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Treatment of Hypoglycemia during Exercise in Children and Adolescents with Type 1 Diabetes

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Abstract

Background: The risk of hypoglycemia is increased with moderate-intensity exercise in patients with type 1-diabetes (T1D), and strategies to prevent hypoglycemia during or after exercise typically involve adjustment of insulin dosing and/or Carbohydrate (CHO). In case of hypoglycemia during unplanned exercise, international guidelines consider treatment as for standard hypoglycemia correction.

The aim of this review was to provide an up to date summary of the available evidence on amount and type of carbohydrate to correct hypoglycemia during exercise, in children and adolescents with T1D.

Methods: following a literature search on hypoglycemia treatment during exercise in T1D, in subjects 0-18 years, without Predictive Low Glucose Suspend (PLGS) augmented insulin pumps, or Predictive Low Glucose Management (PLGM) or Hybrid Closed Loop (HCL) systems, and limited to the last 15 years was performed. A total of 131 studies were identified and 5 studies were included in the review.

Results: The studies we analysed in the review are concordant with current international guidelines to use the calculation 0.3 g/Kg to estimate the quantity of rapid acting CHO for treating hypoglycemia in the pediatric population during exercise. In the context of moderate intensity exercise, forms of glucose and sucrose can perform similar efficacy that could be lower for fructose. Few studies suggest considering repeated treatment or a snack in particular in case of unplanned exercise.

Conclusion: This review collected available evidence on hypoglycemia treatment in the particular context of exercise; more data comparing different strategies in children and adolescents are necessary.

Keywords: Treatment; Hypoglycemia; Type 1 diabetes; Exercise; Children-adolescents

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Introduction

In children and adolescents with type 1 diabetes (T1D), a glucose value ≤ 3.9 mmol/L (70 mg/dL) is considered as hypoglycemia because of the potential for glucose to fall further [1]. Treatment of hypoglycemia should increase the blood glucose (BG) by nearly 3 to 4 mmol/L (54 to 72 mg/dL) and this can be accomplished by giving glucose tablets or sweetened fluids [1].

The amount of carbohydrate required will depend on the size of the child, type of insulin therapy, active insulin on board, the timing and intensity of antecedent exercise as well as other factors; approximately 0.3 g/Kg of rapid acting carbohydrate is needed [1]. The type of carbohydrate is also important: Few studies in adults [2-4] concluded that oral glucose and sucrose act faster than forms of fructose to correct insulin-induced hypoglycemia. In 2 out of three of these studies, sucrose requires a greater amount to provide the same increase in BG compared to oral glucose [2,3].

In children and adolescents with T1D the blood glucose response to exercise is affected by many factors including the duration, intensity and type of exercise, the time of day when exercise is performed, plasma glucose and insulin levels, and the availability of supplemental and stored carbohydrates. The risk of hypoglycemia is increased with moderate-intensity exercise, during, immediately after as well as 7 to 11 hours after exercise. Instead there is minimal data to support an increased risk of hypoglycemia with less than 30 mins of activity [5].

Strategies to prevent hypoglycemia during or after exercise typically involve adjustment of insulin dosing and/or Carbohydrate (CHO) intake and are well reported in ISPAD guidelines [5] and in the EASD-ISPAD-ADA position statement on the use of CGM systems during exercise [6]. Regarding hypoglycemia treatment during exercise, international guidelines often consider standard hypoglycemia correction and are usually based only on Level 4 evidence (expert opinion). According to ISPAD 2018 guidelines, approximately 9 g of glucose tablets or other form of quick-acting carbohydrate should be given for a 30 kg child (0.3 g/kg) and 15 g for a 50-kg child, to treat hypoglycemia [5].

The aim of this review was to provide an up to date summary of the available evidence on amount and type of carbohydrate to correct hypoglycemia during exercise in children and adolescents.

Criteria for Study Selection

We searched electronic database Pubmed for studies published from December 9, 2006 up to December 9, 2021. Search terms, or "MESH" (Medical Subject Headings) for this review included different combinations: Teen* or adolesce* or child* AND "type 1 diabetes" or "diabetes" or "T1D" or "IDDM" (Insulin-Dependent Diabetes Mellitus) AND "hypoglycemia" AND "treatment" AND "exercise" or "physical activity". To avoid missing any relevant studies, we also screened the reference list of eligible studies.

Inclusion criteria: Inclusion criteria were:

i. Study population: Children and adolescents (aged 1-18 years) with T1D

ii. treated by Multiple Daily Injections (MDI) or Continuous Subcutaneous Insulin Infusion (CSII);

iii. Study type: observational studies (cohort, case-control, cross-sectional studies), exploratory studies, mix of qualitative and quantitative studies; review articles or position statements were excluded, but their reference lists were screened to identify potential eligible studies;

iv. Data available on hypoglycemia treatment;

v. Publication date: Last 15 years (2006-2021).

Exclusion criteria: Exclusion criteria were:

i. Data available only for adults >18 years;

ii. Case reports; studies with <10 patients with reported hypoglycemia treatment;

iii. Patients in therapy with predictive low glucose suspend (PLGS) augmented insulin pumps, or with Predictive Low Glucose Management (PLGM) or Hybrid Closed Loop (HCL) systems;

iv. Full paper not available or abstract only;

v. Study not yet published;

vi. Languages other than English were not "a priori" exclusion criteria.

Data Extraction and Management

A total of 131 studies were identified following the literature search, and other 12 were identified with reference screening of review articles. After reviewing the 143 titles and abstracts, 115 records were excluded: 20 review articles, 21 studies including only participants older than 18 years, 3 studies with sample sizes less than 10, 42 studies reporting outcomes different from those of interest, 28 studies including patients in therapy with Predictive Low Glucose Suspend (PLGS) augmented insulin pumps, or with Predictive Low Glucose Management (PLGM) or Hybrid Closed Loop (HCL) systems, 1 study in Russian.

A total of 28 full-text manuscripts were assessed for eligibility: after full text examination 23 studies were excluded: 2 review articles, 8 studies including only participants older than 18 years, 1 study with sample sizes less than ten, 12 studies reporting outcomes different from those of interest.

A final number of 5 studies were included in this review **(Table 1)**. In Supplementary material **(Table S1)** a list of the studies screened for this review along with the reason for exclusion are reported.

Table 1: Characteristic of the five studies included in the review. Data are given in Mean ± standard deviation or median (interquartile range).

Setting	Study design	T1D sample size (n)	Age (years)	Diabetes duration (years)	HbA1c (%)	Activity (type, intensity, duration, time and frequency)	Rapid acting CHO (type, amount)	Results
New Zealand Diabetes Camp (5 days)	RCT Hypo: <4 mmol/L; Capillary BG checks	43 (9 on CSII)	10.4 ± 1.2	Not reported	8.6 ± 1.4	Not reported	Number of hypoglycemia: Average 0.9 episodes per child per day; Glucose tablets, Jellybeans, orange juice, sugar mints (Mentos dragees® 0.3 g/Kg)	Jellybeans are less effective treatment than the other three treatments. Glucose tablets, Mentos dragees® and orange juice are of similar efficacy. Treatment with 0.3 g/kg of CHO (excluding jellybeans) effectively resolved hypoglycemia in most children, with 15 min.

New Zealand At home	RCT Hypo: <4 mmol/L; Capillary BG checks	11 CSII	11.4 ± 3.2	Not reported	7.4 ± 0.7	Not reported	Glucose tablets (If BG 3-3.9 mmol/l 0.3 g/kg body weight Vs. 10 g) If BG <3 mmol/l 0.6 g/kg body weight Vs. 20 g Capillary BG test. BG were re-tested 10 min after treatment, with a repeat dose if still <4 mmol/l.	Weight-based treatment using 0.3 g/kg glucose was more effective than standard treatment recommended in international guidelines in children.
Canada At home	RCT Hypo: <4 mmol/L; Capillary BG checks	33	5.4 -15.5	3.1 ± 2.3	Not reported	Not reported	BD Glucose Tablets™ (Glucose) Skittles™ (sucrose) Fruit to Go™ (fructose) Children ≤ 10 yr: 10 g of total CHO; Children >10 yr: 15 g of total CHO	No significant difference between treatment with glucose and with sucrose was noted, but the treatment effectiveness for fructose was significantly lower than sucrose ($p<0.001$). Skittles™ are as effective in treating hypoglycemia as more expensive BD Glucose Tablets™ in children with type-1 diabetes. Capillary BG test. BG was checked again after 15' and if the next meal or snack were more than 1 h away, a snack containing 15 g of carbohydrate and protein was taken.
Canada Outpatient clinic	Longitudinal Hypo: <4 mmol/mol	10	14.0 ± 1.5	5.3 ± 3.3	7.6 ± 0.7	60-min ergocycle of moderate-intensity exercise (50% VO2 max), 120 min after breakfast; followed by a 30-min recovery period	The amount of glucose in the form of tablets taken to treat late hypoglycemia was recorded. During exercise, 5 patients experimented hypoglycemia and needed 5-6 g of CHO to correct BG.	This study compared two nutritional strategies that limit BG decrease and therefore may prevent hypoglycemia during and shortly after exercise.
Italy Diabetes camp	RCT Hypo: <4 mmol/L; Capillary BG checks	21 (3 on CSII)	13.8 (12.0-15.9)	5.4 (1.4-12.4)	7.6 (6.8-8.2)	Trekking camp for 5 days, with 70 Km itinerary.	0.3 g/Kg glucose Group 1: a preparation (Glucosprint Plus®); Group 2: sugar fondant candies (Perugina®); Group 3: fruit juice On average 1.3 episodes per child per day. Patients wore isCGM	Time below range: no difference. Rise in blood glucose levels: no difference N° of hypoglycemic events after correction of hypoglycemia: no difference. 0.3 g pro Kg of rapidly acting CHO in the form of glucose, sugar fondant or orange juice, effectively resolve hypoglycemia in children during aerobic prolonged physical activity.

Abbreviations: CSII: Continuous Subcutaneous Insulin Infusion; Hypo: Hypoglycemia; BG: Blood Glucose; T1D: Type 1 Diabetes; isCGM: intermittently scanned Continuous Glucose Monitoring; CHO: Carbohydrate.

Outcomes

Among the 5 manuscript analyzed for this review, in three physical activity was not quantified.

McTavish et al. enrolled in a RCT 43 children with T1D (range 8-12 years) [7]. When experimented hypoglycemia, they were randomly assigned for each episode using a sealed envelope: glucose tablets, jellybeans, orange juice, and sugar mints (Mentos dragees®). An equivalent CHO dose was calculated for each patient for each treatment (0.3 gCHO/kg) and provided to camp leaders. The authors concluded that Jellybeans are less effective treatment for hypoglycemia than the other three treatments. Glucose tablets, Mentos dragees® and orange juice are of similar efficacy. Treatment with 0.3 g/kg of CHO (excluding jellybeans) effectively resolved hypoglycemia in most children, with 15 min often required to normalize blood glucose. The setting was a diabetes camp, but physical activity was not quantified and time spent in hypoglycemia could not be reported because participants had only capillary BG checks [7].

A similar weight-based approach was also found to be effective in 11 children, aged 11.4 ± 3.2 years, on CSII [8]. At each episode subjects were randomly assigned to one of two treatment protocols using glucose tablets: for BG levels 3-3.9 mmol/l either 0.3 g/kg body weight or usual treatment with 10 g; for BG levels <3 mmol/l, either 0.6 g/kg body weight or usual treatment with 20 g. Weight-based treatment using 0.3 g/kg CHO was more effective for symptomatic hypoglycemia in children and adults with T1D who were using CSII, than treatment based on current international recommendations (not weight-based). In this study physical activity was not quantified [8].

Husband et al. studied at home 33 children (range 5.4-15.5 years). In a randomized crossover design they compared glucose, sucrose and fructose [9]. BD Glucose Tablets™ was chosen as glucose, Skittles™ as sucrose, and Fruit to Go™ as the fructose choice as it is easier to carry than juice; treatments were prepackaged and provided to the subjects. Children ≤ 10 years of age were given 10 g of total CHO, whereas those >10 years were given 15 g of total CHO. After 15 minutes, BG was checked again and if the next meal or snack were more than 1 h away, a snack containing 15 g of carbohydrate and protein was taken. This recommendation was implemented because the glycemic response to the ingestion of oral glucose is known to be transient [10]. Each subject treated five hypoglycemic events with glucose, five with sucrose, and five with fructose; subjects were randomized into order of treatment. Effectiveness for fructose was significantly lower while no differences between glucose and sucrose were detected. Author concluded that Skittles™ are as effective in treating hypoglycemia as more expensive BD Glucose Tablets™ in children with T1D. Only capillary BG measurements were performed and physical activity was not quantified [9].

Dubè et al., in their study, aimed to compare the effect of two nutritional strategies to prevent exercise-induced hypoglycemia, reported also data on different amount of CHO needed to correct hypoglycemia [11]. Ten subjects with T1D, aged 14 ± 1.5 years, performed 60-min ergocycle of moderate-intensity exercise (50% VO2 max), 120 min after breakfast. Each exercise session was followed by a 30-min recovery period. According to the protocol they reported, during exercise, if BG fell <4 mmol/L or symptomatic hypoglycemia occurred, the session was stopped and CHO tablets were provided in sufficient amount to correct hypoglycemia. The amount of glucose in the form of tablets taken to treat late hypoglycemia was recorded. During exercise, 5 patients experimented hypoglycemia and needed 5-6 g of CHO to correct BG; during recovery hypoglycemia occurred in 7 subjects and they needed 5 to 13 g of CHO. There was no significant difference in the quantity (g) of CHO tablets given during exercise and after exercise [11].

Fumanellli et al. compared the response to three types of frequently used rapid acting CHO to correct hypoglycemia, during prolonged aerobic exercise in 21 adolescents aged 12-16 years with T1D [12]. All participants took part in a trekking camp for 5 days, with 70 Km itinerary. Every participant wore a intermittently scanned continuous glucose monitoring (IsCGM) system and insulin and nutritional adjustments were done according to a protocol. Subjects have been randomized into three different groups: group 1 had to correct hypoglycemia with 0.3 g/Kg of a glucose preparation (Glucosprint Plus®); group 2 used sugar fondant candies (Perugina®); group 3 used fruit juice. It is noteworthy that foods used "in real life" to correct hypoglycemia, with different structure and form, were used and not glucose, sucrose and fructose. Each patient experimented a mean of 1.3 episodes of hypoglycemia per day. No significant differences were highlighted among the three treatments in terms of time spent in hypoglycemia, rise in blood glucose levels and number of hypoglycemic events after correction of hypoglycemia. These results suggested that 0.3 g/Kg of rapidly acting CHO in the form of glucose, sugar fondant or orange juice, effectively resolve hypoglycemia in children during aerobic prolonged physical activity [12].

Discussion

Strategies on how to prevent exercise-induced hypoglycemia are available and are the most important approach to planned exercise [5,6] in combination with new technologies. Using rtCGM systems, hypoglycemia alert should be set at 5.6 mmoL/L (100 mg/dL) or individualized if required, and the rate-of-glucose-change alerts should be used to initiate an earlier action [6]: in children and adolescents with T1D, at a glycemic threshold of 7.0 mmol/L (126 mg/dL) accompanied by a slightly downward trend arrow, 5 g (0.2 g/Kg) of carbohydrates should be consumed immediately; 10 g (0.3 g/Kg) of carbohydrates should be consumed if the valued is accompanied with a downward trending arrow [6]. Currently available technologies like automated insulin suspensions (suspend on low, suspend before low) as well as artificial pancreas systems have reduced time below range ≤ 3%-4% [13-16].

However adolescents in MDI or CSII treatment can experiment hypoglycemia in particular when they engage in unplanned exercise, and guidelines often consider standard hypoglycemia treatment and not in the particular context of exercise, probably for the lacking of evidence.

This review aimed to compare real life studies that reported different rapid acting CHO strategies to correct hypoglycemia in children and adolescents with T1D, during exercise.

Only 5 studies were concordant with the outcomes selected for this review. We had to exclude two studies that tested carbohydrate intake algorithms designed for maintaining euglycemia during sports in children and adolescents [17,18] they suggested amounts of CHO (dextrose or glucose tablets) at specific thresholds to prevent hypoglycemia but did not consider values <4.0 mmol/L. Moreover only two studies out of 5 included in this review, quantified physical activity: in Fumanelli et al. subjects did 70 Km of trekking in 5 days [12], while in Dubè et al. patients performed a 60 minutes moderate intensity exercise [11].

All the studies we analyzed in the review are concordant with the current international guidelines to use the calculation 0.3 g/Kg to estimate the quantity of rapid acting CHO for treating hypoglycemia in the pediatric population during exercise [5].

Regarding type of rapid acting CHO previous studies on adults [2-4] reported glucose as the most effective carbohydrate for the initial treatment of hypoglycemia: glucose preparations could act faster than the other foods containing rapid acting CHO; the glycemic index of glucose is 99, of sugar is 70 and of fruit juice is 40-60 [19,20]. Results on sucrose compared with glucose are not concordant. Brodows et al. using a modification of the glucose clamp technique tested the efficacy of commonly used foods to correct hypoglycemia in T1D adult patients [2]. After lowering the plasma glucose level to 55 mg/dL, they found that ingestion of 20 g of D-glucose provides an effective glycemic response for periods of at least 40 minutes. 40 g of carbohydrate in the form of orange juice results in approximately the same rise, as well as 20 g in the form of glucose tablets. Chocolate, milk and other foods containing fat will cause the glucose to be absorbed more slowly and should be avoided as the initial treatment of hypoglycemia [2]. Georgakopoulos et al. compared the effects of saccharose and glucose on the recovery from insulin hypoglycemia in 17 normal adult volunteers. The authors concluded that oral glucose acts faster than sucrose in insulin-induced hypoglycemia and sucrose requires a greater amount to provide the same increase in BG compared to oral glucose [3]. Slama et al. induced hypoglycemia in 41 adult volunteers with T1D [4]. Subjects were randomized to 7 different carbohydrate preparations to test the most effective method of treatment. In this study, subjects were given seven orally administered carbohydrates: glucose in solution, tablets, and gel; sucrose in solution and tablets; a hydrolyzed polysaccharide solution; and orange juice; each of which provided 15 g of carbohydrate. Authors concluded that ingestion of 15 g of carbohydrate in the form of glucose or sucrose tablets or as a solution provide an effective therapy; both sugars seem equivalent. Carbohydrate in a gel form and orange juice were found to be significantly less effective in resolving hypoglycemia [4]. Regarding hypoglycemia treatment in the particular context of physical activity, in 2016 De Fazio et al. recruited 100 adults T1D athletes. The authors demonstrated that a mean of 12 g of glucose vials (Glucosprint®, Harmonium, Italy) stopped exercise-related hypoglycemic events leading glucose levels to about twice as high as starting ones. Average glycemic increase within 8-15’ measured by capillary BG was +53.2 mg/dL [21].

For children and adolescents, in two studies included in our review, set in clinical practice at diabetes camps [12,9] forms of glucose, sucrose and fructose performed similar efficacy, therefore delay of the absorption was not so decisive. In another study no significant difference between treatment with glucose and with sucrose was noted, but the treatment effectiveness for fructose was significantly lower than sucrose. In the same study, authors reported that the amount of rapid acting CHO calculated by 0.3 g/Kg could be sometimes insufficient when unplanned exercise is practiced and if the next meal or snack is more than 1 h away, they suggested considering a snack containing 15 g of carbohydrate and protein, after a capillary blood glucose retesting [9]. Indeed we have to consider that the glycemic response to oral glucose or other forms of short acting CHO is transient, typically last less than two hours [10].

Conclusion

In conclusion, available evidence suggests treating hypoglycemia during exercise starting with 0.3 g/Kg of a rapid acting CHO. In this context forms of glucose or sucrose can perform similar efficacy that could be lower for fructose. Few studies suggest considering repeated treatment or a snack in particular in case of unplanned exercise. More data comparing different strategies to correct hypoglycemia treatment in adolescents performing exercise are necessary.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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