Adjusting Insulin Delivery to Activity (AIDA):

Use of Activity Data to Adjust Insulin Pump Therapy for Children with Type 1 Diabetes

AIDA Investigation Protocol

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Summary/Abstract

Being diagnosed with type 1 diabetes at a young age places a lifelong burden on the child together with new challenges and responsibilities for the parents of that child. New technologies such as continuous glucose monitors (CGM) and high resolution insulin pumps with the ability to deliver the low basal rates required for very young children have reduced the burden, but the pumps need to be carefully configured with some of the setting needing to be subtly adjusted following exercise, which if performed later in the day has been shown to reduce the nighttime basal requirements. Many adults with type 1 diabetes (T1D) are able to intuitively make adjustments based on prior activity; however, parents of younger children may not even be aware of their child's activity levels while at day-care or school. Moreover, the amount and timing of the adjustments are not well defined and may be highly variable between subjects. The present study looks to assess the feasibility of combining new generation activity monitors (FitBit or similar), with data obtained from CGM and insulin pump records to improve insulin dose adjustments and prevent hypoglycemia in the pediatric population.

Abbreviations: SAP – sensor augmented pump therapy; CGM – continuous glucose monitor; T1D – type 1 diabetes; TDD – total daily dose;

1. Specific Aim:

To determine the feasibility of using activity monitor data to predict the need to make temporary insulin pump dose adjustments to prevent nighttime hypoglycemia.

2. Background and significance

The 1993 landmark Diabetes Control and Complications Trial (DCCT) showed intensive insulin therapy reduced the rate of long-term micro vascular complications from T1D (1). Since the trial, new insulin formulations with more rapid absorption kinetics have been developed, pumps delivering the insulin have been improved, and continuous glucose monitors (CGM) providing glucose values every 1 to 5 minutes have become available. These advances have provided renewed hope that a fully automated artificial pancreas (AP) will soon be available; however, a substantial number of hurdles still need to be overcome. CGM devices first available in 1999 are not as yet approved by the FDA for calculating insulin doses, reflecting ongoing concerns that the devices are still not sufficiently accurate or reliable. In addition, many researchers believe insulin absorption from the most likely delivery site (subcutaneous) is still too slow. At best, the timeline for the first commercially available AP is unclear. What is clear however, is that the level of control now achieved with the best available technology – widely considered as insulin pump therapy combined with CGM - is less than optimal.

Insulin pump therapy requires the managing physician or patient to set basal insulin rates, which may vary throughout the day. Bolus estimators included with the pumps require a subject specific carbohydrate-to-insulin ratio (CIR) to estimate the insulin needed to cover a meal, and an insulin sensitivity factor (ISF) to calculate correction boluses in the event of an error in estimating the carbohydrate content of meal. An insulin-on-board (IOB) time is also required to prevent the patient from taking a second correction bolus before the first bolus has had time act. While guidelines exist to aid the physician in initially configuring the pump settings, changes in the configuration are often made with the final values often arrived at simply by trial and error. Complicating the trial-and-error approach is that some settings may need to be acutely adjusted in response to stress, illness, or exercise, with the latter often having what could potentially be a prolonged effect to lower the insulin requirement (2; 3).

CGM, when first introduced, was widely thought to be a transformative technology. Hypo- and hyper-glycemic alarms were anticipated to provide an added level of safety. Information on the trend, or rate-of-change, of glucose was anticipated to improve boluses estimates which could be increased if the levels were increasing or lowered if decreasing. And, having a retrospective continuous trace of the patient's glucose profile was thought to be a mechanism by which pump settings could logically be set. Unfortunately, false alarms limited the effectiveness in preventing hypoglycemia, no clear guidelines emerged on how to incorporate rate information into the bolus estimate, and the sheer volume of data obtained over multiple days or weeks, and the need to merge that data with meal information, insulin dosing, and patient logbook records, made it virtually impossible for a physician to go through the tracings in sufficient detail to make an informed decision on how to adjust pump settings. Moreover, the reliance on logbook records to identify instances of nighttime hypoglycemia that might have been related to an elevation in daytime activity is unrealistic. Most individuals with T1D simply do not maintain records with this level of detail and parents of younger children may not even be aware of all the activities their child participates in during school hours.

The effect of physical activity on glycemic control in diabetic patients can often be complex. However, there is significant evidence linking increased physical activity with risk of overnight hypoglycemia. The DirectNet study group, for example, found that children 11 to 17 years old made to exercise under a controlled setting were more likely to develop hypoglycemia the night following the exercise intervention compared to sedentary days (2). A more recent study reported overnight and next-day hypoglycemia was most likely in adolescents with type 1 diabetes who had > 30 min/day of moderate-to-vigorous physical activity (MVPA); measured using data from accelerometers (3).

The present study looks to assess the feasibility of combining information from an activity monitor, with CGM and pump data, and determine if the combined data can be used to guide adjustments in insulin-pump settings. We

seek to determine whether the activity data can identify instances when those settings may need to be adjusted in response to activity, as well as help determine the extent of the dosing change required. Our long-term goal is to create a cloud-based software tool that will alert the patient when the settings may need to be lowered in response to high activity. This is a pilot study to gather data regarding feasibility of using activity monitors to adjust insulin pump therapy and obtain preliminary data to power a larger outcome study. We include children from 1 to 17 years, in order to observe energy expenditure in children of different ages.

3. Preliminary studies

Our prior studies controlling blood glucose have been in fully automated glucose control in individuals with T1D (aka the artificial pancreas), and in physician supervised control of critically ill patients (aka tight glycemic control; TGC). The studies were performed by at Boston Children's Hospital (BCH), and combined CGM with different Proportional-Integral-Derivative (PID) control algorithms to guide insulin dose adjustments in the subcutaneous insulin infusion pumps used by individuals with T1D, and in the intravenous insulin infusion pumps used to manage critically ill patients in the ICU (4-10).

In the current study we plan to use a version of the same algorithm to guide changes in the basal insulin rates used in today's open-loop pump therapy. Specifically, we look to identify more appropriate rates for use during nights following high daytime activity level. It is on these nights that many subjects find it necessary to lower their basal rates. To assess the ability of the PID algorithm to identify and adjust these rates, we performed a preliminary computer simulation study of the algorithm (Figure 1). Such simulations are increasingly being used to assess algorithms used to adjust insulin delivery (11; 12) in advance of performing a clinical studies. In our simulation study, the P and I components of the PID algorithm were used to make a sequence of recommendations on the midnight to 3 am basal rate in order to achieve target glucose values in the range 110-130 mg/dL. Adjustments were made following an equation in the form of:

In the equation, the basal rate from midnight to 3 am on a future day, is denoted with a superscript N+1, is calculated from the value used on the current day, denoted by superscript N. Recommendations to increase or decrease the basal rate are based not just on whether the CGM glucose value is below target, but also on what the rate of change of glucose is at that time. Thus, a 3 AM CGM value that is consistently at target but decreasing may result in a recommendation to decrease the midnight to 3 AM basal rate, and a value is above target but approaching target at a desired rate may leave the basal rate un-changed, the desired rate being set by parameter T_I. Changes are not made from day-to-day; rather, the value is updated each day but needs to pass a threshold set by the user (0.05 U/hr in this simulation). Thus, a value slightly above target range on one day, and slightly below target on a subsequent day,

has no net effect, with a change only occurring following an interval where the values are consistently above or below target. In the simulation study, the pump basal rates were initially set to be higher than needed, leading to a 3 AM glucose value of 50 mg/dL on the first observation (simulating a night following a high level of activity during the day). For the values of K_P and T_I chosen, the first recommended change requires a repeat occurrence at 50 mg/dL, and a total 6

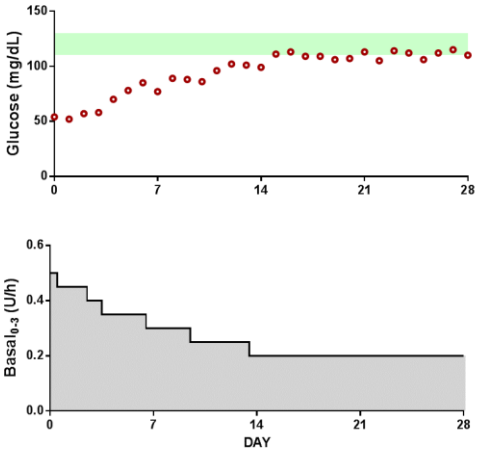

Figure 1. Simulated pump adaptation showing changes in 3 am glucose over 28 days of adaptive pump therapy.

changes are required to decrease the basal rate from the initial 0.5 U/hr to 0.2 U/hr. Different values of K_P and T_I lead to more rapid or slower adaptation. As well, the target range can be decreased, but will require additional pump adjustments that the physician or patients may find unnecessary.

Figure 2.

$$BASAL_{0-3}^{N+1} = BASAL_{0-3}^{N} + K_P(G_{3am} - target)/T_I + K_P \frac{dG_{3am}}{dt}$$

To identify high activity days, subjects will be provided with activity monitors (FitBit or similar). These monitors have become popular but are not medical devices *per se;* thus, we will be taking care not to rely solely on the device for identifying high activity days. While not approved as a medical device, our evaluation of one device (FitBit) indicated it could provide a reasonable estimate of the number of calories burned and steps taken and that the data was easily accessed through the cloud (Figure 2). Other research groups have used similar devises to show days that include 30 min of moderate to vigorous physical activity are flowed by a 31% increase in hypoglycemia (95% CI 1.05–1.63; P = 0.017)(3).

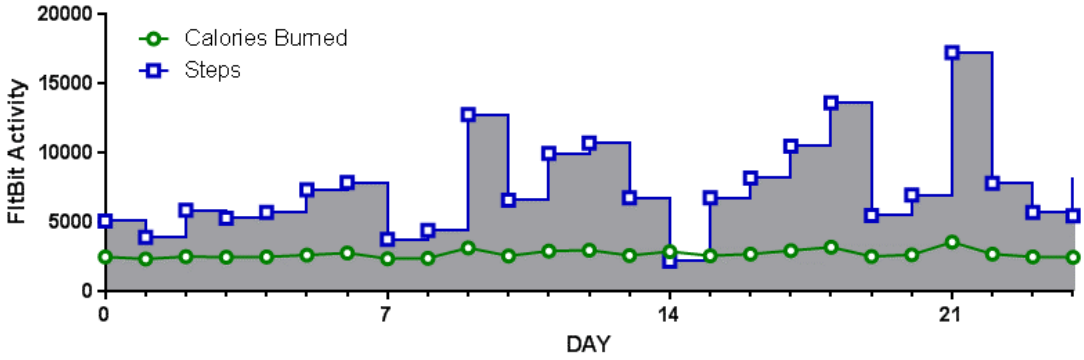

Figure 3. FitBit activity data obtained from cloud.

The devices are small (about the size of a quarter) and rely on accelerometers to estimate activity. They are, however, subject to errors whenever the activity does not involve acceleration of the device *per se* (e.g. riding a stationary bike). Software provided with the devices allows these events to be separately tracked. Still, published studies have validated that these devices provide objective, reliable assessments of activity completed and calories expended per day (14-17). Therefore, we believe that they will provide a more reliable estimate of activity than can be inferred from log-book records, and allow us to assess the validity of using daytime activity to effect changes in nighttime insulin basal rates. However, changes in the rates will not be recommended to the patient without physician approval. Rather, if we determine a relationship between high daytime activity and low overnight basal requirements, the physician will discuss with the patient how best to identify days involving high activity without relying solely on FitBit device.

4. Design and Methods

a. Study design

This study is a pilot trial investigating the feasibility of using activity monitoring data to adjust insulin pump therapy and prevent hypoglycemia. The study will enroll 20 patients 1-17 years old with type 1 diabetes mellitus on insulin pump therapy. Subjects will be provided with continuous glucose monitors (DexCom G4) and FitBit activity monitors. Study duration will be 3 to 4 months. During the course of the study patients will continue to receive routine care by their primary endocrinologist and DNE. Insulin dose adjustments unrelated to activity monitor data will continue to be at the discretion of the patient's primary diabetes team.

Activity level (steps and calories burned) will be uploaded over the web in a secure fashion to our central firewall-protected database on a daily basis while

CGM glucose values and insulin pump data will be collected once a week. Data from the activity monitor is automatically sent to a secure study team RedCap database once a day. This occurs by automatic, wireless syncing of the activity monitor with the patient/family's computer or smartphone. The activity monitor and activity monitor data is not associated with any personal health information. The activity monitor is only set up with a study identification number. Only study team members have access to the list of study identification numbers and associated patient information and this is stored in a secure computer a locked office. CGM and insulin pump data will be downloaded onto a patient or study team computer and then emailed to the study team once a week. Families will also have the option of coming to clinic once a week and having a study team member download the CGM and insulin pump data for them.

The initial 2 weeks of a subject's enrollment in the study will be used to establish his or her baseline activity level and no changes to the insulin regimen will be made based on the activity monitor data. During weeks 3-6 to 12-16, activity data will be reviewed daily and an alternate basal insulin rate will be recommended on days considered to be increased activity days. We will use an adaptive algorithm to help guide suggested nighttime insulin basal rate changes. All recommendations will be reviewed and approved by a study physician prior to implementation. The alternate rate will be derived using the subject's usual care pump settings as an initial starting point from which to make incremental changes in the 3 hour interval leading up to the hypoglycemic event. Target will be the overnight nadir obtained with usual care settings. Residual error (CGM-target) will be used to assess the validity of using the 3 hour window prior to the event to effect lower basal. The patient's primary diabetes team will be informed about the recommended nighttime basal insulin dose change and this will be documented in the patient's medical record in powerchart. The primary diabetes team will not give recommendations regarding nighttime insulin rate dose changes based on activity monitor data; however, they will continue to guide all other aspects of the patient's diabetes management.

b. Patient Selection and Inclusion/Exclusion Criteria

Subjects will be recruited from the outpatient endocrinology clinic based on physician recommendation and approval to approach at Boston Children's Hospital (BCH) as well as through public notice. 20 subjects will be recruited in two different age designations.

Inclusion Criteria:

- Age: 1 to 17 years old
- Type 1 diabetes (as clinically diagnosed by outpatient endocrinologist).
- Treated with insulin pump therapy for greater than or equal 3 months

- Families will need to have access to Wi-Fi and a compatible smartphone in order for the data from the activity monitor and other devices to be transmitted to the research team

Exclusion Criteria:

- Current glucocorticoid use or other medication known to affect insulin action at investigator's discretion.
- Hospitalization within the last month

c. Description of Study Treatments and Procedures

RECRUITMENT, SCREENING AND CONSENT:

Subject will be recruited from the Boston Children's Hospital Endocrinology Clinic. We will screen the clinic schedule for eligible candidates. Eligibility will be assessed.. Primary providers will be approached regarding eligible patients and asked to introduce the research team at the time of the clinic visit. Consent, and assent for patients older than 7 years old, will be obtained during the patient's clinic visit. Additionally, we will contact by email all diabetes providers to inform them of our study and ask them to give interested families the approved study information sheet, which has study team contact information (email and phone number is given on the sheet). For interested subjects who contact us but do not have an upcoming clinic visit, consent will be obtained at the Training and Education visit.

TRAINING AND EDUCATION:

After initial recruitment discussions, subjects will be requested to come to the Endocrine outpatient clinic located at 333 Longwood. A trained research team member will teach during a 1-2 hour session use of the continuous glucose monitor and the activity monitor. Families will also be instructed how and when to upload data from the insulin pump, CGM and activity monitor. Families will have the choice to use their own computers, use a study team-provided computer or come to clinic in order to upload data once a week. Activity monitor data will be uploaded automatically on a daily basis when subjects are near a Wi-Fi connection.

CGM Education: A trained research team member (nurse or physician) will provide education surrounding the use of the CGM, including technical aspects related to insertion and removal of the device, alarms, and calibration. Subjects will be informed that sensor values are not to be used to dose insulin and that prior to administering insulin they should obtain a blood glucose value from their standard meter (i.e., follow normal routines). Subjects will be

instructed to calibrate the CGM a minimum of twice daily, before breakfast and before going to bed. Additional calibrations may be performed at the subject's discretion as in clinical practice. Sensors will be provided for replacement as needed (e.g. sensor falls off or fails internal quality checks included in the manufacture's product). Sensors may also be replaced at the subject's discretion should they observe the sensor is consistently not tracking blood glucose values as is standard practice. Subjects' CGM will be programmed with a low glucose alarm at 60 mg/dl. Subjects will also be requested to confirm episodes in which the sensor reports hypoglycemia with a capillary blood glucose meter measurement, and to treat hypoglycemia as per their home routine. At the completion of the study, CGMs devices will be collected.

Use of the FitBit Device. Combined with the initial training on CGM will be a short description of how the FitBit device works, and how the data obtained from the device will be used. Subjects will be encouraged not to make adjustments in insulin delivery based on the device readings, unless instructed by a research team member. At the completion of the study each subject will be allowed to keep FitBit monitors (valued at $49.95 - $99.95).

STUDY PROCEDURES:

Insulin Pump Therapy: Participants will continue to use their own insulin pump and home blood glucose meter. All subjects will continue to receive routine care from their primary diabetes team. We propose to enact insulin dosing changes if we discover significant hyperglycemia and informing the diabetes providers of these changes." All other insulin dose changes unrelated to activity monitor data and energy expenditure estimates will be at the discretion of the primary team. We recognize that initial use of CGM may reveal previously undetected hypo- or hyperglycemia. Subjects and their families should discuss these findings with their primary diabetes team as they would for any other concerning blood glucose levels. If significant nocturnal hyperglycemia is detected, an increase in nighttime insulin basal rate will be recommended by the study team after being reviewed by the study endocrinologist. The dosing changes to address the hyperglycemia will be made by the study team directly in order to prevent delays in correction of the hyperglycemia as can occur if forced to wait for a response from the primary provider. Nevertheless, Tte recommended changes will also be sent as a powerchart message to the subject's primary diabetes care team and they will be given the option to opt out of the recommendation and contact the patient directly to address the discovered hyperglycemia. If the provider responds after the changes have been enacted then we will simply contact the family and ask them to resume their prior settings and discuss with their provider an alternative plan to treat the hyperglycemia.

Changes in Pump Therapy Based on Activity: During the first two to six weeks of the study, a baseline activity level will be established for each subject (average and standard deviation of first 14 days of available data). High activity

days will be initially defined as any day where the activity is greater than one standard deviation above the mean. This definition, however, may need to be adjusted on a subject specific basis as it may vary due to physical fitness. Nadir glucose on increased activity days will be inputted into an adaptive basal algorithm. The algorithm is initialized with the subject's baseline insulin rate settings. Once the algorithm detects a need to modify the basal rate based on activity level, then an alternate basal profile will be recommended by the study physicians if deemed appropriate. The change will be made by the parent during one of the scheduled weekly phone calls or any other time of the week if needed. A study team member will walk the parent through the required steps to change insulin pump settings and confirm by verbal read back, screenshot or download that the pump settings are correct. Any changes to insulin pump therapy will be communicated to the subject's primary diabetes team via a note entered into the patient's BCH medical record.

Subject-Study Team communication: All subjects/families will be asked to contact the study team and perform a data download on a weekly basis. Families will be asked if they were compliant with CGM and activity monitor, it they had issues with blood glucose levels and if there were any intercurrent illnesses. Additionally, participants should contact a study team member if they experience any technical difficulties with their CGM or activity monitor, if they experience any nocturnal hypoglycemia (confirmed by home glucometer) or if they have concerns regarding a high activity day. Study team members will review daily activity data and call subject's families if an insulin dose change is recommended. A study team member will be available on page 24 hours a day.

Safety Monitoring: If CGM review reveals significant and recurrent hyperglycemia or activity-unrelated hypoglycemia, the subject's diabetes team will be alerted so that they may decide if changes to the subject's baseline insulin regimen are required. The study team may enact nighttime basal insulin dosing changes if significant nocturnal hyperglycemia is encountered while simultaneously alerting the patient's primary diabetes providers of these changes and giving them the option to change or refuse the recommendation.

d. Definition of Primary and Secondary Outcomes/Endpoints

This is a pilot study to determine the feasibility of combining activity monitor data with CGM and pump data to make prospective recommendations to reduce basal insulin delivery following high activity days. There is no planned hypothesis for the pilot phase; however, planed comparisons for a larger study will be powered from the data obtained. The primary endpoint for the larger study will be a reduction in the incidence of nighttime hypoglycemia. Secondary outcomes will include the ability of activity data to predict nighttime nadir glucose.

Hypoglycemia will be defined as home meter glucose < 70 mg/dl for all subjects, CGM values below threshold for >30 minutes with no concomitant blood sugar reading (i.e. subject is sleeping at home and ignores the low glucose

alarm but the CGM is <70 for more than 30 minutes). Hypoglycemia episodes within one hour of each other will be considered as one event. Two hypoglycemic events with an intermittent blood glucose value above 70 mg/dL will be treated as a single event. Hypoglycemia and "use-of-supplemental- carbohydrate-to-prevent-hypoglycemia" will be treated identically.

5. Data Management and Statistical Analysis

One study folder, with IRB approved consent forms and case report forms (CRF), will be maintained for each subject recruited into the study. Sensor information, as provided by the manufacturer, will also be recorded on CRFs (identification numbers such as lot or serial together with expiration). Electronic data downloads for the insulin pump, containing a history of insulin delivery commands; glucose meter and glucose sensor, containing a record of all glucose values received and any alarms will be obtained weekly and the downloaded files copied to a password protected study computer in subdirectory labeled with the patient identification number. A copy of the spreadsheet used to screen blood glucose and activity data will also be placed in this directory.

a. Data Analysis Plan

Data analysis will begin by calculating the baseline (average and standard deviation) activity level for each subject during the first two to six weeks. High activity days will be defined as any day where the activity is greater than one standard deviation above the mean. Correlations will be performed to assess if there is relationship between daytime activity (8- am to 9 pm) and nighttime nadir blood glucose level (continuous). Nadir glucose will also be categorized as hypo- or no-hypo (binary), with a binary logistic regression model used to assess the significance of daytime activity, insulin dosing, and carbohydrate intake, as independent factors increasing the risk of hypoglycemia. Analysis will proceed with generalized estimating equations (not powered but in preparation of the larger study to be conducted). Characteristics of the nighttime glucose profile (nadir glucose, time in target, time below target) will be calculated weekly, with mean and 95% confidence plotted by week. In the event usual-care pump settings are adjusted during the course of the study, the average nighttime glucose values observed for the week following the most recent adjustment will be compared to average values obtained during the final week (assures improvements are due to the availability of the FitBit data rather than the CGM data). Chi2 analysis will be used to assess differences in the incidence of hypoglycemia. Statistical analyses will be performed both as intention to treat and per protocol. The intention to treat analysis will include all data; per protocol analysis will exclude cases in which the subject does not comply with recommendations of the study team or does not complete all 12 weeks of the study. The algorithm will be considered feasible if all data can be assembled, and recommendations deemed reasonable (accepted) in a majority of cases.

Statistical Power and Sample Considerations

This is a feasibility study and therefore is not powered; however, the choice of 10 subjects with any one group is generally considered acceptable for feasibility/pilot-studies and should provide sufficient data to power a larger study.

Study Organization

This is a single center study with limited enrollment. There are three participating physicians (medical team: Drs. Paulina Ortiz-Rubio, Carmen Soto-Rivera, and Michael Agus). This team will be responsible for guiding subjects on the use of CGM and for approving pump therapy changes. Dr. Steil will be responsible for incorporating input from the medical team into the adaptive pump therapy (APT) algorithm, overseeing data analysis, and publication of results. Recruitment at BCH will be primarily performed by Dr. Steil's research assistant.

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