Progress Report: Comparison of two carbohydrate intake strategies to improve glucose control during exercise in adolescents and adults with type 1 diabetes

Description of activities

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This study proposes to determine the optimal timing of CHO intake for the reduction of exercise-induced hypoglycemia among adolescents and adults with T1D.
It is an open-label, randomized, two-way crossover trial comparing the efficacy of two snacking strategies to avoid exercise-induced hypoglycemia.

Introduction:

Exercise is encouraged for children with type 1 diabetes (T1D) mellitus for its important physiological and psychological benefits (1). Regular physical activity can contribute to HbA1c reduction (2) and have a positive impact on multiple cardiometabolic risk factors including body composition, endothelial function, and lipids (3–5). It might thus decrease cardiovascular disease risk, which is a major cause of morbidity in young adults with T1D (6). Physical activity is also associated with psychological health, well-being, and general quality of life in patients with T1D (7,8). However, fear of hypoglycemia remains the main barrier to physical activity practice in both children (9) and adults alike (10). In pediatric patients, parental fear of hypoglycemia especially for nighttime episodes could also contribute to limiting physical activity (11). In support of these concerns, recurrent severe hypoglycemia may have a deleterious impact on diabetic children’s cognitive functions (12). Indeed, despite all the proven and potential benefits, children and adolescents with T1D have been shown to be less physically active, while engaging in more computer time than their healthy peers (13).

During physical activity, patients face a double risk for hypoglycemia: the first, at the time of exercise, and the second 6-12 hours after exercise, which frequently coincides with nighttime. The main cause of hypoglycemic risk during exercise is the inability for patients with T1D to reduce previously administered insulin levels as observed in non-diabetic subjects. Delayed hypoglycemic risk is related to glycogen store restoration in the context of increased insulin sensitivity, absence of a recent meal (particularly for night-time risk) and deficient counter-regulatory hormone responses (e.g. glucagon) (14). In addition, multiple factors modulate hypoglycemic risk including type, intensity and duration of exercise, timing since last meal and insulin injection, glucose value at exercise onset, training status, stress, etc. making glucose regulation during exercise complex (15).

The prevention of exercise-induced hypoglycemia is a research priority which has been highlighted in the recent international guidelines for exercise and T1D (3,15). Two main factors are accessible to reduce hypoglycemic risk: insulin dose reduction and carbohydrate (CHO) intake addition. Strategies to reduce hypoglycemic risk with insulin reduction are useful, but require anticipation of exercise which is more difficult in the pediatric population, mainly applies if exercise is undertaken within 3 hours of the last meal, can be insufficient if exercise lasts longer than 30 min, and is associated with post-exercise rapid glucose rise (16). While under-studied, CHO intake remains a frequently needed and commonly used strategy to prevent exercise-induced hypoglycemia. To our knowledge, few studies have compared the efficacy of different CHO intakes to prevent exercise-induced hypoglycemia. Murillo et al. tested in adults a pre-exercise CHO supplement of 0.7g/kg (55g) or 0.35g/kg (30g) taken 30 minutes before the start of a 10km run, and found that 0.35g/kg was more effective to maintain stable blood glucose levels. In addition to the amount of CHO ingested, the timing of CHO intake could also have an impact on the occurrence of exercise-induced hypoglycemia. In 2011, it was shown in adolescents that if patients ingested CHO during physical activity when real-time continuous glucose monitoring alerted them of a drop in glycemia, it maintained euglycemia during exercise (17).

It is also important to consider that an excessive CHO consumption could also induce hyperglycemia (15), thus emphasizing the importance of both the amount and the timing of carbohydrates intake during physical activity.

This study proposes to determine the optimal timing of CHO intake for the reduction of exercise-induced hypoglycemia among adolescents and adults with T1D.

METHODS :

It is an open-label, randomized, two-way crossover trial comparing the efficacy of two snacking strategies to avoid exercise-induced hypoglycemia.

We aim to enroll 12 adolescents and 21 adults with T1D using multiple daily injections.

HYPOTHESIS:

We hypothesize that CHO intake distributed before and during the exercise period will be more efficient to maintain glucose levels in the target range (4.0-10.0 mmol/L) than a single snack given before exercise.

OBJECTIVE

Primary Objective: To compare the efficacy of two snacking strategies to maintain glucose levels in the target range during exercise in adolescents and adults with T1D:

- Strategy 1: a snack containing ~0.5g of CHO per kilogram of body weight – rounded to the nearest 5g - given 5 minutes before exercise.

- Strategy 2: a snack containing ~0.5g of CHO per kilogram of body weight – rounded to the nearest 5g - distributed this way: ~40% given 5 minutes before exercise, ~30% at 20 minutes of exercise and the last ~30% at 40 minutes of exercise.

Secondary objective: To investigate the usefulness of a bedtime snack on the frequency of post-exercise induced hypoglycemia (exploratory analysis). Our hypothesis is that in the context of reduced basal insulin, a bedtime snack does not bring additional hypoglycemic risk reduction.

Recruitment:

Adolescents subjects are approached by the research team at CHU Sainte Justine type 1 diabetes clinic and adults subject at IRCM (Institut de Recherches Cliniques de

Montréal). Interested subjects that meet basic eligibility criteria are scheduled for the admission visit.

Visit schedule:

Admission visit (Visit 1)

At the admission visit, the following procedures are undertaken:

• Signature of the consent form

• Medical examination

• A1c test is obtained if not recent (< 3 months for adolescents; < 2 months for adults)

• Weight, height and waist circumference is obtained.

• $VO_{2\ peak}$ test on ergocycle.

Peak oxygen consumption (VO_{2peak}), the gold standard to measure aerobic fitness in youth, is used to estimate fitness. VO_{2peak} is determined during an adaptation of the standard incremental exercise test on an stationary bicycle until volitional exhaustion with use of indirect calorimetry measurements throughout the test (18,19).

Contrary to adults, body composition using DXA (Dual X-Ray Absorptiometry) is not evaluated and the electrocardiogram is not done.

• Records of insulin therapy are obtained.

• Training is given by a nurse on how to install a glucose monitoring system (Dexcom G4 Platinum, Dexcom) or is installed at the IRCM by the research nurse.

- On the day of the intervention visit, participants have a standardized lunch (50g of CHO for females and 70g of CHO for males) at 12:00 and are asked not to eat afterwards (except for correction of hypoglycemia). Visit 1 and Visit 3 are separated by a maximum of 6 weeks. Intervention visits are separated by 3-30 days.

Study procedures

- Participants are admitted at 14:00.
- At 15:30 : participants consume a snack
    - containing ~0.5g of CHO per kilogram of body weight (strategy 1) or
    - ~40% of a snack containing ~0.5g of carbohydrate per kilogram of body weight (strategy 2).

  The total amount of CHO in each snack is rounded to the nearest 5g.

- At 15:30, the exercise consists of a 60-minute exercise on the ergocycle at 60% of VO_{2peak} (moderate intensity).
- During the exercise period,
    - A heart rate sensor is installed.
    - With strategy 2, a snack containing ~30% of ~0.5g of CHO per kilogram of body weight is given at 15:50 and 16:10.
    - Capillary blood glucose is measured just before exercise (i.e. at 15:30) and then every 10 minutes until the end of exercise.
    - The perceived effort is measured using the OMNI scale for adolescents and the BORG scale for adults at the start of exercise and then every 10 minutes until the end of exercise.
- At 16:30, the exercise is completed and glucose levels are monitored every 20 minutes for 1 hour.
- At 17:30
    - The participant is discharged and asked to eat a standardized dinner at home (60g of CHO for females and 80g of CHO for males).

In order to investigate the usefulness of a bedtime snack on the frequency of post-exercise induced hypoglycemia (exploratory analysis), patients are asked to:

- Reduce their usual bedtime basal insulin dose by 20%, a strategy which has proven to reduce nocturnal hypoglycemic risk following and afternoon exercise [3].
- Then, the following strategies are applied in a random order:
    1. No bedtime snack:

- If bedtime glucose is < 7.0 mmol/L, participants are allowed to take a bedtime snack (30g of CHO and ~10g of protein without insulin bolus).

2. A bedtime snack of 30g of CHO and ~10g of protein without an insulin bolus.

Randomization

Each study participant is assigned a unique anonymous identification number (ID), which is used throughout the study. A block-balanced randomization is used to determine the order of the interventions.

Preliminary Results.

Preliminary results in the adult population (16 adults) suggest that both snacking strategies seem appropriate in order to maintain blood glucose levels within glycemic targets (4-10mmol/L). Percentage of time in target range was 86±25% with the pre-exercise snack and 95±11% with the distributed snack. The number of hypoglycemic episodes is low (0 with pre exercise snack and 2 with distributed snack). There is a trend for less glycemic variability with the distributed snack.

	Single snack	Distributed snack	P-value
Number of hypoglycemia (<4 mmol/L)	0	2	
Average glycemia at start (mmol/L)	6.85 ±1.89	6.55 ±1.72	0.419
Mean glycemia (Mean ±SD) (mmol/L)	7.12 ±1.91	6.52 ±1.39	0.160
% of time between 4 -10 mmol/L	86±25	95 ±11	0.096
% of time >10 mmol/L	0 (0-9)	0 (0-0)	0.048
Glycemic Δ (mmol/L) (Peak glycemia – start glycemia)	+1.60±1.38	+0.58±0.68	0.006

Table 1: Comparison between single snack and distributed snack strategies (n: 16 adults).

Perspective: Developing optimal strategies could reduce hypoglycemic risk and translate into higher levels of physical activity among adults and adolescents with T1D, which could lead to an improved cardiometabolic risk factor profile and a better quality of life.

Timeline and current status:

Timeline:

09-2017**:** start of enrolment of adult population

12-2017 submission to pediatric ethic committee

03-2018 approval by pediatric ethic committee

03-2018 start of enrolment of pediatric population

07-2018: 16 adults included, 5 adolescents included. (after 6 drop out (3 adolescents and 3 adults)

11-2018: End of recruitement

02-2019: Manuscrit submission

Publication plan: ISPAD support will be acknowledged in publication arising from this work

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