Wang et al. implemented a digital photography method, actual weighed foods method, and a 24-hour dietary recall around one day of meal tracking for 28 food and nutrition majors. It was found that none of them were significantly different in terms of energy intake or macronutrients[56].

Additionally, some studies recognize the limitations of traditional methods in terms of variations in underreporting of energy intake based on weight status and gender. When controlling for these factors, the photography method indicates no significant association between these variables for females, but Kikunaga et al. found the photography method did show underreporting for obese males[53,54]. Therefore, there are still questions as to whether the digital photography method could potentially eliminate typical biases seen in self-reported dietary intake.

A common denominator seen among many of the studies is the participant preference of the digital photography method for meal tracking. Feasibility and ease of documenting food intake via digital photography is noted as a positive over traditional methods, as participants report it is less burdensome[53,54,57,58]. Though, the digital photography method occasionally has many of the same challenges as traditional methods: 1) participants forget to take photos or document foods consumed; 2) participants provide poor descriptions of the foods; 3) poor lighting can make it hard to analyze the photos[52,53,57].

Chapter 3: Materials & Methods

General Design

This was a secondary analysis of the "A randomized, three-way, cross-over study to assess the impact of nocturnal hypoglycemia on sleep in patients with type 1 diabetes" study, principal investigator Peter Jacobs, PhD. The overall study was a prospective, single-center, randomized, three-treatment, open, crossover trial designed to determine the impact of aerobic exercise and resistance training on glycemic control, and carbohydrate and energy intake in those with T1D. The study recruited ten adults with T1D, aged 21 to 45.

The study duration was four weeks long, during which subjects underwent a one week run-in period followed by three randomized weeks of observational study: 1) a resistance training week; 2) an aerobic exercise week; and 3) a control week with no exercise intervention. For the aerobic exercise and resistance training weeks, there were two interventions completed per week. There was at least a one-day washout period prior to repeating an exercise intervention,

and five-days prior to starting the next intervention, as depicted below in Figure I. During each intervention week, subjects documented dietary intake on the day of exercise and the day after exercise, as depicted below in Figure I. Subjects continued to perform daily activities during each of the weeks. The overall study protocol is provided in the Appendix. For the purposes of this thesis, the methods for measuring food intake and energy expenditure are described in further detail below.

Figure I: Study Design

Randomized Intervention Week	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Aerobic Week		Aerobic Exercise		Aerobic Exercise			
Resistance Week		Resistance Training		Resistance Training			
No Exercise Week		No Exercise		No Exercise			

Randomized Intervention Week	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Aerobic Week		Aerobic Exercise		Aerobic Exercise			
Resistance Week		Resistance Training		Resistance Training			
No Exercise Week		No Exercise		No Exercise			

*Gray shaded areas indicate days of diet data collection: each day of exercise and the day after.

Population Characteristics

The population characteristics collected for description purposes included gender, age, BMI (kg/m^2), duration of T1D diagnosis, lean body mass using dual-energy X-ray absorptiometry

(DEXA), and HbA1c. Additional information about inclusion and exclusion criteria and the structured exercise sessions can be found in the study protocol in the Appendix.

Digital Food Photography

Each of the participants were given a Samsung Galaxy S4 phone with a loaded food photography application. The participants took photos of all of their meals and snacks throughout the duration of the study. A ruler provided to each of the participants was asked to be included in each photo for size perception. If the participant did not finish 100 percent of the meal, they were to take an after photo demonstrating the left-over food. The application asked the participants to estimate how many carbohydrates they consumed, their mood, and whether they were eating at home or away. The participants also had the ability to provide text details along with the photo. The photo was then uploaded to the study's database and was not able to be edited or viewed again by the participant. The blood glucose from the CGM was also uploaded with the photo, as well as date, time, and location from the Global Positioning System in the smartphone. During the training visit, the participants were taught to use the application. They were also trained and provided with instruction on what makes a good food photo: 1) inclusion of the ruler for perspective of size; 2) inclusion of the entire plate setting; and 3) use of the text feature to provide details of the meal (i.e. type of dressing, type of drink, etc.)

Digital Food Photography Analysis

At the end of each week, the food photographs were analyzed to identify and quantify foods documented and translated into macronutrient and energy composition. All of the meals and snacks for the day of the exercise intervention, and the day after, were analyzed, totaling four days each week, as depicted above in Figure IB. For the week where there was no explicit exercise intervention, the days analyzed were consistent with the days when the exercise interventions occurred. For meals that included nutrient information within the photograph through a nutrition label or the ability to obtain the nutrition label, that information was used with the assumption of one serving unless otherwise noted in the text portion provided by the participant. For all other food items without a nutrition label, the USDA food database was used to estimate the energy and macronutrient composition of the consumed food. For mixed dishes, an estimate was determined by building the meal using the USDA food database nutrient information. For meals prepared by a restaurant, the nutrient information provided by the restaurant was used, if available. At the end of each week, if there are questions regarding any food item, the participant was contacted by an investigator and the photograph was used to assist the participant to recall the food item. The analysis included total energy intake (kcalories), total fat (grams), total carbohydrate (grams), and total protein (grams). The percent of calories from each macronutrient was also part of the analysis, as well as energy intake per kilogram of body weight and macronutrient gram per kilogram of body weight. The calorie and macronutrient data were averaged for the 4-day nutrition study period as depicted above in Figure 1. Within the 4-day nutrition study period, the 24-hour period immediately following the end of the exercise interventions were also assessed for calorie and macronutrient intake.

Standardized Meals

After each exercise intervention, the participants were provided with a standardized meal from Oregon Clinical and Translational Research Institute (OCTRI). The meal was provided four times to each participant throughout the duration of the study. Its nutrient composition consisted of 540 kcalories, 47 percent carbohydrate, 30 percent fat, and 23 percent protein.

Continuous Glucose Monitoring (CGM)

Each subject was fitted with one subcutaneous CGM system – Dexcom™ G4 or Dexcom™ G4 Share which measured their blood glucose every five minutes. Additional details regarding the CGM system are detailed in the "A randomized, three-way, cross-over study to assess the impact of nocturnal hypoglycemia on sleep in patients with Type 1 diabetes" study, which is also provided in the Appendix.

For analysis of specific aim 2, the data obtained from the CGM system was distributed into minutes in euglycemia (70-180 mg/dL), hypoglycemia (<70 mg/dL), and hyperglycemia (>180 mg/dL) over the 4-day study period for each exercise intervention.

Exercise Energy Expenditure

Based on a method described by CB Scott, energy expenditure was calculated by summing the oxygen uptake for each second, and then calculating the total oxygen uptake for the exercise period [59]. The conversion from oxygen uptake to kilocalories is based on the relationship between heart rate and oxygen uptake measured during VO_{2max} testing. The conversion factors

per liter of oxygen uptake are as follows:

Aerobic Exercise: 5.0 kilocalories

Resistance Training Work Periods: 5.0 kilocalories

Resistance Training Rest Periods: 4.7 kilocalories

Measured Total Energy Expenditure

The participants wore an accelerometer (ActiGraph wGT3X-BT) for the duration of the study. The measured hourly Metabolic Equivalent of Task (MET) was converted to kilocalories utilizing the following conversion factor[60]:

$$1\ MET = \frac{1\ kcalorie}{kg \times hour}$$

Outcome Variables

Primary outcome variables assessed during each intervention week included total energy and carbohydrate intake, accuracy of carbohydrate estimation of the OCTRI-provided meal, and percent of time spent in euglycemia (70-180 mg/dL).

Statistical Analyses

Ten participants completed the protocol. Data regarding participant characteristics, including gender, age, BMI, lean body mass, and HbA1c, were summarized. Means were calculated for the energy intake (kcal) for each participant for the 4-day periods during each exercise intervention (aerobic exercise, resistance training, no explicit exercise). This was also completed for carbohydrate (g) consumed. If in a 24-period, less than 1000 kcals were

reported, those days were compared to glucose trends observed from the participant's insulin pump data. If it was determined that documentation of more than one meal was missed, that day was considered underreported and was not included in the average intake for that 4-day period.

To investigate whether energy and carbohydrate intake change with the different exercise interventions, the change in energy intake for both resistance and aerobic exercise as compared to no exercise was calculated. The change in carbohydrate intake was also calculated. Paired t tests were used to compare the mean change in energy and carbohydrate intake between the aerobic exercise and sedentary interventions, and also between the resistance training and sedentary interventions.

Glycemic control was measured by CGM and summarized by calculating the percent of time spent in each glycemic range over the length of the study, and during the 24-hours following the exercise interventions. Paired t tests were used to compare the mean difference in time spent in the different glycemic ranges between the different exercise interventions. A similar analysis will be conducted with total insulin dosed to see if total insulin (bolus and maintenance) differed by exercise routine.

To determine whether those who more accurately estimated carbohydrate have better glucose control, glucose was summarized as minutes spent in euglycemia (70-180 mg/dL) throughout the study. The accuracy of the participants' carbohydrate estimates was determined using the

standardized OCTRI meal (known carbohydrate content) provided post-exercise. The participants were divided into categorical groups, and paired t tests were utilized to determine if glycemic control differed by ability to accurately estimate carbohydrate. Data was analyzed with STATA (Version 14.2, College Station, Tx) and Prism 6.0 (Graphpad, Inc, La Jolla, Ca). Results will be considered significant at $p<0.05$.

Chapter 4: Results

Participant Characteristics

Ten participants detailed in Table 1 enrolled in the study, consisting of six females and four males ranging in age from 26 to 45 years (34±6 years), with time since T1D diagnosis ranging from 3 to 33 years (18±10 years). The participants had a BMI ranging from 20 to 27 kg/m^2 (24±2 kg/m^2), and a body fat mass ranging from 17.4 to 41.2 percent (29.8±7.7%). HbA1c ranged from 5.3 to 8.7 percent (7.4±1%) (Table 1). All participants completed the study.

Table 1. Participant Characteristics

Participant	Sex (M/F)	Age (Years)	BMI (kg/m^2)	HbA1c (%)	Duration of Diabetes (Years)	Fat Mass (%)
9001	F	34	26	7.8	30	39.4
9002	F	38	23	7.3	24	31.1
9003	F	28	20	7.5	10	24.5
9004	M	29	27	6.3	3	29.3
9005	F	45	26	8.1	10	36.6
9006	F	40	24	7.2	30	31.5
9007	M	33	23	5.3	18	25.1
9008	M	36	23	6.9	33	17.4
9009	F	26	27	8.6	10	41.2
9010	M	28	26	8.7	10	22.1
Mean±SD	-	34±6	24±2	7.4±1.0	18±10	29.8±7.7

Participant Nutrient Intake Reporting Accuracy

Each participant photographed 12 days of food intake totaling 120 days of intake data. Participant 9004 significantly underreported intake, with two days of no food intake documentation, and seven of the remaining ten days reporting less than 1000 kcals. Participant 9004 was eliminated from all intake analyses. Of the remaining nine participants, 18 days had estimated intake of less than 1000 kcals. For these 18 days, insulin pump data was pulled and glucose trends and insulin boluses were analyzed and compared to food photograph documentation to determine the degree of underreporting. If a participant missed documentation of more than one main meal, the day was considered underreported and

eliminated from the nutrition intake analyses. Ultimately, there were nine underreported days removed from the analysis (Table 2).

Table 2. Number of Days Removed from Analysis per Participant

Participant	Control	Resistance	Aerobic
9001	0	0	1
9002	0	0	0
9003	0	0	0
9005	3	0	0
9006	0	0	0
9007	0	0	0
9008	0	0	0
9009	0	1	0
9010	2	2	0
Total	5	3	1

For the 18 days that had estimated intake less than 1000 kcals, insulin pump data was also utilized to estimate missed carbohydrate intake. For any observed missed photo documentation for meals and snacks, carbohydrate estimations documented by the participant in the insulin pump was added to their daily carbohydrate and kcal total. However, this adjustment did not make a significant difference in the overall analyses, and the analyses proceeded with the above description of the elimination of underreported days. This resulted in the kcal intake estimates shown in Table 3, which represents the daily average for each intervention week.

Table 3. Mean Estimated Energy Intake (kcal/day) per Participant

Participant	Control	Resistance	Aerobic
9001	1096 ± 217	1320 ± 313	1160 ± 164
9002	1500 ± 716	2218 ± 532	1886 ± 1032
9003	1594 ± 313	1750 ± 732	2044 ± 248
9005	1138 ± 0	1418 ± 347	1882 ± 499
9006	1893 ± 263	1680 ± 290	1716 ± 319
9007	1449 ± 260	1947 ± 198	1879 ± 237
9008	1792 ± 446	1582 ± 417	1824 ± 458
9009	1195 ± 82	1343 ± 52	1210 ± 102
9010	2790 ± 1010	2228 ± 88	3032 ± 395
Mean ± SD	1605±525	1720±349	1848±540*

Mean ± SD
*p<0.05 compared to control

Assuming participants are weight stable during the study, total energy intake would be equal to total energy expenditure. To assess the degree underreporting still present in the kcal estimates in Table 3, energy intake was compared to the measured energy expenditure (Table 8) and presented as a percentage of total energy expenditure (Table 4). The control, resistance, and aerobic intervention weeks had an average energy intake less than estimated energy expenditure (Table 4, 68 ± 23%, 73 ± 28%, and 74 ± 28%). The intervention weeks did not differ significantly in their estimated energy intake as a percent of energy expenditure suggesting underreporting was consistent across interventions weeks and reported energy intake was approximately 30% less than energy expenditure (Table 4, p=0.31).

Table 4. Estimated Energy Intake of Total Measured Energy Expenditure (%)

Participant	Control	Resistance	Aerobic
9001	51 ± 7%	58 ± 12%	50 ± 5%
9002	70 ± 34%	103 ± 25%	84 ± 51%
9003	78 ± 17%	95 ± 54%	108 ± 20%
9005	33 ± 0%	42 ± 9%	54 ± 13%
9006	89 ± 15%	79 ± 19%	71 ± 16%
9007	59 ± 12%	72 ± 6%	69 ± 10%
9008	76 ± 20%	67 ± 18%	72 ± 16%
9009	49 ± 5%	54 ± 3%	49 ± 3%
9010	97 ± 20%	86 ± 9%	104 ± 15%
Mean ± SD	68 ± 23%	73 ± 28%	74 ± 28%

P=0.31, similar underreporting for all intervention weeks.

Nutrient Intake

Mean four-day reported energy intake was 1605±525 kcals (23±8 kcal/kg) during the control week. Average energy intake during the resistance week was not significantly different from the control week, 1720±349 kcals vs. 1605±525 kcals (24±6 kcal/kg vs. 23±8 kcal/kg), respectively (Table 5, Figures 2A, 2C, 2D and 2F; p=0.37, Wilcoxon rank sum test for total kcal; p=0.42, paired t test for total kcal/kg). Energy intake during the aerobic week was significantly greater than energy intake during the control week, 1848±540 kcals vs. 1605±525 kcals (Table 5, Figures 2B and 2C; p=0.03, Wilcoxon rank sum test). Energy intake on a per kilogram basis was also significantly greater during the aerobic week as compared to the control week, 26±8 kcal/kg vs. 23±8 (Table 5, Figures 2E and 2F; p=0.03).

Mean four-day reported carbohydrate intake was 161±70 g (2.3±1 g/kg) during the control week. Average carbohydrate intake during the resistance week was not significantly different from the control week, 172±67 g versus 161±70 g, respectively (Table 5, Figures 3A and 3C; p=0.95, Wilcoxon rank sum test). Mean carbohydrate intake on a per kilogram basis was also not significantly different between these two weeks, 2.5±1.1 g/kg vs. 2.3±1 g/kg, respectively (Table 5, Figures 3D and 3F; p=0.95, Wilcoxon rank sum test). Mean carbohydrate intake during the aerobic week was significantly greater than carbohydrate intake during the control week, 193±80 g vs 161±70 g, respectively (Table 5, Figures 3B and 3C; p=0.02, Wilcoxon rank sum test). Average carbohydrate intake on a per kilogram basis was also significantly greater during the aerobic week as compared to the control week, 2.8±1.3 g/kg vs. 2.3±1 g/kg, respectively (Table 5, Figures 3E and 3F; p=0.03, Wilcoxon rank sum test).

Table 5. Mean Nutrient Intake Day of and Day after Exercise

Nutrient	**Control**	**Resistance**	**Aerobic**
Kcalories	1605±525 (1201, 2008)	1720±349 (1452, 1989)	1848±540* (1432, 2264)
Kcalories/kg	23 ± 8 (17, 29)	24 ± 6 (19, 29)	26 ± 8* (20, 33)
Carbohydrate g	161±70 (107, 215)	172±67 (120, 223)	193±80* (132-254)
Carbohydrate g/kg	2.3 ± 1.0 (1.5, 3.1)	2.5 ± 1.1 (1.6, 3.3)	2.8 ± 1.3* (1.8, 3.8)

Mean ± SD (95% CI)
*p<0.05 compared to control

Figure 2. Energy Intake during Intervention Weeks

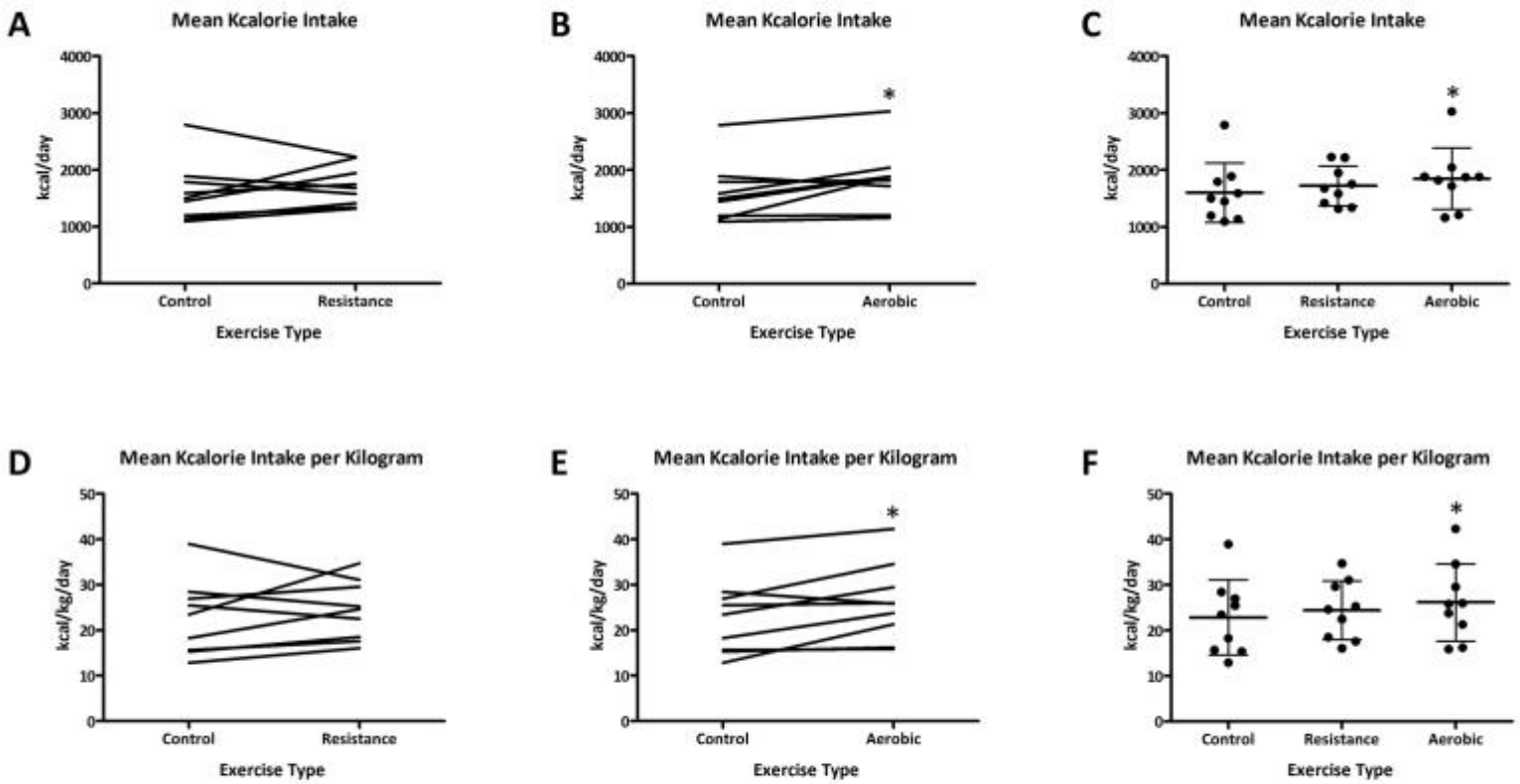

FIGURE 2. Mean kilocalorie consumption in (A) control and resistance weeks and (B) control and aerobic weeks. Mean ± SD kilocalorie consumption in (C) control, resistance, and aerobic weeks. Mean kilocalorie per kilogram consumption in (D) control and resistance weeks and (E) control and aerobic weeks. Mean ± SD kilocalorie per kilogram consumption in (F) control, resistance, and aerobic weeks. For (C) and (F) the center horizontal line represents the mean and the top and bottom represent the standard deviation.
*significant at $p<0.05$

Figure 3. Carbohydrate Intake during Intervention Weeks

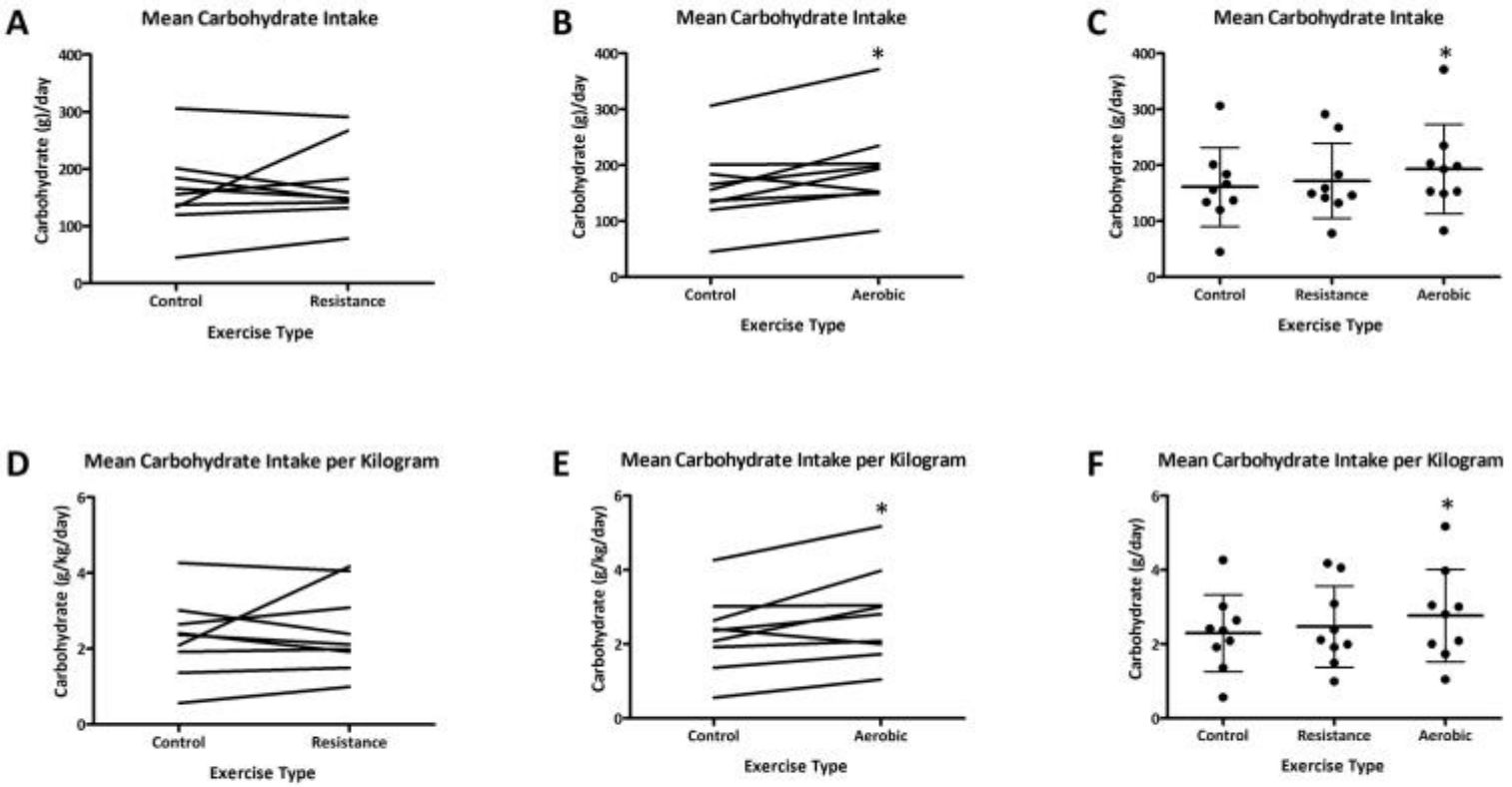

FIGURE 3. Mean carbohydrate consumption in (A) control and resistance weeks and (B) control and aerobic weeks. Mean ± SD carbohydrate consumption in (C) control, resistance, and aerobic weeks. Mean carbohydrate per kilogram consumption in (D) control and resistance weeks and (E) control and aerobic weeks. Mean ± SD carbohydrate per kilogram consumption 24-hours post-exercise in (F) control, resistance, and aerobic weeks. For (C) and (F) the center horizontal line represents the mean and the top and bottom represent the standard deviation.
*significant at $p<0.05$

To better address intake specifically as a function of the exercise intervention, mean energy and carbohydrate intakes were both analyzed for the 24-hour period immediately following the conclusion of the exercise intervention. Mean reported energy intake post-exercise was 1347±512 kcals (20±3 kcal/kg) during the control week. Average energy intake during the resistance – 1816±265 kcal – and aerobic – 1970±597 kcal – weeks were significantly greater than the control week (Table 6, Figure 4; p=0.03 and p=0.04, respecitvely). Average energy intake on a per kilogram basis during the 24 hours post-exercise during the resistance – 26±5 kcal/kg – and the aerobic – 28±10 kcal/kg – were significantly greater than the control week (Table 6, Figure 4; p=0.02 and p=0.03, respectively).

Mean reported carbohydrate intake 24-hours post-exercise was 142±65 g (2.1±0.3 g/kg) during the control week. Average carbohydrate intake 24-hours post-exercise during the resistance week increased as compared to the control week but was not statistically significant, 184±49 g versus 142±65 g, respectively (Table 6, Figure 5A and 5C, p=0.12). Mean carbohydrate intake per kilogram during these two weeks followed the same trend as total carbohydrate, 2.6±0.3 g/kg vs. 2.1±0.3 g/kg (Table 6, Figures 5D and 5F; p=0.12). Mean carbohydrate intake 24-hours post-exercise during the aerobic week was significantly greater than carbohydrate intake during the control week, 219±70 g vs 142±65 g, respectively (Table 6, Figures 5B and 5C; p=0.01). Average carbohydrate intake on a per kilogram basis was also significantly greater during the aerobic week as compared to the control week, 3.1±0.4 g/kg vs. 2.1±0.3 g/kg (Table 6, Figures 5E and 5F; p=0.01).

Table 6. Nutrient Intake 24 Hours Post-Exercise

Nutrient	Control	Resistance	Aerobic
Kcalories	1347 ± 512 (954, 1740)	1816 ± 265* (1612, 2019)	1970 ± 597* (1511, 2429)
Kcalories/kg	20 ± 3 (13, 26)	26 ± 5* (22, 30)	28 ± 10* (21, 35)
Carbohydrate g	142 ± 65 (92, 192)	184 ± 49 (146, 222)	219 ± 70* (165, 272)
Carbohydrate g/kg	2.1 ± 0.3 (1.3, 2.9)	2.6 ± 0.3 (2.0, 3.2)	3.1 ± 0.4* (2.2, 4.1)

Mean ± SD
(95% CI)
*$p<0.05$ compared to control

Figure 4. Energy Intake 24-Hours Post-Exercise

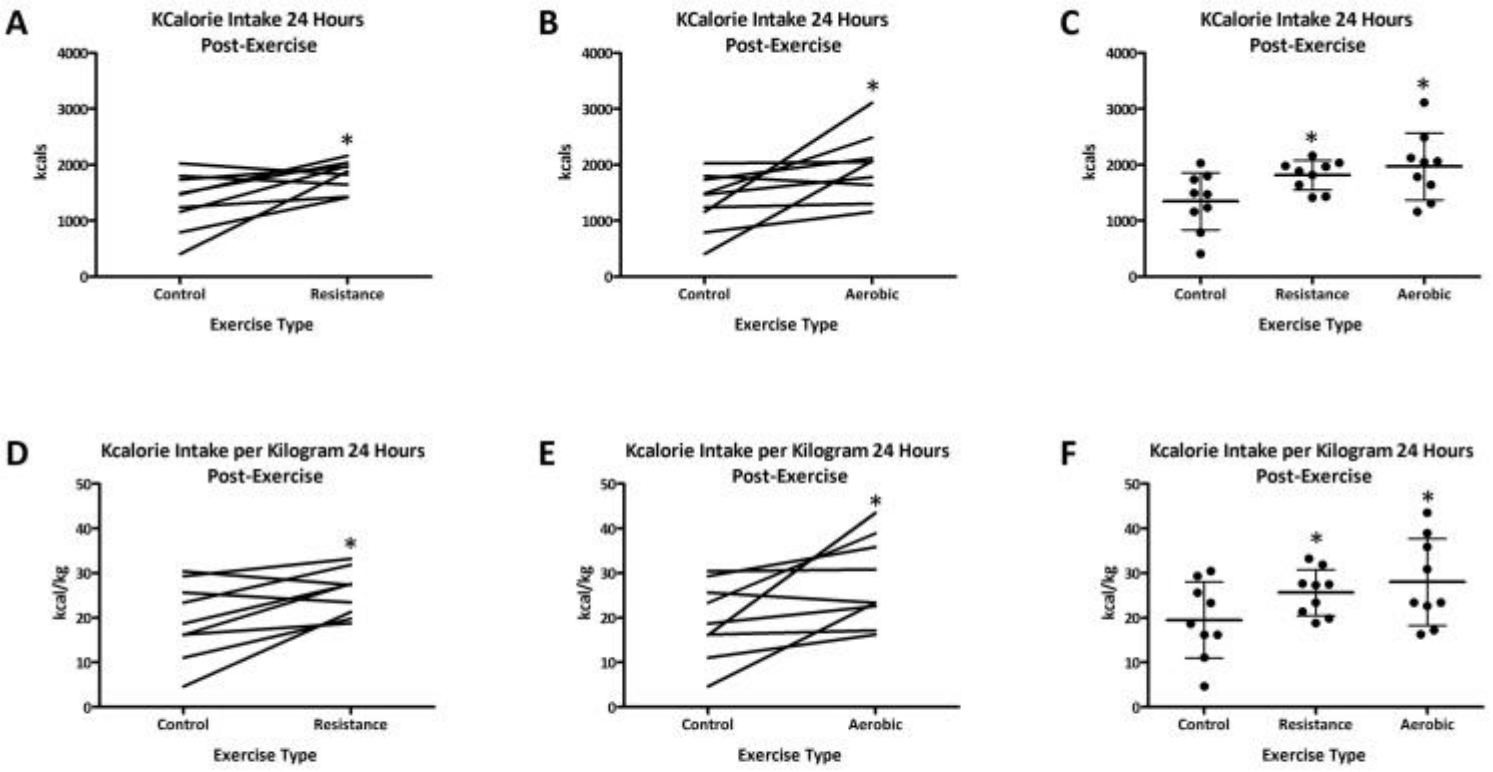

FIGURE 4. Mean kilocalorie consumption 24-hours post-exercise in (A) control and resistance weeks and (B) control and aerobic weeks. Mean ± SD kilocalorie consumption 24-hours post-exercise in (C) control, resistance, and aerobic weeks. Mean kilocalorie per kilogram consumption 24-hours post-exercise in (D) control and resistance weeks and (E) control and aerobic weeks. Mean ± SD kilocalorie per kilogram consumption 24-hours post-exercise in (F) control, resistance, and aerobic weeks. For (C) and (F) the center horizontal line represents the mean and the top and bottom represent the standard deviation.
*significant at $p<0.05$

Figure 5. Carbohydrate Intake 24-Hours Post-Exercise

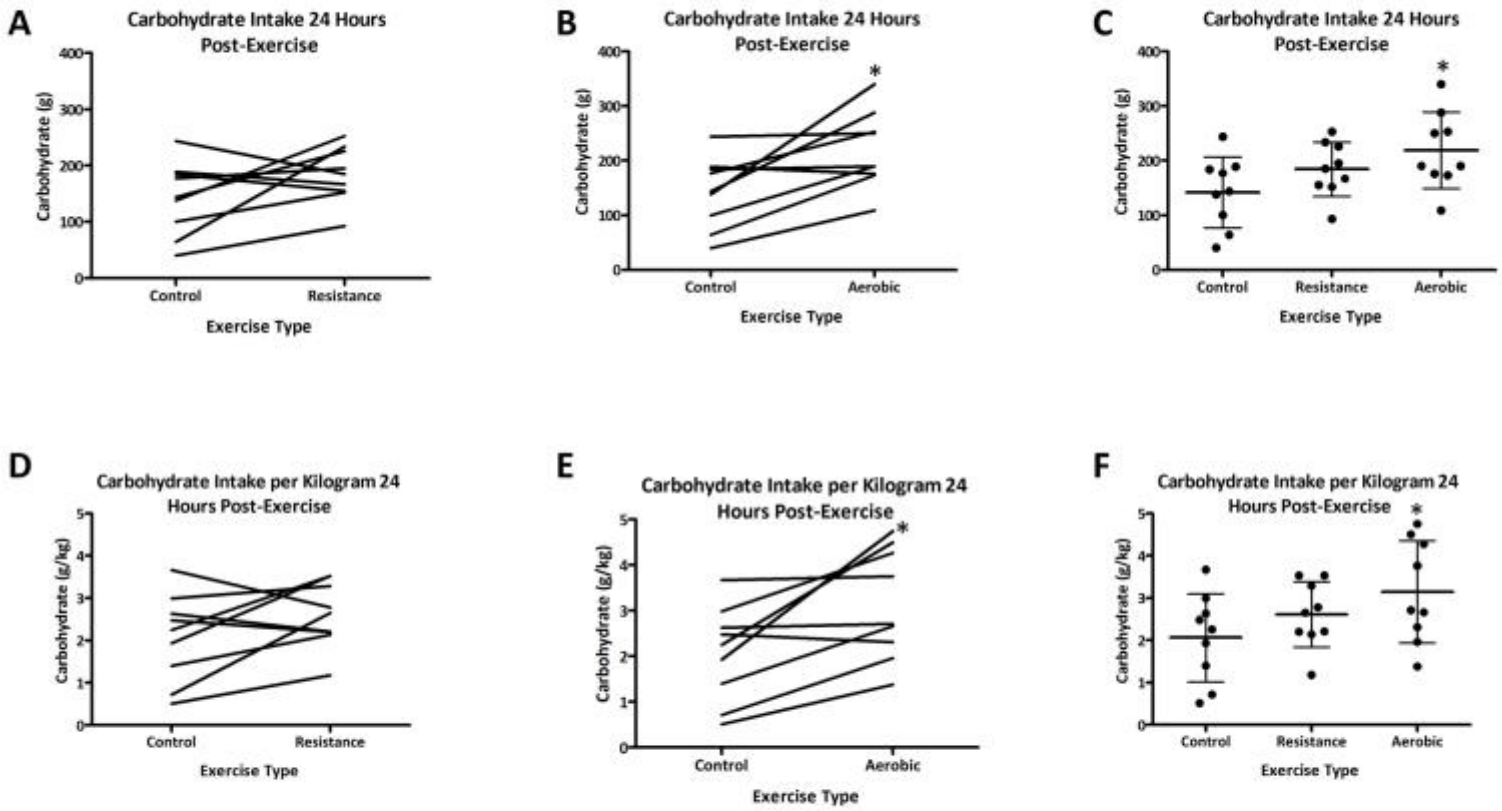

FIGURE 5. Mean carbohydrate consumption 24-hours post-exercise in (A) control and resistance weeks and (B) control and aerobic weeks. Mean ± SD carbohydrate consumption 24-hours post-exercise in (C) control, resistance, and aerobic weeks. Mean carbohydrate per kilogram consumption 24-hours post-exercise in (D) control and resistance weeks and (E) control and aerobic weeks. Mean ± SD carbohydrate per kilogram consumption 24-hours post-exercise in (F) control, resistance, and aerobic weeks.
*significant at $p<0.05$

Energy Expenditure

Average energy expenditure during the exercise intervention was significantly greater during the aerobic exercise intervention days as compared to the resistance exercise interventions, 417±128 and 431±112 vs. 245±54 and 248±71, respectively (Table 7 and Figure 6; $p<0.05$).

Table 7. Energy Expended During Exercise Intervention (kcal)

Participant	Resistance Day 1	Resistance Day 2	Aerobic Day 1	Aerobic Day 2
9001	281	195	288	260
9002	231	289	452	432
9003	239	271	245	416
9005	286	202	475	463
9006	302	283	248	325
9007	138	126	536	415
9008	272	271	433	436
9009	249	376	553	586
9010	169	189	347	347
Mean ± SD	245 ± 54	248 ± 71	417 ± 128*	431 ± 112*

P<0.05 as compared to resistance days.

Figure 6. Energy Expended During Exercise Period

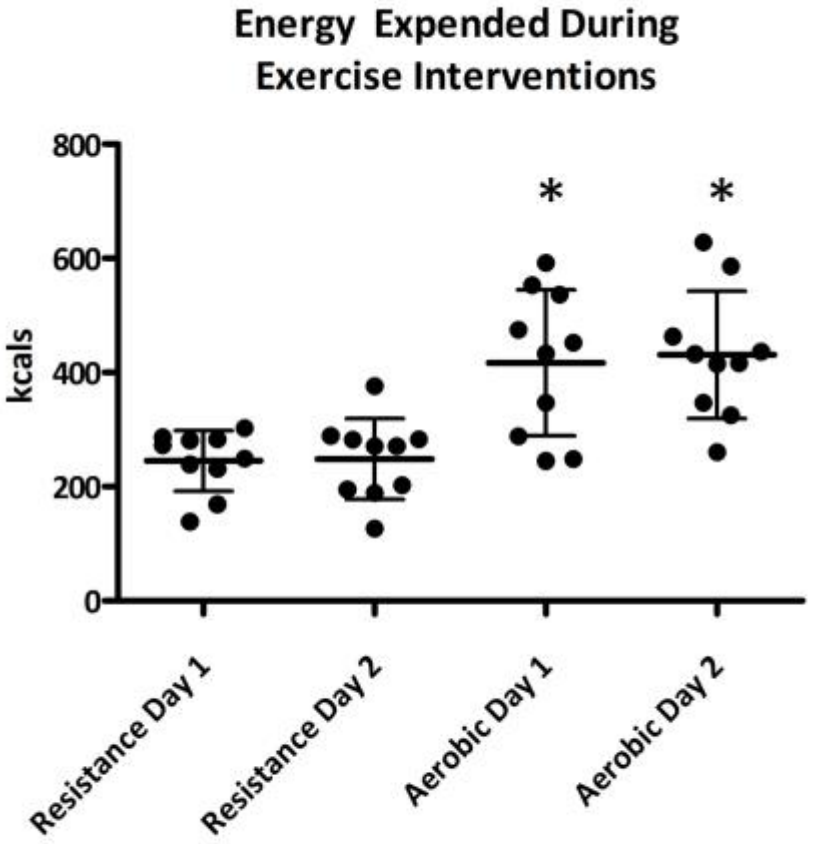

FIGURE 6. Mean ± SD kilocalorie expenditure during resistance and aerobic exercise interventions. The center horizontal line represents the mean and the top and bottom represent the standard deviation. *significant at $p<0.05$ as compared to resistance exercise

Total energy expenditure was obtained for each participant from their Actigraph data over the 4 study days of each intervention week (Table 8). Mean four-day energy expenditure was 2459 ± 479 kcal/day during the control week, which was not significantly different from the resistance week of 2450 ± 443 kcal/day (Table 8, Figure 7A and 7C; p=0.88). Mean total energy expenditure during the aerobic week was greater than the control week, but was not statistically significant, 2566 ± 434 kcal/day vs. 2459 ± 479 kcal/day, respectively (Table 8, Figure 7B and 7C; p=0.08).

Table 8. Mean Total Measured Energy Expenditure (kcal/day)

Participant	Control	Resistance	Aerobic
9001	2142 ± 161	2280 ± 101	2376 ± 134
9002	2136 ± 40	2160 ± 215	2313 ± 219
9003	2040 ± 78	1926 ± 237	1906 ± 180
9005	3325 ± 365	3346 ± 179	3446 ± 170
9006	2142 ± 121	2148 ± 177	2427 ± 132
9007	2446 ± 67	2712 ± 83	2735 ± 115
9008	2384 ± 289	2380 ± 57	2510 ± 107
9009	2451 ± 115	2416 ± 129	2468 ± 164
9010	3063 ± 508	2679 ± 452	2919 ± 110
Mean ± SD	2459 ± 479	2450 ± 443	2566 ± 434

No significant differences in daily energy expenditure.

Figure 7. Mean Total Measured Energy Expenditure

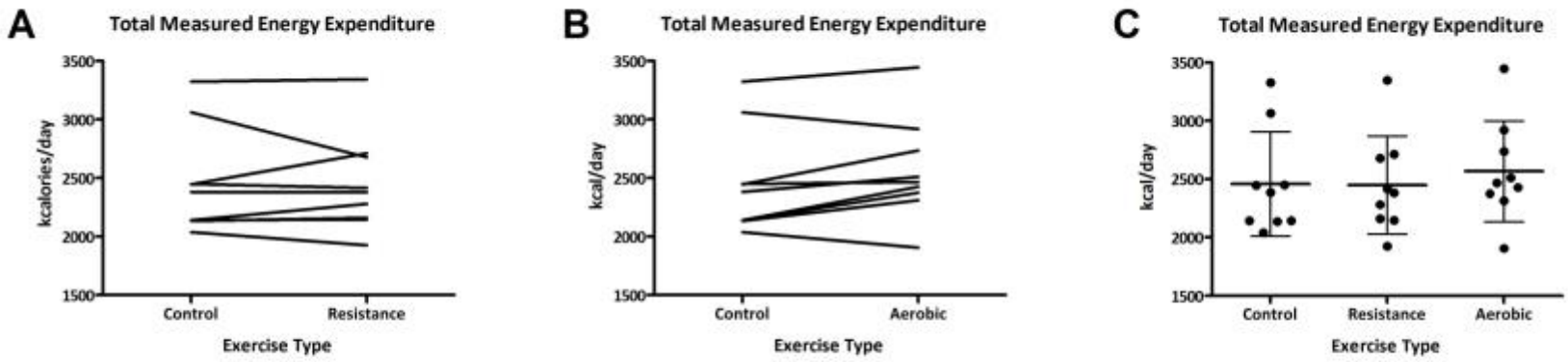

FIGURE 7. Mean total measured energy expenditure (A) control and resistance w eeks and (B) control and aerobic w eeks. Mean ± SD total estimated energy expenditure in (C) control, resistance, and aerobic w eeks. For (C), the center horizontal line represents the mean and the top and bottom represent the standard deviation.
*significant at $p<0.05$

Carbohydrate Estimation Accuracy for OCTRI-Provided Meals

The participant's carbohydrate estimate of the OCTRI-provided meal subtracted from the actual carbohydrate content was used to determine each participant's carbohydrate estimation accuracy. Participants generally underestimated the OCTRI-provided meal by an average of 28±11 g, with underestimations ranging from -10 to -45 g (Table 9). The participants were divided into two groups – "Good" and "Poor" – using an order rank and dividing them at the 50th percentile (Tables 9 and 10). "Good" estimators estimated carbohydrate content within 25 g, with "Poor" estimators exceeding a 25 g difference. The average difference between the participant's carbohydrate estimation and the food photography analysis of all documented meals was also determined, -3±3 g (Table 9). The Pearson's Correlation Coefficient between the OCTRI carbohydrate estimations and the carbohydrate estimations for all of the meals is 0.37.

The amount of time spent in the euglycemia did not differ between the "Good" estimators and the "Poor" estimators based on OCTRI-provided meals (Table 11).

Table 9. Difference Between Actual and Participant Estimated Carbohydrate Content

Participant	Estimator Type	Carbohydrate (g) Estimation Difference OCTRI Meals	Carbohydrate (g) Estimation Difference All Meals
9001	Good	-25±0 (-25, -25)	-2±8 (-27, 16)
9002	Poor	-38±12 (-48, -20)	-2±17 (-49, 44)
9003	Poor	-31±10 (-38, -18)	-4±14 (-50, 22)
9004	Poor	-45±8 (-53, -38)	-5±21 (-53, 30)
9005	Good	-25±10 (-40, -17)	-4±13 (-45, 21)
9006	Good	-17±9 (-29, -11)	2±13 (-29, 49)
9007	Good	-19±5 (-26, -17)	-1±6 (-26, 16)
9008	Poor	-30±15 (-43, -13)	-3±13 (-63, 30)
9009	Good	-10±15 (-30, 6)	-6±12 (-44, 19)
9010	Poor	-38±9 (-51, -33)	-9±16 (-51, 28)
Mean ± SD (Min, Max)		-28±11 (-45, -10)	-3±3 (-9, 2)

Table 10. Difference Between Actual and Participant Estimated Carbohydrate Content by Group

	"Good" OCTRI Carbohydrate (g) Estimation Difference	**"Poor" OCTRI Carbohydrate (g) Estimation Difference**
	-25±0 (-25, -25)	-38±12 (-48, -20)
	-25±10 (-40, -17)	-31±10 (-38, -18)
	-17±9 (-29, -11)	-45±8 (-53, -38)
	-19±5 (-26, -17)	-30±15 (-43, -13
	-10±15 (-30, 6)	-38±9 (-51, -33)
Mean ± SD	-19±6	-36±6

Table 11. Percent of Time Spent in Euglycemia Between "Good" and "Poor" Estimators for OCTRI-Provided Meals

Carbohydrate Estimator Type	**Euglycemia (70-180 mg/dL)**
Good	59 ± 15
Poor	64 ± 16

*No significant differences

Nutrient Estimation from Photograph Analysis

To determine the consistency of nutrient estimation from participant-provided food photographs, five meals or snacks were randomly selected for reanalysis (Table 12). The first macronutrient and kcal analysis correlated with the reanalysis with Pearson's Correlation Coefficients greater than 0.98 for all macronutrients and kcals (Table 13). Additionally, a different analyzer estimated macronutrient and kcal content of these same five meals, which

also correlated strongly with the first analyzer's estimations with Pearson's correlation coefficients ranging from 0.76 to 0.89 (Table 14).

Table 12. Randomly Selected Meals or Snacks for Reanalysis

Participant	Week Type	Food Notes	Provided Photograph
9001	Resistance	Harvest Snaps	
9002	Aerobic	Arby's French Dip and Swiss a jus, Snack Curly Fries	
9003	Control	Kirkland's Trail Mix	
9006	Control	Hamburger Bun with Cheese	
9010	Aerobic	Frozen Yogurt, Kiwi, Peanut Butter Chips, Butterfinger	

Table 13. First and Second Macronutrient and Kcalorie Analysis

	Fat (g)	Carbohydrate (g)	Protein (g)	Kcalories
Harvest Snaps 1	6	16	5	138
Harvest Snaps 2	6	16	5	138
Arby's 1	36	79	38	792
Arby's 2	36	79	38	792
Trail Mix 1	25	30	13	395
Trail Mix 2	24	28	12	376
Hamburger Bun 1	14	29	14	298
Hamburger Bun 2	18	21	17	314
Frozen Yogurt 1	5	55	7	293
Frozen Yogurt 2	9	49	8	311
Pearson's Correlation Coefficient	0.99	0.99	0.99	0.998

Table 14. Macronutrient and Kcalorie Analysis by Two Different Analyzers

	Fat (g)	Carbohydrate (g)	Protein (g)	Kcalories
Harvest Snaps 1	6	16	5	138
Harvest Snaps 2	21	56	18	483
Arby's 1	36	79	38	792
Arby's 2	52	115	41	1092
Trail Mix 1	25	30	13	395
Trail Mix 2	24	28	12	374
Hamburger Bun 1	14	29	14	298
Hamburger Bun 2	20	25	32	406
Frozen Yogurt 1	5	55	7	293
Frozen Yogurt 2	11	46	5	305
Pearson's Correlation Coefficient	0.89	0.76	0.80	0.86

Chapter 5: Discussion

Calorie and Carbohydrate Intake 24-hours Post-Exercise

In one of the few studies to describe changes in free-living food intake with structured aerobic or resistance exercise, we observed that subjects with T1D increased their energy intake after exercise. However, the increase in energy differed between the two different types of exercise; subjects consumed more carbohydrate after aerobic exercise and more protein and fat after resistance training. To our knowledge, there are minimal studies that have collected free-living diet intake in relation to exercise in those with T1Ds. Many studies have determined the effect of hypoglycemia prevention with carbohydrate supplementation or have controlled diet and exercise together, but have not collected diet information on how nutrient intake changes in those with T1Ds with controlled exercise interventions[19,20,29,44,61]. Yardley et al. collected participant-reported carbohydrate intake for six hours after no exercise, 45 minutes of resistance training, and 45 minutes of aerobic exercise at 60% VO_{2max}. While there was an increasing trend in carbohydrate intake for the aerobic intervention, no significant difference in carbohydrate intake was observed for the six hours post-exercise during the control, resistance, or aerobic exercise interventions (99±50 g, 94±44 g, and 101±55 g, respectively)[62]. In contrast, we observed increased total energy intake over the 24 hours after exercise with both resistance and aerobic exercise sessions and higher carbohydrate intakes after aerobic exercise in particular. The average increase in the daily energy intake during the intervention weeks as compared to the control week (469±175 kcal during the resistance week and 623±249 kcal during the aerobic week) exceeded the average energy expended during the exercise interventions. However, when considering overall energy balance for the 24-hour period post-

exercise, the participants were on average in a reported energy deficit by 27 percent during the resistance week and 23 percent during the aerobic week, most likely related to underreporting of energy intake.

It is clear that exercise benefits glycemic control in those with T2D by lowering HbA1c, particularly in conjunction with dietary couseling[63]. However, physical exercise in those with T1D has struggled to show a clear impact on HbA1c[10,11,64-67], with resistance training trending towards an improvement in HbA1c[11,67] over aerobic exercise. We showed an increase in carbohydrate and energy intake associated with aerobic exercise, which could be offsetting the glycemic benefit from exercise. This could be part of the reason previous studies have been unable to measure an impact of aerobic exercise on HbA1c.

Carbohydrate Estimation Accuracy and Glycemic Control

A standardized post-exercise meal was provided to the participants consisting of approximately 540 calories (23 percent protein, 47 percent carbohydrate, and 30 percent fat). It was specifically designed as a mixed meal to assess the participants' ability to accurately estimate carbohydrate content. Surprisingly, the entire cohort of experienced carbohydrate counters underestimated the carbohydrate content of the meal by an average of 10 g to 45 g (group average of -28±11 g). Rhyner et al. provided six meals to 19 participants with T1D and compared their carbohydrate estimates to the actual carbohydrate content and found that the mean absolute error was 28±38 g, with a majority (61 percent) being underestimations[68]. When Brazeau et al. compared 72-hour food records of 50 participants with T1D to glucose

excursions from the participants' continuous glucose monitors, he found that 63 percent of the meals' carbohydrate content was underestimated[69]. Brazeau et al. also had a registered dietitian analyze the participants' 72-hour food records and found that the mean absolute difference between the dietitian's and participants' carbohydrate estimates was 15±8 g with a majority of the meals underestimated[69]. Our study supports that participants with T1D generally underestimate carbohydrate intake. However, while it is not known how the general public without T1D compares in their ability to estimate carbohydrate content of foods, it is generally accepted that people significantly underestimate their energy intake[70].

The mainstay of medical nutrition therapy for those with T1D is carbohydrate counting[31]. However, the efficacy of carbohydrate counting and its impact on glycemic control is still questioned, as studies have produced varying results[33]. Although, randomized controlled trials in adults that include carbohydrate counting have produced promising results. The Dose Adjustment for Normal Eating (DAFNE) randomized controlled trial and Scavone et al. both found that after intensive education courses on type 1 diabetic management including carbohydrate counting, HbA1c dropped significantly by an average of 1 percent (DAFNE) and 0.4 percent (Scavone et al.)[32,71]. The reduction in HbA1c observed by Scavone et al. was to a lesser degree than observed by in the DAFNE study, but there was also a group observed by Scavone et al. that did not receive any education and this group had no change in HbA1c[32]. Our primary assessment of glycemic control was not through HbA1c, but instead through time spent in euglycemia using continuous glucose monitors (CGM). We did not observe a statistically significant difference in time spent in euglycemia based on the participant's

carbohydrate estimation accuracy. Brazeau et al. found that inaccurate carbohydrate counting is associated with a greater degree of glucose variability and a reduced time in the euglycemic range[69]. Smart et al. found that when carbohydrate was under- or over-estimated by 20 g, participants were at higher risk of hyperglycemia or hypoglycemia, respectively[72]. Our participants had generally good glycemic control, which could mean they are experienced in carbohydrate counting and insulin management. It is also possible that we did not observe an association between the participant's ability to estimate carbohydrate and glycemic control as the standardized meal may not translate to their overall ability to estimate carbohydrate. Each participant's defined carbohydrate estimation ability based on the standardized meal correlated only weakly with the carbohydrate estimation accuracy for all of the participants' free-living meals based on nutrient estimation from the participant-provided food photographs. This inconsistency and individual variation in the participants' ability to accurately estimate carbohydrate content is one plausible reason for the standardized meal not directly translating into a glycemic control outcome. Additionally, our study had a small sample size of ten participants. Therefore, it is reasonable that the small sample size coupled with the participants' predicted abilities to estimate carbohydrate are not divergent enough to define differences in glycemic control based solely on the measure of carbohydrate estimation accuracy. Lastly, it is challenging to capture accurate estimates of carbohydrate intake in a free-living population, and errors in the estimation of nutrient intake based on their provided photographs could also prevent accurate assessment of the relationship between carbohydrate estimation accuracy and glycemic control.

Digital Photography Method for Nutrient Intake Estimation

Collecting free-living diet data has proven to be an ongoing challenge in nutrition research. Free-living diet collection methods (e.g. food frequency questionnaires, 24-hour dietary recalls, food journals, etc.) often under- or over-report specific nutrients[73]. Depending on gender, weight status, athletic status, underreporting of energy intake is estimated to be up to 38 percent[46-48]. However, it is unknown as to whether or not there is a bias associated with dietary reporting in those with T1D. Toeller et al. found good reproducibility in reported food and nutrient intake between two 3-day diet records (collected 3 weeks apart) in 216 participants with T1D[74].

We utilized a digital photography method to quantify each participant's nutrient intake. Many studies report that participants prefer using the digital method for documenting their dietary intake due to ease of use and the minimal participant burden[53,54,57,58]. However, despite ease of use, our study shows that there still appears to be limitations – similar to other diet record methods – to using this method for quantifying accurate nutrient intake estimates: 1) Remembering to document; and 2) Accuracy of nutrient estimation.

Remembering to photograph each meal or snack is a challenge for the participants. Some participants executed with precision, while others missed occasional meals or snacks. One participant had to be completely removed from the analysis due to the lack of photo documentation, which is reported to be due to forgetting to bring the study-administered phone with him when he left his home. Many participants reported forgetting to take

photographs of their food until after it was consumed. This is supported by the fact that participants would sometimes take a photograph of something other than the food consumed and include a note of what they had previously consumed. The note of what they ate would be similar to a typical food journal without the benefit of also having an actual photograph or the exact time of their food intake. Martin et al. found that text reminders individualized to the participants' meal and snack times significantly improved reporting and minimized missing data[75]. With the personalized text reminders, reported energy was underestimated by -9±30 percent as compared to doubly labeled water[75]. However, when the text reminders were not personalized to the participants' meal and snack times, reported energy was underreported to a greater degree – -34±28 percent – as compared to doubly labeled water[75]. We did not use text reminders, and it is suspected that underreporting was present. Of the nine participants that were included in the dietary analyses, there were 18 days of the 108 days recorded (17 percent) that energy intake was less than 1000 kcals. However, when comparing the glucose trends from their insulin pump data to food photo documentation on these 18 days, only half of them were missing more than one main meal. The nine days that were missing more than one main meal were removed from the analyses (8 percent of the total days were dropped). Total measured energy expenditure from the participants' accelerometers were compared to their reported energy intake to assess the degree of underreporting. This assessment indicates that the reported energy intake group mean is 68 ± 23%, 73 ± 28%, and 74 ± 28% of energy expenditure for the control, resistance, and aerobic intervention weeks. This suggests that mean underreporting ranged from 26 to 32 percent, which is consistent with the findings noted above by Martin et al. when text reminders were not utilized.

Average estimated energy intake ranged from 1605 kcal/day to 1848 kcal/day depending on the intervention week. Martin et al. estimated energy intake using the digital photography method on his participants to be 1907±536 kcal/day, though these participants did not have T1D[75]. Additionally, the EURODIAB complications study collected 3-day diet records for 1591 participants with T1D and the estimated interquartile range for energy intake was 1832 to 2764 kcal/day[76]. Ahola et al. estimated energy intake in 817 participants with T1Ds using 3-day food records, and the estimated average was 1864±502 kcal/day[77].

While all three of these studies estimated energy intake slightly over our upper-end, none of them provided energy intake on a per kilogram basis, which could provide a better estimation of comparison. Additionally, none of these studies had controlled exercise interventions included in their study design.

The second primary challenge with the digital photography method was quantifying the nutrient intake from the uploaded food photographs. To determine consistency and accuracy of nutrient estimation, five meals were randomly selected to be reanalyzed by the analyzer. Additionally, these five meals were quantified by another analyzer. Correlation between the first and second nutrient analysis were all greater than 0.98, indicating good reproducibility. The correlation of energy estimation between the two different analyzers ranged from 0.76 to 0.86, signifying strong inter-rater agreement. Martin et al. also observed strong correlations – 0.76 to 0.97 – between registered dietitians quantifying participant's free-living food

photograph documentation, again indicating strong inter-rater agreement[53]. One of the challenges with estimating nutrients from photographs is determining portion size. Martin et al. solved this by creating a database of photographs of foods frequently consumed at standard portion sizes for the analyzers to reference to assist in their portion size estimates[53]. Additionally, the participants included a reference card in the photographs for perspective[53]. We provided our participants with a six-inch ruler to include in their photographs to assist the analyzer with determining portion sizes. However, the ruler was not always included in the photographs, which made assessment of portion size challenging. Sometimes the photos were unclear and it was hard to determine the food item if the participant did not provide a text message identifying the food. The digital photography method takes the burden off of the participant to estimate portion size, which then falls on the analyzer. Martin et al. showed that energy intake could be estimated within ten percent of actual energy intake using this method, indicating a strong case for utilization of this method for collecting free-living diet data[53]. We showed good reproducibility of quantifying nutrient intake from the photographs, and were able to use the data to minimize the effect of inaccurate estimations of portion sizes. Reminders to document digital food intake photos and diligence by study staff to minimize missed photos can substantially decrease underreporting.

Study Strengths and Limitations

The study design – a randomized, crossover trial – is a strength of this study. However, the sample size was small and limited to ten participants. Another strength is the ease of food intake documentation for the participants. It negated the need for the participants to estimate

portion size, and was a relatively quick and easy process. However, the challenges associated with quantifying the food photographs was a limitation, as a few photographs were unclear and many did not include the ruler for reference size to adequately estimate portion size. Variability in the nutrient analysis was measured by randomly selected food photographs to reanalyze by both the same analyzer and a different analyzer. Both inter and intra-observer analysis strongly correlated to the original nutrient quantification. Underreported energy intake by the participants by missing photo documentation of their meals was also a limitation. The analysis took into consideration the presence of underreporting and eliminated underreported days on a methodological basis, strengthening the conclusions from nutrient intake. Lastly, this is the first study of our knowledge that has collected free-living dietary data in those with T1D in the context of controlled exercise interventions. Larger randomized controlled trials need to be completed to see more definite effects between free-living diet, glucose control, and exercise interventions in those with T1D.

In conclusion, individuals with T1D tend to underestimate their carbohydrate intake. It is important to further understand the degree of underreporting for individualized care in terms of insulin dosing. Aerobic exercise leads to chronic intake of hypoglycemic treatments. This in turn leads to an increase in carbohydrate and energy intake, which potentially offsets the glycemic benefit of exercise in those with T1D. The digital photography method of collecting diet data is a viable option, but careful attention to participant training and follow-up is needed to ensure quality photographs (e.g. inclusion of item for reference of size in photographs and photographs before and after meal intake) and adequate reporting.

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Appendix

PROTOCOL TITLE: A randomized, three-way, cross-over study to assess the impact of nocturnal hypoglycemia on sleep in patients with Type 1 diabetes.

STUDY SITE: Oregon Health Science University
3181 SW Sam Jackson Park Rd
Portland, OR 97239

FUNDING: M.J. Murdock Charitable Trust

PRINCIPAL INVESTIGATORS: Peter Jacobs PhD

CO-INVESTIGATORS: Jessica R. Castle MD
Joseph El Youssef MBBS

Background:
Growing evidence provided by many observational studies has established a strong link between decreased sleep duration and poor glucoregulation. Sleep deprivation and poor sleep quality induce insulin resistance and decrease glucose tolerance in healthy individuals. However, the influence of poor sleep quality on glycemic control of patients with Type 1 diabetes mellitus (T1DM) is unknown. Persistent sleep deprivation among patients with T1DM has been reported, and this sleep loss can be attributed in part to nocturnal hypoglycemia. Nocturnal iatrogenic hypoglycemia is a limitation of current intensive insulin therapies. Although severe hypoglycemia is associated with adverse events such as seizures and death, less severe nocturnal hypoglycemia has been linked to broad range of adverse consequences [1], both acutely [2,3] and long term [4]. Hypoglycemia stimulates the sympathetic nervous system as a stress response, leading to the stimulation of the hypothalamic–pituitary–adrenal axis (HPA). This results in a counter regulatory hormone cascade, which elicits an excessive cortisol secretion, which is known to cause sleep disturbance and could impair glucose homeostasis after the hypoglycemic event [5]. The hyperinsulinemia in T1DM patients promotes HPA hyperactivity as well [6], which is also associated with impaired sleep quality by leading to sleep fragmentation, decreased slow wave sleep and shortened sleep duration [7]. Sleep disturbances due to nocturnal hypoglycemia can exacerbate HPA axis dysfunction, adversely affecting the sleep–wake cycle. Another impact of poor sleep is the deterioration on insulin sensitivity the following day, it has been shown that reduction in sleep can reduce insulin sensitivity by as much as 20% [8,9] and this further exacerbates the cycle of poor glycemic control. Brod et al.[10,11] reported on a multinational survey of the consequences of non-severe nocturnal hypoglycemia, and found that among the participants who awoke to treat a hypoglycemic event, the average time to return to sleep was over an hour, and some did not return to sleep at all that night.

Regular exercise has been shown to improve glycemic control, reduce cardiovascular risk factors, lower insulin requirements, improve lipid profiles, decrease cardiovascular disease risk, improve endothelial function, delay onset and/or progression of peripheral neuropathy and increase self-reported quality of life in patients with T1DM [12]. However, the risk of hypoglycemia increases considerably during and after exercise [13]. Increased glucose utilization occurs during exercise and increased insulin sensitivity occurs both during and after exercise [14,15]. As a result, many patients with T1DM avoid physical activity, in order to avoid the unpleasant symptoms associated with hypoglycemia. A handful of recent short exercise studies indicated that anaerobic forms of exercise (weight lifting, sprinting and so forth) may reduce this risk [16, 17].

A better understanding of the antecedents of nocturnal hypoglycemia (iatrogenic, exercise, diet, etc.), its impact on sleep and the effect on glycemic control the following day could both improve routine clinical diabetes management and help inform the ongoing development of closed-loop insulin delivery systems.

The pilot study described within this protocol is designed to obtain and analyze data listed below:

- Subcutaneous blood glucose data from the continuous glucose monitor (CGM)
- Capillary blood glucose data from the blood glucose meter
- Daily insulin dosage data from the insulin pump
- Daily activity and sleep data from the activity monitor containing a 3-axis accelerometer and an ambient light sensor. The daily activity patterns will be analyzed in the context of location using the location data from the phone.
- Daily food intake using a photographic diet diary using an app on the phone.

The goal of the study is to understand the impact of nocturnal hypoglycemia on sleep.

Specific Objectives:
Primary Objectives:

- To measure the sleep patterns of patients with T1DM during weeks that include exercise events as compared to a week without exercise.
- To measure the changes in insulin requirements in patients with T1DM during weeks that include exercise events as compared to a week without exercise.

Secondary Objective:

- To measure the changes to insulin sensitivity during the nights with sleep loss compared with insulin sensitivity during nights with undisturbed sleep.

Study Hypothesis:
We propose that the nocturnal hypoglycemia causes loss of sleep in patients with T1DM after moderate exercise as opposed to days with no explicit exercise.

Endpoints
Primary Endpoints: (Time duration: From start of exercise till morning - 7am)

- Percent of time with sensed glucose <70 mg/dl
- Percent of time with sensed glucose between 70 – 180 mg/dl
- Loss of sleep as measured by time spent awake after sleep onset (WASO)

Secondary Endpoints: (Time duration: Entire study duration)

- Glycemic variability during the different treatment weeks
- Duration of sleep in patients with T1DM
- Sleep quality metrics such as time in bed (TIB), sleep start, sleep duration, sleep onset latency (SOL), total sleep time (TST), sleep efficiency (SE), number of wake bouts (# WB), mean wake bout time (MWBT), number of sleep bouts (# SB) and mean sleep bout time (MSBT).
- Number of carbohydrate treatments to treat hypoglycemia
- Daily carbohydrate intake
- Daily insulin intake
- Daily activity level
- Percent of time with sensed glucose <50 mg/dl
- Percent of time with sensed glucose >180 mg/dl

- Percent of time of capillary blood glucose (CBG) <70 mg/dl. Time with CBG <70 mg/dl defined as from the time the CBG is <70 mg/dl until the next CBG that is ≥70 mg/dl. Each time interval is summed and divided by the total time interval and expressed as a percentage.
- Percent of time of CBG between 70 – 180 mg/dl.
- Percent of time of CBG <50 mg/dl
- Percent of time of CBG>180 mg/dl

Study Type
This is a single center, randomized, three treatment, open, crossover trial designed to compare the sleep loss resulting from hypoglycemia during the weeks with days of aerobic exercise, resistance training and no explicit activity.

Study Population
Study population will be adults with type 1 diabetes, ages 21 – 45 years of age. Older subjects are excluded due to higher risk of unrecognized coronary artery disease. Younger subjects are excluded as it is appropriate to assess safety first in the adult population. 14 subjects will be recruited to participate in studies.

Power Analysis
A Paired Means Power Analysis was used to carry out a sample size power analysis. A total sample size of 14 achieves 95% power to detect a mean of paired differences of 30 minutes in sleep loss. This is with an estimated standard deviation of differences of 25 and with a significance level (alpha) of 0.05 using a two-sided paired t-test comparing sleep loss during the weeks of exercise interventions with the week without any explicit exercise.

Protocol Summary:

The study duration is 4 weeks long, during which subjects will undergo a 1 week run-in period followed by 3 randomized weeks of observational study. During the 1 week run-in period, subjects will familiarize themselves with the CGM and the other data collection procedures. Following the run-in week, the subject will be randomized to a specific order of observation weeks. The three observation weeks are a resistance training week, an aerobic exercise week and a control week with no explicit exercise. During the observation weeks, there will be 4 interventions planned, two during both the aerobic exercise and the resistance training week. See Schematic below for details. During both the aerobic exercise week intervention visits, subjects will exercise for ~45 minutes on a treadmill and during the resistance training week, subjects will perform strength training exercises for 1-3 sets per exercise at a weight that can be lifted for 8–12 repetitions (~60-80% of 1-repetition max). The duration of the resistance training period is expected to be ~45min. Subjects will continue to perform daily activities during each of the weeks.

Schematic of Study

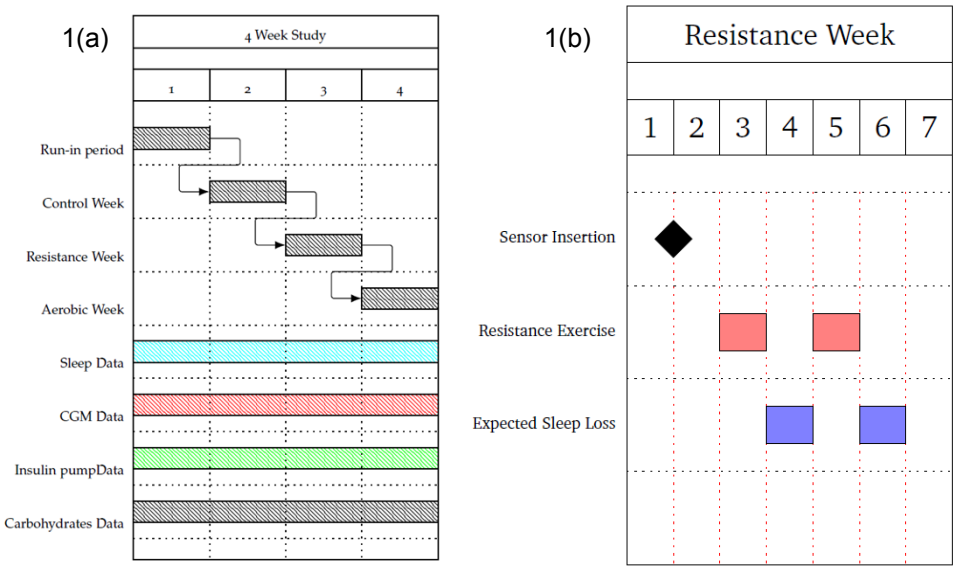


Figure 1(a) is an example of the proposed timeline for the study in which the control week with no exercise is followed by a week during which monitored resistance training is performed for 2 days of the week as shown in figure 1(b). Both the resistance training and aerobic exercise weeks follow a similar time course, the subject performs the exercise visits on the 3rd and 5th day of the week, with at least 5 days between the next set of exercise visits.

During each week, the subject will wear one subcutaneous Dexcom™ G4 or Dexcom™ G4 Share continuous glucose monitoring (CGM) system, one activity monitor- ActiGraph wGT3X-BT or ActiGraph GT9X, one insulin pump (subject's own pump) and one Samsung Galaxy S4 phone loaded with two applications- meal memory and moves. The CGM system will provide sensed glucose data every 5 minutes. The CGM data will be blinded to the patient to prevent any abrupt changes in behavior. The accuracy of the sensed data will be obtained by reference measurements of capillary blood glucose. The activity monitor will be secured on the dominant wrist and uses an accelerometer to collect movement data at a high frequency (80Hz). The activity monitor measures both motion and ambient light, this data would be used to determine the various sleep quality measures. The subject's insulin dosage information from the pump will be downloaded for data analysis purposes. The subject's daily meal intake (photographic log and note diary) and daily movement pattern information will be downloaded from the phone. During the 4 exercise intervention visits, subject's heart rate, accelerometry information from the torso and oxygen consumption measured breath by breath may be collected for data analysis purposes.

In order to try to minimize risks, all exercise interventions will be conducted by trained research study personnel. An on-call investigator will be available at all times during the intervention visits. The study investigators also retain the authority to modify any aspects of the protocol at his/her discretion if he/she believes the subject's safety is a concern.

Subject Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female subjects 21 to 45 years of age.
3. Physically active on a regular basis, i.e. at least 3 days of physical activity per week.

4. Physically willing and able to perform 45 min of exercise (as determined by the investigator after reviewing the subjects activity level)
5. Current use of an insulin pump.
6. Willingness to follow all study procedures, including attending all clinic visits.
7. Willingness to sign informed consent and HIPAA documents.

Exclusion Criteria:

1. Female of childbearing potential who is pregnant or intending to become pregnant or breast-feeding, or is not using adequate contraceptive methods. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
2. Any cardiovascular disease, defined as a clinically significant EKG abnormality at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.
3. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as report by the OHSU laboratory).
4. Impaired liver function, defined as AST or ALT ≥2.5 times upper limit of normal, according to OHSU laboratory reference ranges.
5. Hematocrit of less than or equal to 34%.
6. History of severe hypoglycemia during the past 12 months prior to screening visit or hypoglycemia unawareness as judged by the investigator.
7. Adrenal insufficiency.
8. Any active infection.
9. Known or suspected abuse of alcohol, narcotics, or illicit drugs (except marijuana use).
10. Seizure disorder.
11. Active foot ulceration.
12. Severe peripheral arterial disease characterized by ischemic rest pain or severe claudication.
13. Major surgical operation within 30 days prior to screening.
14. Use of an investigational drug within 30 days prior to screening.
15. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
16. Bleeding disorder, treatment with warfarin, or platelet count below 50,000.
17. Insulin resistance requiring more than 200 units per day.
18. Need for uninterrupted treatment with acetaminophen.
19. Current administration of oral or parenteral corticosteroids.
20. Any life threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the past 5 years prior to screening (except basal and squamous cell skin cancer).
21. C peptide level of ≥0.5 ng/ml
22. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
23. Beta blockers or non-dihydropyridine calcium channel blockers.
24. A positive response to any of the questions from the Physical Activity Readiness Questionnaire.
25. Any chest discomfort with physical activity, including pain or pressure, or other types of discomfort.
26. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the subject's safety or compliance with the protocol.

Subject Recruiting:
Subjects will be recruited from OHSU clinics, from flyers to be posted in approved places at OHSU, or from the OHSU Subject Recruitment website. Records from OHSU Harold Schnitzer Diabetes Clinic patients may be screened to find potential subjects. Subjects will also be recruited from a list of subjects who participated in past OHSU studies, past studies involving Drs. Castle or El Youssef and from the OHSU diabetes research registry.

Non-English speaking subjects will not be recruited since this protocol will require use of devices and mobile software (Dexcom G4 Share, moves and meal memory) that do not have non-english versions available yet for users.

Up to 50 subjects may be screened in this study. Goal enrollment is 14 subjects, two blocks of seven patients. Up to four subjects will be replaced if needed, with a total enrollment of up to 18 subjects.

Withdrawal Criteria
The subject may withdraw at will at any time or at the discretion of the Investigator.

A subject must be withdrawn if the following applies:
1. Hypoglycemia during the treatment period posing a safety problem as judged by the investigator.
2. Hyperglycemia during the treatment period posing a safety problem as judged by the investigator.
3. Protocol deviation having influence on efficacy or safety data as judged by the Investigator.
4. Substantial and repeated non-compliance with trial procedures.
5. Pregnancy.
6. Intention of becoming pregnant.

Visit Procedures
Screening (Visit 1)
Screening will take place within 12 weeks prior to the first sensor insertion and training visit (Visit 2). All screening visits, will take place at OHSU's Oregon Clinical Translational Research Institute (OCTRI) or at the Harold Schnitzer Diabetes Health Center. Upon arrival and prior to any procedures, the consent form will be signed. A copy of the consent/authorization form will be given to the subject. The original will be kept for the source document.

Study personnel will review medical history, and medications. Height, weight, pulse, waist and hip circumference will be measured (mean of 3 measures) in a standing position to the nearest 0.1 cm using a non-stretchable tape over the unclothed abdomen at the top of the iliac crest and over the underwear at the largest circumference around buttocks, respectively and blood pressure will also be obtained. A study investigator will perform a physical examination, excluding breast and pelvic exams. Females of childbearing potential will take a urine pregnancy test, which must be negative to participate. A venous blood sample will be taken for the following tests: hemoglobin A1C, complete blood count, complete metabolic set (including creatinine, liver set, and electrolytes), and c-peptide. An EKG will be performed. A study investigator will assess inclusion/exclusion criteria and review the subject's medical record for clarification as needed. A three-digit subject ID number will be assigned to the subject.

Subjects may undergo VO2max testing for cardiorespiratory fitness and the DEXA scan at the end of this screening visit if all inclusion criteria are met, and no exclusion criteria are met, with the exception of blood test results, which may not be immediately available. Research study personnel will be present during the VO2max testing for cardiorespiratory fitness. Research study personnel will assist the subject in locating the different labs where the tests are being performed. Additional CBG samples will be taken

immediately before and after completion of the VO2max test. Subjects will be given 15-20 grams of carbohydrates for CBG values of <70 mg/dL at any point during the screening visit. CBG values will be reviewed by an investigator and subjects will be given juice and the VO2max test will be delayed by approximately 1 hour for CBG values of <80 mg/dL. Heart rate and accelerometry data may be optionally collected from the subject during the screening visit.

VO2max testing for cardiorespiratory fitness
VO2max testing will take place at the Human Performance Lab, which is located within OHSU and is attached to the main hospital. A code cart is on site within the Human Performance Lab and a code team is available by page at all times. Subjects will be asked to fast before the screening visit for 3 hours. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded after consenting. Prior to measurement of any blood samples, the meter will undergo quality control testing with two different glucose levels, one high and one low, and both values must fall within the accepted range for a meter to be used. After the CBG is obtained, the study investigator may adjust the subject's basal insulin rate as necessary in preparation for VO2max testing to avoid hypoglycemia. This testing is expected to last about 30 min.

DEXA for Bone Mineral Density, Body Composition and Body Fat Distribution:
Whole body and regional skeletal bone mineral density/content, whole body composition (total lean and fat mass and skeletal mineral content) and body fat distribution will be measured using Dual Energy X-ray Absorptiometry (DEXA) scans. A trained technician in OHSU's Body Energy and Composition Core or OHSU School of Nursing Health and Human Performance Lab will perform DEXA scans. Measurements will be made using a Lunar/GE iDXA Densitometer (GE Healthcare, Wauwatosa, WI) or Hologic Discovery WI and are expected to take 15-30 minutes. Actual scan time is less than 10 minutes.

Study procedures training visit and sensor insertion visit (Visit 2)
After arrival at the OHSU School of nursing or OHSU OCTRI or Harold Schnitzer Diabetes Health Center clinic, women of childbearing potential will receive a urine pregnancy test. This test must be negative before further participation is allowed.

Subjects will undergo the one repetition maximum (1-RM) to accurately assess the maximal muscle strength during this visit.

Muscle strength (1-RM):
Muscle strength testing will take place at the Human Performance Lab, which is located within OHSU School of Nursing building. Three distinct exercises, leg press, bench press and seated row will be evaluated to ascertain the maximal muscle strength of the subject. Lower extremity muscle strength will be measured with the 1-repetition maximum (1-RM) for leg press and isokinetic dynamometry of the lower extremity. Upper body chest muscle strength will be measured with 1-RM, for the bench press. Back and shoulder muscle strength including the erector spinae, middle and lower trapezius, rhomboids, latissimus dorsi, teres major and minor, posterior deltoid and the infraspinatus will be measured with 1-RM for the seated row. The 1-RM test is a safe and effective means of evaluating strength, even in populations that have never lifted weights before. The 1-RM is the most commonly used technique for measuring maximal strength in adult populations. The 1-RM test will be conducted according to the American College of Sports Medicine protocols by trained personnel. After the CBG is obtained, the study investigator may adjust the subject's basal insulin rate as necessary in preparation for 1-RM testing to avoid hypoglycemia or hyperglycemia. If CBG value is > 300 mg/dl, the subject may be managed at the discretion of the investigator. Serum ketones will also be checked. If serum ketones are ≥ 0.6 mM, the test may be halted and insulin therapy will be guided by the onsite investigator. Subjects will be given 15-20 grams of carbohydrates for CBG values of <70 mg/dL at any point during the visit.

Each subject will be fitted with one Dexcom™ G4 or Dexcom™ G4 Share CGM system. The wire glucose sensor is sterile and commercially available from Dexcom™ and will be used for single use only as directed by the manufacturer. The sensor will be inserted into the subcutaneous tissue of the abdomen or flank by study personnel after appropriate preparation of the abdominal skin as per the manufacturer's directions. The sensor expires after 7 days of use, the subject will be trained by the study personnel on how to the use the sensor insertion device and also how to insert the wire glucose sensor. The subject will be trained on how to use and calibrate the CGM system. The CGM system will be calibrated at home according to the manufacturer's directions. Subjects will be clearly instructed to use capillary glucose levels, not sensed glucose values, for the purpose of managing their diabetes at home. The sensed glucose values will be blinded to the subject, the subject will not know these values to manage their diabetes at home. The CGM alarms will be activated: 55mg/dL for hypoglycemia and 300mg/dL for hyperglycemia. Subjects will be given a Contour Next meter for measuring their capillary blood glucose in order to calibrate the Dexcom sensor prior to the study. Subjects will be instructed to change the wire glucose sensor in a sterile fashion weekly and follow the instructions available from the manufacturer Dexcom™ on the proper insertion of the wire glucose sensor. Subject may be given the documentation provided by the manufacturer Dexcom™ on the proper use of the glucose sensor and the sensor insertion device. Subjects will be instructed to discontinue the use of acetaminophen for the duration of the study.

The subject will also be asked to check his/her CBG before driving to the clinic and to bring a snack in the car in case hypoglycemia does occur (in which case, the subject must park and treat the hypoglycemia).

During this visit, the subject will also complete a training course on how to photographically record the diet diary, how to use the activity device, how the keep the devices charged and understand the proper use of the devices for the duration of the study. The first week of the study will be a run in period, to acclimatize the subject with the various devices and the procedures the subject is expected to perform. The subject will need to demonstrate competency in operating the devices before beginning the research study. During this visit, the subject may be asked to fill the questionnaires located in the appendix A of this protocol. The duration of this study visit is expected to be approximately 2 hours.

Study procedures follow-up (Visit 3)
The study procedures follow-up visit will be conducted by phone call to the subject at the phone number obtained during screening, to determine the general status of the subject after the study procedures. The subject will be contacted 48 hours (+/- 24 hours) after visit 2 of the study takes place.

2 Hour Intervention Visits (Visits 4, 6, 8 & 10)
These study visits will occur approximately 1 week after the sensor insertion visit (Visit 2). There are 2 visits during both the resistance training week and aerobic exercise weeks. After the last 2 hour intervention visit (either week), a washout period will be 5 days from the day of admission to the research center until the start of the next admission. Subjects will be asked to avoid vigorous activity within the 24 hours prior to all intervention visits. The subject will arrive at the exercise facilities at approximately 4pm. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded. Prior to measurement of any blood samples, each meter will undergo quality control testing with two different glucose levels, one high and one low, and both values must fall within the accepted range for a meter to be used. A new meter will be used for each subject and all CBG testing will be done on a Contour Next glucose meter. When they arrive, subjects will be given 15-20 grams of oral carbohydrate if the CBG reading is less than 70 mg/dl. CBG values > 300 mg/dl will be managed at the discretion of the investigator with a correction bolus. Serum ketones will also be checked. If serum ketones are ≥ 0.6 mM, the study will be halted and insulin therapy will be guided by the on-call investigator. At the start of each

intervention visit, subjects may be fitted with an accelerometer, heart rate monitor and a mobile indirect calorimetry system.

Aerobic Exercise Week visits
Subjects will exercise at a fixed intensity level to a target heart rate (±10%) based on the heart rate achieved at 60% of their VO_{2max} determined at screening. This protocol will allow the exercise to be graded according to each participant's relative capacity. The speed and grade of the treadmill will be adjusted by trained research personnel with a goal of keeping participants within their target heart rate range for the entire 45 minutes. Study personnel will monitor the heart rate and the sensed glucose of the subject during the exercise. Each exercise session will be followed by 60 min of monitored resting recovery.

Resistance Training Week Visits:
Subjects will perform multiple-joint exercises with slow to moderate lifting velocity, for 1-3 sets per exercise at a weight that can be lifted for 8–12 repetitions (~60-80% of 1-repetition max). The exercises may include leg press, bench press, leg extension, leg flexion and seated row. Subjects will perform the exercises through the full range of motion. Between each set of repetitions, there would be a 2 minute rest period. The duration of the exercise testing would be approximately 45 minutes.
Study personnel will monitor the heart rate and the sensed glucose of the subject during the exercise. Each exercise session will be followed by 60 min of monitored resting recovery.

During the exercise period, there will be defined rules for stopping exercise, including:

1. If the subject feels unwell,
2. If the subject develops hypoglycemic symptoms, such as excessive sweating, shaking/tremors, palpitations, feelings of dread or panic, light-headedness, nausea, difficulty concentrating or the like.
3. If the subject develops chest pain/pressure,
4. If the subject develops undue shortness of breath (SOB),
5. Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
6. If the maximum heart rate of the subject (MHR) is exceeded,
7. For patient preference.

If the exercise is stopped prematurely, the duration of exercise will be noted by the study personnel and if the subject is deemed safe to participate in future visits, the exercise will be stopped after that same time duration for subsequent visits. If capillary blood glucose is < 70 mg/dl at any point during the exercise period, the subject will treat with carbohydrates and delay completion of exercise until blood glucose rises above this level.

Discharge Procedures
The accelerometer, heart rate monitor and the indirect calorimetry device will be removed from the subject. A capillary blood glucose value will be taken immediately prior to discharging the subject. Subjects will be given oral carbohydrate for values below 85 mg/dl, and will be given an insulin bolus if deemed appropriate by the investigator for values above 300 mg/dl. The research on-call physician may consult with the subject regarding appropriate insulin dosing for the remainder of the day. Subjects may also be given a predetermined chosen meal after each exercise visit.

Study intervention follow-up (Visits 5, 7, 9 &11)

The study intervention follow-up visit will be conducted by phone call to the subject at the phone number obtained during screening, to determine the general status of the subject. The subject will be contacted the next day after each exercise intervention of the study takes place. If necessary, an on-call investigator will be notified and will consult with the subject via phone or in person.

Study completion visit (Visit 12)
Subjects will return to OHSU OCTRI or Harold Schnitzer Diabetes Health Center clinic after the completion of the 3 week study period. Subjects will return all the sensors, the smartphone and may complete a questionnaire about the experience. Subject's insulin pump data will be downloaded at this visit.

Cleaning and Disinfecting
All devices will be cleaned and disinfected between subjects. If the heart rate monitor is a chest strap, it will be disinfected through OHSU Sterile Processing where they hand wash the straps and use CIDEX OPA to sterilize. The belt/carrier, smartphone, Dexcom G4 or G4 Share receiver and transmitter, the heart rate device, and activity monitor device watch bands are cleaned by study personnel. Study personnel who are disinfecting units will wash hands thoroughly and wear gloves. All items will undergo intermediate-level disinfection using SANI-CLOTH AF3 Germicidal disposable wipes. The disinfectant will be applied and allowed to air dry. Study personnel will dispose of gloves as biohazard waste and wash their hands immediately after completing disinfection. After disinfection, when the units are completely dry, they will be placed in a sealed bag labeled with the cleaning method, date and initials of study personnel that performed the disinfection.

Confidentiality and Protection of Human Subjects
RISKS and BENEFITS
Risks: The risks of the protocol procedures are considered minor. It should be noted that an investigator skilled in the treatment of diabetes mellitus will be immediately available during intervention visits.

Risks from exercise include falls, sprains, bruises, very low risk of bone fractures and head trauma. The likelihood of significant harm is quite low. In order to try to minimize risks, all testing will be conducted by trained personnel. Precautions to make the exercises as safe as possible have been taken.

Benefits: The subject may not directly benefit from being in this study; however, their participation may help to advance automated insulin and glucagon delivery technology.

Monitoring Entity:
Monitoring is described in a separate Data Safety Monitoring Plan uploaded as part of this submission.

Data Collection:
Subject privacy will be protected by using a three digit identifying number to code study documents. Study staff will record data required by the protocol onto the Case Report Forms (CRF). Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data repository housed at Oregon Health Science University and administered by the Oregon Clinical and Translational Research Institute (OCTRI). Investigators and research coordinator will verify that the procedures are conducted according to the approved protocol. All paper source documents will be kept in a locked cabinet for a minimum of five years. Original, completed CRF's will be kept with the PI in a designated repository. All data from CRF's will subsequently be entered into the authorized electronic REDCAP database.
Recording of Data:

Investigators and staff will record data collected during the clinical trial on the CRF's. Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data repository housed at Oregon Health Science University and administered by the Oregon Clinical and Translational Research Institute (OCTRI). The REDCAP CRFs will include:

1. Screening form
2. Sensor Insertion Visit form
3. 2 hour intervention visit
4. Follow up Telephone Update form
5. Adverse Event form
6. Serious Adverse form
7. Concomitant Medications
8. Note to File

The Principal Investigator may authorize other personnel to make entries in the CRF.

Monitoring Procedures:

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and amendments and clarifications adopted by the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, South Africa, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), and 59th (Seoul, 2008) General Assemblies. The investigator will ensure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies. Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. Unanticipated problems will be detected by reviewing descriptions of known or foreseeable adverse events and risks in the IRB-approved research protocol and the current IRB approved consent form, any underlying disease or conditions of the subject experiencing the adverse event, and a careful assessment of whether the adverse event is related or possibly related to the subject's participation in the study.

Triggers for reporting unanticipated problems are seizure, hospitalization, death or any other occurrence considered serious by the PI. If studies in two subjects are stopped for severe hypoglycemia or severe hyperglycemia, then the entire study will be halted. In addition, if there is any unexpected event such as death or patient hospitalization, the studies will be stopped until the root cause is evaluated.

Any adverse event and/or unanticipated problem (UP) will be reported to the PI and medical monitor immediately by one of the investigators. One of the investigators will always be on-call during the studies and will write up a description of the adverse event/unanticipated problem. All unanticipated problems will be reported to the IRB within five calendar days. A summary of all UP's and adverse events will be submitted with the continuing review.

Confidentiality Procedures:

To protect confidentiality, standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Upon enrollment, subjects will be assigned with a three-digit code that will be used instead of their

name, medical record number or other personally identifying information. The key associating the code and the subjects personnal identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive in a limited access folder.

Electronic files for data analysis will contain only the subject code. Access to data/specimens is restricted to study personnel and requires OHSU ID/password authentication. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. Electronic data is stored on restricted drives on the OHSU network or stored on encrypted computers as well as on the web-accessible REDCap database housed on an OHSU secure server. User passwords will be changed every 3 months and a firewall will be enabled at all times. After the study, source documents will be maintained at the participating clinical center (or offsite record storage facilities) 2 years after a marketing application is approved for our group's artificial pancreas/decision support device since the data from this study will be included in future software revisions or discontinuance of pursuit of marketing approval. At the end of the study, an electronic copy of the database will be provided on a CD for long-term storage under lock.

Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

YES	NO		
☐	☐	1.	Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?

If you answered:

YES to one or more questions

Talk to your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want – as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- Start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- Take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

Delay becoming much more active:

- If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- If you are or may be pregnant – talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed use of the PAR-Q: Reprinted from ACSM's Health/Fitness Facility Standards and Guidelines, 1997 by American College of Sports Medicine

Devices

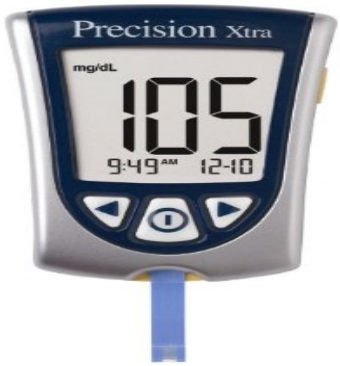
ActiGraph wGT3X-BT

Dexcom Continuous Glucose Monitoring System which includes Sensor, Sensor Receiver and Sensor Transmitter

Samsung Galaxy S4 Smart phone

Contour Next EZ Blood Glucose Meter

Abbott Precision Xtra Meter



Appendix A : Questionnaires

Table 1—*Survey items used to categorize aware or having reduced awareness of hypoglycemia in subjects*

1) Check the category that best describes you: (check one only)
_____ I always have symptoms when my blood sugar is low (A)
_____ I sometimes have symptoms when my blood sugar is low (R)
_____ I no longer have symptoms when my blood sugar is low (R)

2) Have you lost some of the symptoms that used to occur when your blood sugar was low?
_____ yes (R) _____ no (A)

3) In the past six months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)
_____ Never (A) _____ Once or twice (R) _____ Every other month (R)
_____ Once a month (R) _____ More than once a month (R)

4) In the past year how often have you had severe hypoglycemic episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)
_____ Never (A) _____ 1 time (R) _____ 2 times (R) _____ 3 times (R)
_____ 5 times (R) _____ 6 times (R) _____ 7 times (R) _____ 8 times (R)
_____ 9 times (R) _____ 10 times (R) _____ 11 times (R)
_____ 12 or more times (U)

5) How often in the last month have you had readings <70 mg/dl with symptoms?
___ Never ___ 1 to 3 times ___ 1 time/week ___ 2 to 3 times/week ___ 4 to 5 times/week
___ Almost daily

6) How often in the last month have you had readings <70 mg/dl without any symptoms?
_____ Never _____ 1 to 3 times _____ 1 time/week _____ 2 to 3 times/week
_____ 4 to 5 times/week _____ Almost daily

(R = answer to 5 < answer to 6, A = answer to 6 > answer to 5)

7) How low does your blood sugar need to go before you feel symptoms?
_____ 60–69 mg/dl (A) _____ 50–59 mg/dl (A) _____ 40–49 mg/dl (R)
_____ <40 mg/dl (R)

8) To what extent can you tell by your symptoms that your blood sugar is low?
_____ Never (R) _____ Rarely (R) _____ Sometimes (R) _____ Often (A)
_____ Always (A)

Four or more R responses = reduced awareness; 2 or fewer R responses = aware.

Berlin questionnaire [1]

Ravi Reddy

September 30, 2015

Height (m)——Weight (kg)——Age——Male/Female

Please choose the correct response to each question

CATEGORY 1

1. **Do you snore?**
   (a) Yes
   (b) No
   (c) May be

If you snore:

2. Your snoring is:
   (a) Slightly louder than breathing
   (b) As loud as talking
   (c) Louder than talking
   (d) Very loud - can be heard in adjacent rooms
3. **How often do you snore**
   (a) Nearly every day
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never
4. **Has your snoring ever bothered other people?**
   (a) Yes
   (b) No
   (c) Don't know
5. **Has anyone notices that you quit breathing during your sleep?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after you sleep?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never
7. **During your waking time, do you feel tired, fatigued or not up to par?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never
8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
   (a) Yes
   (b) No

If yes:

9. **How often does this occur?**
   (a) Nearly everyday
   (b) 3-4 times a week
   (c) 1-2 times a week
   (d) 1-2 times a month
   (e) Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
    (a) Yes
    (b) No
    (c) Don't know

[1] Adapted from : Netzer, N. C., R. A. Stoohs, C. M. Netzer, K. Clark, and K. P. Strohl. 1999. *Using the Berlin Questionnaire to Identify Patients at Risk for the Sleep Apnea Syndrome.* Annals of Internal Medicine 131 (7), 485-91.

Epworth Sleepiness Scale [1]

Ravi Reddy

October 6, 2015

[1] Adapted from : Johns, M. W. 1991. *A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale.* Sleep 14 (6) : 540—45.

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent past. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation :

- 0 = no chance of dozing
- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

Height (m)——Weight (kg)——Age——Male/Female

Please choose the correct response to each question

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

International physical activity questionnaire [1]

Ravi Reddy

October 2, 2015

[1] Adapted from : Craig, Cora L., Alison L. Marshall, Michael Sjöström, Adrian E. Bauman, Michael L. Booth, Barbara E. Ainsworth, Michael Pratt, et al. 2003. "International Physical Activity Questionnaire: 12-Country Reliability and Validity." Medicine and Science in Sports and Exercise 35 (8): 1381—95.

This document will used to understand the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the *vigorous activities* which take *hard physical effort* that you did in the last 7 days. *Vigorous activities* make you breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Think about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities? Please consider only those physical activities that were at least 10 minutes at a time.
   (a) _____ Days per week
   (b) Don't know or Not sure
   (c) Refuse to answer
2. How much time did you usually spend doing **vigorous** physical activities on one of those days? Please consider only those physical activities that were at least 10 minutes at a time.
   (a) _____ Hours per day
   (b) _____ Minutes per day
   (c) Don't know or Not sure
   (d) Refuse to answer

Now think about activities which take *moderate physical effort* that you did in the last 7 days. Moderate physical activities make you breathe somewhat harder than normal and may include carrying light loads, bicycling at a regular pace or doubles tennis. Do not include walking. Please consider only those physical activities that were at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do moderate physical activities?
   (a) _____ Days per week
   (b) Don't know or Not sure
   (c) Refuse to answer
4. How much time did you usually spend doing **moderate** physical activities on one of those days? Please consider only those physical activities that were at least 10 minutes at a time.

4. How much time did you usually spend doing **moderate** physical activities on one of those days? Please consider only those physical activities that were at least 10 minutes at a time.

   (a) _____ Hours per day

   (b) _____ Minutes per day

   (c) Don't know or Not sure

   (d) Refuse to answer

Now think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

   (a) _____ Days per week

   (b) Don't know or Not sure

   (c) Refuse to answer

6. How much time did you usually spend **walking** on one of those days?

   (a) _____ Hours per day

   (b) _____ Minutes per day

   (c) Don't know or Not sure

   (d) Refuse to answer

Now think about the time you spent sitting on the week days during the last 7 days. Please include time spent at work, at home while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.

7. During the *last 7 days*, how much time did you spend **sitting** on a week day?

   (a) _____ Hours per day

   (b) _____ Minutes per day

   (c) Don't know or Not sure

   (d) Refuse to answer

Subject post study survey:
Please circle your answer below.
5 = extremely helpful, 4 = very helpful, 3 = somewhat helpful, 2 = slightly helpful, 1 = not at all helpful

- How satisfied were you with the study?

  Not helpful at all 1 2 3 4 5 (extremely helpful)

- How do you rate the usability of the app?

  Not helpful at all 1 2 3 4 5 (extremely helpful)

- Do you think you would like more training on carb estimation?

  Yes No

- Would you like an application that would suggest changes to basal and bolus dosing based on the photos taken of past and current meals?
  Yes No

- Would you like an application that would suggest changes to basal and bolus dosing based on your past or anticipated exercise?
  Yes No
- Would you like an application that would suggest changes to basal and bolus dosing based on your past or anticipated sleep?
  Yes No

- Would you like an application that would suggest changes to lifestyle decisions such as exercise, sleep, and nutrition based on your past glycemic control?
  Yes No

5 = extremely satisfied, 4 = very satisfied, 3 = somewhat satisfied, 2 = slightly satisfied, 1 = not at all satisfied

- How satisfied are you with your current diabetes therapy?

  Not satisfied at all 1 2 3 4 5 (extremely satisfied)

Please include any additional comments regarding the areas of you would like more decision support on:

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