The Effect of Basal Insulin During Exercise on the Development of Hypoglycemia in Children with Type 1 Diabetes

A study being conducted by the Diabetes Research in Children Network

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CHAPTER 1
BACKGROUND INFORMATION AND STUDY SYNOPSIS

1.1 Background Information

There are a number of studies that have evaluated the incidence of hypoglycemia during or immediately following exercise,[1-4] in children and adolescents with T1DM. DirecNet recently completed a study that was designed to more carefully define the effect of afternoon exercise on the relative risk of hypoglycemia during exercise and during the following night in a cohort of 50 children with T1DM, who were using an intensive diabetes management regimen involving either insulin pumps or multiple daily insulin injections. A carefully controlled, cross-over design that involved a supervised and standardized exercise protocol was utilized to compare the frequency of hypoglycemia during exercise and overnight following afternoon exercise with that following a sedentary day in a clinical research center setting. We specifically chose to have the subjects exercise in the late afternoon as children and adolescents often are more active at the end of the school day, when different athletic practice and game sessions take place. In addition, the duration and intensity of the exercise regimen was designed to mimic a typical length of time children are involved in such activities.

The study procedures specified the use of similar insulin doses on both the exercise and sedentary day. Specifically, the subject's usual routine for a sedentary day was followed on the exercise day even if the subject typically would have lowered his or her basal insulin replacement during exercise or overnight, on days of unusually intense physical activity. This approach allowed us to examine the effect of exercise per se on the risk of nocturnal hypoglycemia and it is clinically relevant, since many youngsters on pumps or who receive pre-breakfast doses of glargine insulin do not or cannot adjust their overnight basal insulin.

The findings of this study supported the well-recognized clinical observation that exercise has benefit in lowering plasma glucose levels both during and following exercise in children with T1DM. In 28 percent of the youngsters, hypoglycemia developed during the night of their sedentary day even though only 3 of the subjects had experienced a severe hypoglycemic event at home during the 6 months prior to the study. During exercise the nadir glucose level was $\leq$80 mg/dL in 31 (62%) and $\leq$ 60 mg/dL in 11 (22%) subjects during or at the immediate end of exercise. When the pre-exercise glucose level was <100 mg/dL, most of subjects (9 of the 13) became hypoglycemic ($\leq$60 mg/dL) with exercise. 15 subjects were treated for hypoglycemia based on glucose meter readings (mean 55 ± 4 mg/dL) during the exercise protocol. Fifteen grams of oral carbohydrate resulted in a modest increase in plasma glucose (to 76 ± 15, range 57-102 mg/dL) after ~10min. However, 5 subjects required a second snack to raise glucose levels to >70 mg/dL and two other treated subjects required a second snack at the end of exercise due to recurrent hypoglycemia. Hyperglycemia was more common during the sedentary night, and lower glucose levels were sustained for many hours following exercise on the exercise day compared with the sedentary day. Our findings also supported the use of flexible diabetes management regimens that attempt to adjust food intake and insulin dosing during or on evenings following exercise to reduce the risk of hypoglycemia during exercise or overnight following hypoglycemia. In the present study DirecNet attempts to evaluate the most effective methods of adjusting insulin doses during exercise in order to maximize the benefits and safety of exercise in children with T1DM by preventing hypoglycemia during and following exercise.

In a review of the literature regarding exercise and the management of diabetes in adults [5] it was recommended among other things to decrease insulin doses prior to exercise as the higher circulating levels of insulin suppress hepatic glucose production and do not allow for lipolysis and

use of FFA by the muscle, an effect that is further enhanced by the lower than normal counter-regulatory hormones in subjects with diabetes.

Although it is widely understood that decreasing insulin would prevent hypoglycemia, how much to decrease insulin has not been studied well. Joslin reported the empirical method used by a postman with diabetes,[6] who empirically reduced his insulin dose by the strength of the wind before his daily delivery route. More recently Shiffrin et al[7] in a study of 7 adolescents on pumps and 6 on MDI examined the effect of altering insulin doses and blood glucose levels during a 45 minute exercise session postprandially. Subjects were tested one time resting and 4 times during exercise with full dose or ½ dose or 2/3 dose or no insulin. They found that 50-60% reduction is best for preventing hypoglycemia. In a study by Riddell et al[3] timing of the exercise after a meal was important. Most danger for hypoglycemia was at 90 min after a meal in 8 adolescent boys with T1DM, who exercised for 60 minutes. Insulin regimen was two injections daily (most probably regular and NPH). In the only study on subjects on a basal-bolus regimen,[8] adult men with type 1 diabetes who exercised 90 minutes following a meal, had the pre-meal short acting insulin reduced in order to avoid hypoglycemia during and immediately following exercise. It was recommended in that study that a 50% reduction of pre-meal short acting insulin should be considered for prevention of exercise induced hypoglycemia.

The proposed study aims to examine the effect of no insulin dose during exercise in comparison to full dose.

1.2 Study Overview and Objectives

In this study protocol, each subject has two visits. During each visit, a structured exercise protocol is completed in the late afternoon. During one of the visits (ordered through randomization), the subject's usual basal rate will be continued and during the other visit, the basal rate will be discontinued.

1.2.1 The Relationship of Basal Insulin during Exercise and Hypoglycemia

The primary objective of the study is to determine the effects of discontinuing a subject's basal rate during exercise on the glucose level during and following exercise.

- The primary study question to be addressed is: Does discontinuing the basal rate during exercise reduce the incidence of hypoglycemia compared with continuing the basal rate?

Additional questions include the following:

- Is the decrease in blood glucose during exercise less when the basal rate is discontinued compared with when the basal rate is continued?
- Does discontinuing the basal rate during exercise increase the incidence of hyperglycemia and/or positive ketones compared with continuing the basal rate?
- How do changes in free fatty acids, free insulin, beta-hydroxybuterate, and adiponectin differ under the two study conditions?

1.2.2 Accuracy of a Continuous Glucose Sensor

The accuracy of a continuous glucose sensor will be examined. In our initial exercise study, the Continuous Glucose Monitoring System (CGMS) showed a slight systematic bias during exercise towards higher blood glucose levels compared with the central lab values.

There will be no additional blood requirements to perform this testing.

1.2.3 Accuracy of a Home Glucose Meter

The accuracy of a home glucose meter may be examined. There will be no additional blood requirements to perform this testing.

1.2.4 Accuracy of a Home HbA1c Monitor

HbA1c monitors are available for home use. The accuracy of one or more of these devices will be examined as an ancillary study. There will be no additional blood requirements to perform this testing.

1.3 Synopsis of Study Design

Study Population: 55 subjects between 8.0 and <18.0 years old with T1DM and HbA1c <10.0% using an insulin pump

Study Procedures

Two outpatient visits 1 to 4 weeks apart (the order of the visits will be determined at random):

- One with a 75-minute exercise session in the late afternoon with no change to the subject's usual basal rate
- One with a 75-minute exercise session in the late afternoon with the subject's usual basal rate being discontinued
- Measurement of glucose levels and collection of hormone and plasma substrate samples prior to, during, and following the exercise
- Assessment of accuracy of a continuous glucose monitor
- Assessment of accuracy of a home glucose meter
- Assessment of accuracy of a home HbA1c meter (optional ancillary study)

Study procedures are detailed in chapters 2 and 3.

CHAPTER 2
SUBJECT ELIGIBILITY AND ENROLLMENT

2.1 Study Population

Approximately 55 subjects will be enrolled in this study at five clinical centers with approximately 11 enrolled at each center.

Subjects will include both males and females and an enrollment goal will be to achieve an equal sex distribution.

A goal of recruitment will be to enroll a minimum of 10% minorities.

Subjects who do not complete the protocol for both visits will be replaced in the enrollment quota.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

To be eligible for the study, all subjects must meet the following criteria:

1) Clinical diagnosis of type 1 diabetes for at least 18 months
   The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed.
2) HbA1c $\leq$10.0%
   The DCA2000 will be used to assess eligibility.
3) Age 8.0 to <18.0 years
4) Weight $\geq$39.5 kg at reinfusion centers and $\geq$46.0 kg at discard centers
5) BMI $\geq 5^{th}$ and $\leq 95^{th}$ percentiles for age and gender
6) Stable insulin regimen for at least 1 month and not anticipating a change prior to the subject's completion of the study
   - *Stable is defined as no change in the overall insulin program, i.e., no change from SC injections to pump.*
7) Insulin regimen involves use of an insulin pump
8) Normal thyroid function (measured within the previous year)
9) Parent/guardian and subject understand the study protocol and agree to comply with it
10) Informed Consent Form signed by the parent/guardian and Child Assent Form signed (*unless IRB requirements differ)*

2.2.2 Exclusion

Subjects who meet any of the following criteria are <u>not</u> eligible for the study:

1) A recent injury to body or limb, Addison's disease, muscular disorder, use of any medication or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the exercise protocol
2) Asthma which has been medically treated within the last year
3) Current use of glucocorticoid medication (by any route of administration)
4) Current use of a beta blocker medication

5) Use of pseudoephedrine 48 hours prior to visit (if used in the 48 hours prior to the scheduled visit, the visit will be deferred)

6) Severe hypoglycemia resulting in seizure or loss of consciousness in the 2 weeks prior to a visit (if a severe episode occurs within 2 weeks prior to the scheduled visit, the visit will be deferred)

7) Active infection (if at the time of the scheduled visit an infection is present, the visit will be deferred)

8) Anticipating a significant change in exercise regimen between visits (i.e. starting or stopping an organized sport)

2.3 Subject Enrollment and Baseline Data Collection

Potential subjects will be evaluated for study eligibility through the elicitation of a medical history and performance of a physical examination by a study investigator.

2.3.1 Informed Consent

For eligible subjects, the study will be discussed with the subject and parent/legal guardian. The parent will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Subjects will either be given the Child Assent Form to read or it will be read to the child. If the parent and child agree to participation, the Informed Consent Form and Child Assent Form will be signed and the first outpatient CRC visit will be scheduled. A copy of the consent form will be provided to the subject and his/her parent and another copy will be added to the subject's clinic chart.

Written informed consent must be obtained from the parent or guardian prior to performing any study-specific procedures that are not part of the subject's routine care.

2.3.1.1 Authorization Procedures

As part of the informed consent process, each subject will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review what study specific information will be collected and to whom that information will be disclosed. After speaking with the subject and their parent, questions will be answered about the details regarding authorization.

2.3.1.2 Special Consent Issues

The study population for this study includes adolescents. The consent form and study procedures will be discussed with each subject at a level in which they can understand. The study staff will ask questions of each subject to assess the autonomy and understanding of the study. Each subject will be asked to sign an assent form. Additionally, the parent(s) and/or guardian(s) of each subject will be asked to sign the consent form. They will be given the opportunity to ask questions throughout the study on all study related procedures.

2.3.2 Historical Information

A history will be elicited from the subject and parent and extracted from available medical records. Data to be collected will include: age, gender, race, diabetes history, history of diabetes in other family members, current insulin management, other chronic conditions, use of other medications, and medication allergies.

2.3.3 Physical Exam

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or his or her designee (a pediatric endocrinologist, pediatric endocrine fellow, or a pediatric endocrine nurse practitioner).

2.3.4 Bedtime Snack Information

At the Enrollment Visit, the algorithm the subject uses to determine the bedtime snack will be recorded. This information will be used to determine the snack that will be sent home with the subject following each visit.

CHAPTER 3
STUDY PROCEDURES AND MANAGEMENT

3.1 Overview

The study will consist of the following:

1) Two outpatient visits each lasting about 7 hours with a 75-minute exercise session in the late afternoon.
   - The order of the visits will be determined at random.
2) Assessment of changes in glucose concentrations during exercise.
3) Assessment of changes in hormone and plasma substrate concentrations during exercise.

The second visit should occur between 1 and 4 weeks after the first visit.

- If the subject experiences a severe hypoglycemia episode prior to a visit, the visit will be deferred until at least 2 weeks after the episode.
- If the subject is ill at the time of the scheduled visit, the visit will be deferred.

Subjects participating in the optional ancillary study will be provided with commercially available devices for testing the hemoglobin A1c. Subjects will be given the instructions that are provided by the manufacturer. No additional instructions will be given by study personnel for performing the tests. Subjects will be asked to use the devices the day before one of the visits to check the A1c two times. The second test will be done immediately following the first test. At the same time as these tests, subjects will also check the blood glucose.

3.2 Study Protocol

All procedures in the following sections refer to both visits unless otherwise indicated.

3.2.1 Timing of Visits

On each of the visit days, the subject will come to the center prior to lunch. The timing of the visit will enable the subject to have lunch at the center at approximately 12 noon.

Immediately upon arrival, blood or urine ketone levels will be assessed on the subject. The visit will be deferred if the urine ketone levels are >small or blood ketones are >1.0 mmol/L.

3.2.2 Initial Visit Procedures

At the start of the visit, the following will be done on both days unless otherwise noted:

1) A continuous glucose monitor will be inserted and calibrated one hour later.
2) An intravenous catheter for the reference glucose measurements and collection of hormone and plasma substrate samples will be inserted.
   - The intravenous catheter will be inserted in an arm vein. The area where the catheter will be inserted may be numbed with cream prior to catheter insertion.
3) For subjects participating in the optional ancillary study for A1c assessment at home, during the visit following the testing by the subject at home the study nurse or doctor will test the subject's A1c two times using the devices and the DCA2000. A fingerstick blood sample will also be collected to send to a central laboratory for A1c determination. At the same time, the study nurse or doctor will also test the subject's blood glucose.

3.2.3 Procedures Related to Lunch

The blood glucose level will be checked using the study HGM about 30 minutes prior to lunch, which will be served at about 12 noon.

The pre-lunch bolus dose of rapid-acting insulin analog will be calculated based on the carbohydrate to insulin ratio and correction factor that the subject uses at home. The goal is to have the 4 p.m. blood glucose between 120 and 200 mg/dL. Guidelines are as follows:

If blood glucose level is:

- <60 mg/dL, give 10-15 grams of glucose as glucose tablets and recheck blood glucose level in 15 minutes. Repeat as needed to raise blood glucose value to >60 mg/dL.
- 60-150, give bolus dose 0-5 minutes prior to lunch
- 150-300, give bolus dose 15 minutes prior to lunch
- >300, check blood or urine ketones. If ketones are negative, give bolus dose 30 minutes prior to lunch. If ketones positive, recalculate correction dose and administer new pre-lunch bolus a least 30 minutes before lunch. Recheck blood glucose level after 30 and, if needed, after 60 minutes to ensure that blood glucose levels are decreasing. Check blood or urine ketones every 60 minutes until negative.

3.2.4 Post Lunch Procedures

The subject's blood glucose will be checked with the study HGM at 1:00 p.m., 2:00 p.m. and 3:00 p.m. At each of these times, a blood sample will be collected for the central lab for glucose measurement.

Additional study HGM measurements may be made if necessary to monitor the blood glucose such that it is likely to be between 120 mg/dL and 200 mg/dL at 4:00 p.m. (at the start of exercise).

- If at 2:00 p.m. or after, the glucose is elevated such that it is expected that the 4:00 p.m. blood glucose level may be greater than 200 mg/dL, regular insulin (0.05 to 0.1 units/kg) can be given by IV bolus and repeated after 30 minutes if necessary.
    - No bolus doses will be given with the insulin pump after lunch.
    - IV insulin should not be given within one hour of starting the exercise.
- If the glucose level indicates that the 4:00 p.m. glucose may be <120 mg/dL, a snack consisting of 15-30 grams of carbohydrate can be given and repeated as needed.

3.2.5 Exercise Procedures

The exercise session will begin at about 4 p.m.

Prior to starting the exercise, urine ketones will be checked and blood ketones will be checked by fingerstick.

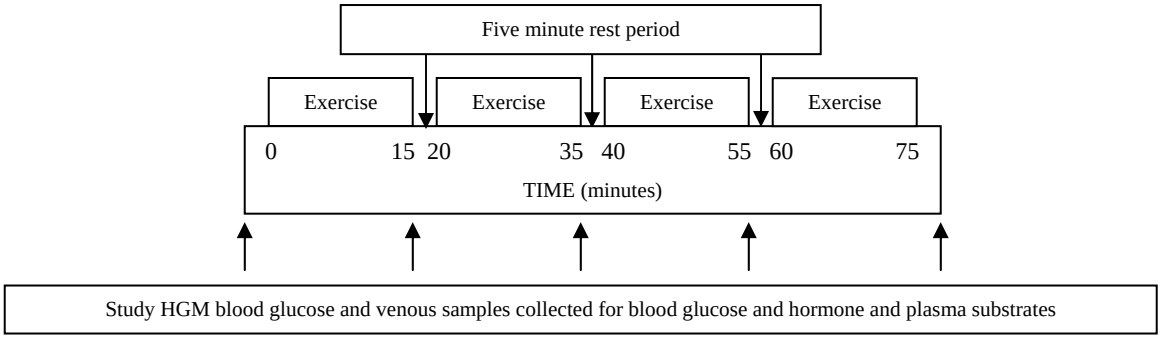
The blood glucose will be checked with the study HGM.

- If the blood glucose is not between 120 and 200 mg/dL, the exercise will be deferred.
- The blood glucose will be checked every 15 minutes until the blood glucose is in range.
- The baseline reference sample will not be collected until the blood glucose is in range and the subject is ready to start exercising.
- If the blood glucose is not in range by 5 p.m., the visit will be rescheduled.

On one of the exercise days, the basal rate will be continued during the exercise. On the other exercise day, the basal rate will be discontinued at the start of the exercise and not restarted until the end of the 45-minute post-exercise observation period.

Exercise will consist of 15 minutes on a treadmill at a heart rate of approximately 140 followed by a 5-minute rest period. This cycle will be repeated 3 more times for a total of four 15-minute exercise periods with 5-minute rest periods in between (75 minutes total).

- Subjects will be encouraged to complete the exercise but will not be coerced to complete any remaining cycles if they are unable.
- If the 4 cycles are not completed in 2 hours, the exercise will be stopped.
- A heart rate monitor will be worn throughout the time of exercise to ascertain the effort exerted.
- At the end of the exercise, urine and blood ketones will be checked.



If during exercise the blood glucose drops to ≤65 mg/dL, treatment will be given for hypoglycemia.

- Subjects who weigh <50 kg will be given 15 g and subjects who weigh ≥50 kg will be given 30 g of carbohydrates.
- After 15 minutes, the blood glucose will be rechecked and an additional 30 g of carbohydrates will be given if the blood glucose is still ≤70 mg/dL. Exercise will not resume until the blood glucose is >70 mg/dL.

3.2.5.1 Blood Glucose Measurements

Blood glucose measurements will be made using the study HGM (see section 3.3.1) (1) at 1, 2, and 3 p.m., (2) prior to starting the exercise, (3) during each of the 3 rest periods, (4) immediately following the exercise session, and (5) at 15 minute intervals for 45 minutes following the completion of the exercise.

- Blood samples for glucose measurements will also be collected for the central lab at these times.
- The pre-exercise (baseline) samples will be collected in duplicate.

3.2.5.2 Blood Samples for Hormone and Plasma Substrate Concentrations

Blood samples will be collected for free fatty acids, free insulin, and beta-hydroxybuterate (1) prior to starting the exercise, (2) during each of the 3 rest periods, (3) immediately following the exercise session, and (4) at 15 minute intervals for 45 minutes following the completion of the exercise session. The pre-exercise (baseline) samples will be collected in duplicate.

Samples will be collected for adiponectin prior to starting exercise and immediately following the exercise session.

Additional volume will be collected for hormones such as epinephrine, norepinephrine, dopamine, and others (1) prior to starting the exercise, (2) during each of the 3 rest periods, (3) immediately following the exercise session, and (4) at 15 minute intervals for 45 minutes following the completion of the exercise session.

All samples collected for hormone and plasma substrates will be collected, frozen, and shipped to the central laboratory for storage. A determination will be made once the primary outcome is known regarding which samples to process.

3.2.5.3 Procedures Following the Exercise Session

At the end of the exercise session, the following will be done:

- a blood sample will be collected for the central laboratory
- the blood glucose will be checked with the study HGM
- urine and blood ketones will be checked

The blood glucose will be checked with the study HGM and a central laboratory sample will be collected every 15 minutes for 45 minutes while the subject is resting.

At the 30-minute post-exercise check, 15 g of carbohydrates will be given if the blood glucose is <250 mg/dL.

- The blood glucose will be rechecked in 15 minutes and the insulin pump will be restarted (if discontinued).
- If the blood glucose is $\geq$250 mg/dL, no snack will be given, the blood glucose will be rechecked in 15 minutes and the insulin pump will be restarted (if discontinued).

If at anytime during the 45-minute post-exercise session the blood glucose is $\geq$325 mg/dL, the post-exercise observation period will be stopped, the insulin pump will be restarted (if discontinued), and a correction dose can be given at investigator discretion.

3.2.6 Procedures Prior to Ending the Visits

Dinner will be served at approximately 6:00 p.m.

A bedtime snack based on the subject's normal algorithm for an exercise day will be provided for the subject to take home.

The subject will be instructed not to exercise for the remainder of the day and will be given a log to complete for treatment of hypoglycemia (any blood glucose $\leq$80 mg/dL) the remainder of the day and night.

The subject will be provided with a home glucose meter and instructed to check his or her blood glucose prior to the bedtime snack, at midnight, 3 a.m., and prior to breakfast the next morning.

The continuous glucose sensor will be downloaded and subjects will have the option of continuing to wear the sensor at home.

The IV will be removed and the visit will be completed by approximately 6:30 p.m.

3.2.7 Procedures Following Each Visit

In the evening following each visit, the subject will have a bedtime snack and insulin bolus based on his/her usual routine following exercise during the day. The snack will be provided by the center.

HGM glucose measurements will be made prior to the snack, at 12 midnight, 3 a.m. and prior to breakfast.

A continuous glucose monitor may continue to be used if desired by the subject for the duration of the life of the sensor (typically 3 to 5 days).

3.3 Miscellaneous Protocol Issues

3.3.1 Glucose Measurements with the Study HGM

The study HGM will be used for the glucose measurements using venous blood from the intravenous catheter or from a fingerstick.

3.3.2 Glucose Measurements with Additional HGMs

At times when samples are collected for central laboratory glucose measurements, fingerstick blood glucose tests will be performed on additional HGMs for accuracy assessment. No additional blood is required for the testing.

3.3.3 Continuous Glucose Sensor

A continuous glucose sensor will be used during each visit. Subjects will have the option of continuing to wear the sensor at home following each visit.

The guidelines provided by the manufacturer will be followed regarding sensor insertion, calibration values, and assurance of proper sensor function.

3.3.4 Treatment of Hypoglycemia

Treatment of hypoglycemia during the exercise session is detailed in section 3.2.5.

3.3.5 Blood Samples for Additional Analyses

A portion of the blood sample taken at the time of the glucose measurements by the central lab will be frozen and stored for possible later analyses, such as for hormones related to glucose regulation such as epinephrine, norepinephrine, cortisol, glycerol, and others.

3.3.6 Accuracy Assessment of Home HbA1c Monitors

As an optional ancillary study, subjects will be asked to use one or more commercially available home HbA1c meters on the day before one of the visits. At the visit the next day, the study staff will perform testing on the same meter along with a test using the DCA2000 and collection of a fingerstick sample for central laboratory determination of A1c. At the same time, the study staff will also check the subject's blood glucose on the study HGM.

3.4 Risks

3.4.1 Exercise Risks

The exercise test involves exercising for a short time while pulse and blood sugars are monitored. The exercise protocol may induce hypoglycemia; however, this can be a regular occurrence at home. Subjects will be informed that hypoglycemia is more common during the night following exercise and will be instructed to monitor blood sugars overnight at home following each visit

3.4.2 Fingerstick Risks

Fingersticks may produce pain and/or ecchymosis at the site. We recommend children with diabetes check their blood sugar at least 4 times daily. This should not be a significant contributor to risks in this study as finger pokes are part of the usual care for people with diabetes.

3.4.3 IV Risks

A hollow needle/plastic tube will be placed in the arm for taking blood samples or giving fluids. When the needle goes into a vein, it can cause pain. A special cream (EMLA®) may be used to numb the area where the needle will be inserted. The most common risks related to putting the numbing cream on the skin are redness, blanching (temporary whiteness of the skin area), swelling, and itching. There will be the minor discomfort of having the needle/plastic tube taped to the arm. In about one in 10 cases a small amount of bleeding under the skin will produce a bruise. Very rarely a blood clot may form in the vein, infection may occur, or significant blood loss may occur.

3.4.4 Subcutaneous Catheter Risks (Continuous Glucose Sensor)

Subjects using the continuous glucose sensor will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours it is possible get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causing a bruise (1 in 10 risk).

3.4.5 Risk of Hypoglycemia

As with any person having insulin-dependent diabetes, there is always a risk of having a low blood sugar (hypoglycemia). In this study, hypoglycemia may occur during or following the time the exercise portion of the study. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days you may not be as aware of symptoms of low blood sugar. Since we will be closely monitoring subjects during this study, a serious low blood sugar is not expected to occur. Even if severe low blood sugar does occur, it almost always goes away quickly with treatment to raise the blood sugar.

3.4.6 Risk of Hyperglycemia

During one of the visits, subjects will disconnect the insulin pump during the exercise session. This may produce a greater rise in the blood glucose than would occur had the pump been left connected. Hyperglycemia is usually acutely benign, but may be associated with thirst, glycosuria, ketoacidosis, and hyperosmolar coma. A serious effect from the hyperglycemia is not expected to occur in a single subject as the insulin pump will be reconnected after completion of the exercise session. Because of the monitoring, the risk is lower than it would be for the subject at home if the pump had been disconnected (a not infrequent occurrence).

3.4.7 Blood Volume Requirements

At the time of enrollment, the maximum number of blood draws that can be performed based on a subject's weight will be determined so that the maximum blood volume in the blood draws for both visits combined will not exceed 5% of the subject's blood volume (calculated by multiplying the subject's weight in kilograms by 70 [70cc / kg blood volume] and then multiplying by .05). The maximum number of blood draws is then determined by dividing this maximum blood volume by the amount of blood in each blood draw at the center.

For reinfusion centers, the blood sampling will remove approximately 68.65 ml of blood during each visit (137.3 ml total). This blood volume is acceptable for subjects weighing $\geq$39.5 kg.

At the discard centers, the blood sampling will remove approximately 79.65 ml of blood during each visit (159.3 ml total). This blood volume is acceptable for subjects weighing ≥46.0 kg.

The study may include other risks that are unknown at this time.

3.5 Adverse Events

Adverse event reporting will be limited to (1) events that meet criteria for a serious adverse event (SAE), (2) events that are considered to have a possible (or greater) relationship to any study procedure, (3) hyperglycemia resulting in diabetic ketoacidosis or hyperosmolar nonketotic coma, and (4) hypoglycemia resulting in seizures or loss of consciousness. Adverse events that occur during the study and up to 1 week after completion of the last visit will be reported.

An adverse event is considered a *Serious Adverse Event* (SAE) when it meets one or more of the following criteria: (1) death, (2) life-threatening, (3) required or prolonged hospitalization, (4) permanent disability, or (5) required intervention to prevent permanent impairment/damage.

The relationship of any adverse event to any aspect of study participation will be assessed and graded by a study investigator on a four-point scale: (1) not related, (2) possible, (3) probable, and (4) definite. The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity; thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

3.6 Reporting Requirements for Serious and/or Unexpected Adverse Events

Any serious or unexpected adverse event occurring during the study and up to 1 week after completion of the last visit will be reported to the Coordinating Center within one working day of occurrence. A written report on such an event will be sent to the Coordinating Center within five days of occurrence, stating a description of the reaction, any required intervention and the outcome. Each principal investigator is responsible for informing his/her IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB. Contact information for the Coordinating Center is located in the front of the protocol as well as in the Study Directory.

3.7 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) provides study oversight for all DirecNet protocols. The DSMB includes three physicians with expertise in type 1 diabetes in children, a statistician, and a psychologist. The DSMB meets at least twice each year either at a meeting or via conference call. The Board will review all serious adverse events on an expedited basis and will review all other adverse events as part of interval reports.

3.8 Benefits

It is expected that the information gained from this study of exercise will have an important role in the management of diabetes in children. Therefore, the results of this study are likely to be beneficial for children with diabetes. In addition, it is possible that the blood glucose information will be useful for the subject's diabetes management by identifying how much the blood glucose varies during and after exercise.

3.9 Subject Compensation

Subjects will receive $50 for each visit for a total of $100 for completion of both visits. Compensation will be prorated for subjects who do not complete both visits. Payment will be made for visits that require rescheduling due to blood glucose values out of range.

3.10 Subject Withdrawal

Participation in the study is voluntary, and a subject may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol.

3.11 Data Confidentiality

For security purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. Information given to the coordinating center will include: diagnosis, general physical exam information (height/weight/blood pressure/etc.) insulin, hemoglobin A_{1C} results, continuous glucose monitor results, blood work results, HGM blood glucose measurements, information pertaining to hypoglycemic excursions and the treatment given, as well as all other study related data gathered during study visits. At the end of each admission, the study devices will be downloaded to a computer that is secured and password protected, the files will be sent directly to the coordinating center via email. All files will include only the subject's identifier; no names or personal information will be included. Laboratory specimens will be sent to the University of Minnesota which serves as the central lab for DirecNet. Specimens may also be sent to other laboratories.

CHAPTER 4
STATISTICAL CONSIDERATIONS

The analysis plan is summarized below. It will be detailed in a separate document.

4.1 Outcome Measures

4.1.1 Primary Outcome

The primary outcome for this study will be the occurrence of hypoglycemia (≤70 mg/dL) during exercise.

4.1.2 Secondary Outcomes

The following outcome measures will also be analyzed. The protocol calls for treatment of hypoglycemia ≤65 mg/dL so for analysis, the nadir glucose during exercise will be truncated at 65 mg/dL.

- Continuous measure:
  - Drop in glucose during exercise
  - Percentage drop during exercise
- Binary outcomes:
  - Drop in glucose from baseline of at least 50% during exercise
  - Hyperglycemia (≥20% glucose rise) and/or presence of ketones during exercise

4.2 Statistical Analysis

4.2.1 Primary Outcome

Percentage of subjects developing the primary outcome (falling ≤70 mg/dL during exercise) with 95% confidence interval will be given by visit type. A repeated measures generalized estimating equations (GEE) model will be fit adjusting for baseline glucose and period effects. If the effect of baseline glucose on the log-odds of the event probability appears non-linear, then baseline glucose will be divided into categories and treated as a discrete variable. Although, this study is not powered for the detection of an interaction, this will be explored by adding a period by visit type interaction term to the model. If a significant interaction is detected then results will be displayed separately for 1st vs. 2nd visits. If the non-linear GEE model fails to converge (e.g., if a group has zero events), then a permutation test will be used instead.

4.2.2 Secondary Outcomes

Analysis of binary outcomes will parallel that described above for the primary outcome.

For each continuous outcome, mean ± SD, minimum and maximum values for be presented by visit type (insulin pump vs. no insulin pump during exercise). If the distribution is skewed, then median and quartiles will also be given.

A repeated measures model will be fit to compare each continuous outcome between visits with and without the insulin pump. The model will adjust for baseline glucose and any period effect (first vs. second visit). If the relationship of baseline glucose to the outcome appears non-linear then baseline glucose will be divided into categories and treated as a discrete variable. A period by visit type interaction will be tested. If a significant interaction is detected then results will be displayed separately for 1st vs. 2nd visits. Residuals from this regression model will be examined and if substantial deviations from a normal distribution are detected, transformations and/or adjustment for the floor effect at 60 mg/dL will be explored.

Secondary analyses will explore the potential role of the following risk factors by adding them as covariates to the regression model (including the primary outcome hypoglycemia):

- Self-reported level of activity
- Gender
- HbA1c
- Clinical site
- Body mass index (BMI)
- Age

HbA1c and age may be divided into categories and treated as discrete variables if non-linearity is suggested. If any of these factors are found to associate with glucose, then a possible interaction with visit type will also be explored.

4.3 Sample Size

A previous DirecNet study of exercise found that 42% with a baseline glucose in the range of 120 to 200 mg/dL had a drop in the glucose level during exercise to ≤70 mg/dL. Simulations were run assuming a correlation of 0.3 between visits from the same subject. Results suggest that N=55 subjects would be required to give 80% power to detect a halving of this rate (i.e., 42% vs. 21%) using a two-tailed test at α=0.05.

The mean drop for these subjects during the previous exercise study was 75 mg/dL with a standard deviation of 37 mg/dL and the mean percentage drop was 46% with a standard deviation of 18%. A sample size of N=55 would give >99% power to detect a halving of the mean (i.e., 75 vs. 37.5 mg/dL and 46% vs. 23%) for both these outcomes.

4.4 Interim Analysis

Once approximately 25 subjects have completed both visits, an interim analysis will be conducted to consider stopping the study early if the observed treatment effect is either considerably smaller (futility) or larger (efficacy) than anticipated. Conditional power curves based on the observed treatment effect so far will be generated for hypoglycemia, drop in glucose and percent drop glucose under different scenarios for the true treatment effect.

Hypothesis tests for treatment effects on hypoglycemia, drop in glucose and percent drop in glucose will be formally evaluated with the intention that stopping for efficacy will be recommended only if $p<0.001$ for the hypoglycemia outcome.

Results of these interim analyses will be presented to the DSMB for determination whether stopping for futility or efficacy is warranted.

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