

Treatment of hypoglycemia during prolonged physical activity in adolescents with type 1 diabetes mellitus

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Summary. *Background:* Management of children with type 1 diabetes (T1DM) during physical activity includes intensive blood glucose monitoring and proper insulin and nutritional adjustments in order to prevent hypoglycemia. Regarding the treatment of hypoglycemia during physical activity, different types of rapid acting carbohydrate (CHO) can be used and recommendations are still debated. *Aim of the work:* Compare the response to three types of frequently used rapid acting CHO to correct hypoglycemia during prolonged aerobic exercise. *Subjects and Methods:* 21 subjects with T1DM, aged 12-16 years, agreed to be recruited in the study. All participants took part in a trekking camp for 5 days, with 70 Km itinerary. A “flash monitoring” device was put on every participant 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; group 2 used sugar fondant candies; group 3 used fruit juice. *Results:* 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. *Conclusions:* our results suggest that 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. (www.actabiomedica.it)

Key words: hypoglycemia, treatment, prolonged aerobic activity, type 1 diabetes, children

Abbreviations:

BGLs: blood glucose levels

CHO: carbohydrate

GI: glycemic index

FSL: free style libre

MET: metabolic equivalent of task

T1DM: type 1 diabetes mellitus

Introduction

Hypoglycemia is the most common acute complication of type 1 diabetes (T1DM) (1). The glucose value of <3.3-3.9 mmol/L (<60-70mg/dL) has been very often accepted as the level for defining hypoglycemia. The goal of hypoglycemia treatment is to restore the blood glucose levels (BGLs) to euglycemia or to 5.6 mmol/L (100 mg/dL). The amount of carbohy-

drate required to treat hypoglycemia depends on the size of the child, the type of insulin therapy, the active insulin on board, the timing and intensity of antecedent exercise as well as other factors. From adults, it is extrapolated that 0.3 g pro Kg of carbohydrate in the form of glucose tablets should be used to treat hypoglycemia (2).

The type of carbohydrate is also important. 20 g of glucose was found to act faster and to give the same rise of 40 g of carbohydrate in orange juice (3), or to provide higher BGLs than 20 g of sucrose (4). One recent study found no differences between the effectiveness for glucose and sucrose, while fructose gave lower BGLs (5); another study asserted that glucose tablets and orange juice at 0.3 g pro Kg carbohydrate had similar efficacy in resolving hypoglycemia in 15

minutes time (6). Therefore this argument is still debated. Moreover, rapid acting carbohydrate should be followed by additional longer acting carbohydrates in the form of fruit, bread, cereal or milk, according to the circumstances, to prevent recurrence of hypoglycemia (2).

Specific recommendations are available to manage physical activity in children with type 1 diabetes in order to prevent hypoglycemia and these strategies include intensive BGLs monitoring, proper insulin and nutritional adjustments (7-9). Regarding the treatment of hypoglycemia during physical activity, a mean dose of 12 g of glucose recovers from exercise/sport associated hypoglycemia within 8-15 minutes in adults with T1DM (10). No data are available on treatment of hypoglycemia during prolonged aerobic physical activity in children with T1DM, therefore we performed this study.

Aim of the study

The aim of the study was to evaluate the impact of different types of rapid acting CHO for the treatment of hypoglycemia during prolonged aerobic activities.

- The primary outcome for the study consisted in the individual mean rise in BGLs after treatment of hypoglycemia and time spent in hypoglycemia <3.9 mmol/L (<70 mg/dL) in the three groups, detected by FSL.

- The secondary outcome consisted in the rate of insulin reduction (total daily insulin and basal one) at the end of the camp, compared to the dosage before starting the trip.

Methods

Subjects

We invited to participate to this study all our patients with T1DM aged 12-16 years, diagnosed for more than a year before (#47), in follow up at the Pediatric Diabetology Centre of Trento (Italy). 21 subjects spontaneously agreed to be recruited in the study. Table 1 shows the baseline characteristics of the

Table 1. Characteristics of the study population

	Mean (range)
Number (n)	21
Gender: female	9
male	12
Age (years)	13.8 (12.0-15.9)
Pubertal Stage (pre/pubertal)	1/20
BMI SDS	-0.7 (-1.3 - + 1.5)
HbA1c (mmol/mol)	60 (51-66)
HbA1c (%)	7.6 (6.8-8.2)
Diabetes duration (years)	5.4 (1.4-12.4)
Insulin per day (IU/Kg)	0.75 (0.55-1.17)

study population. All patients were on the basal-bolus insulin regimen, 10 patients using Degludec in the morning and 8 using Glargine in the evening. A rapid insulin analog before every main meal was adopted. 3 subjects were on insulin pump. Participants were free of diabetic complication, celiac disease and thyroiditis.

The level of physical activity was assessed one week before the camp by a questionnaire and was low (<4 MET) in 6 subjects, moderate (4≤ MET <8) in 11 and intensive (≥8 MET) in 4.

Protocol

This study was carried out after appropriate approval by the Ethics Committee of the hospital institutional board and in agreement with the Declaration of Helsinki. Informed written consent was obtained from the parents.

All participants took part in a trekking camp for 5 days on Trasimeno Lake in central Italy. The trip was 70 Km long, and each day included a 10 to 18 Km stage. The elevation difference was 300 meters along the whole the trip. Three days before starting the camp, a “flash monitoring” device Free Style Libre® (FSL) was put on every participant and the registration was begun in the morning of the day after.

Insulin adjustment protocol: this insulin reduction protocol comes from our precedent experience in trek-

king camps with adolescent with T1DM (unpublished data) and is in agreement with ISPAD Consensus guidelines 2018 (11).

Before starting the trip: basal insulin was reduced by 30%: Glargine was reduced the evening before, Degludec in the same morning and insulin pump one hour before the start.

During the trip: meal and correction boluses were reduced by 10% or 30% if the activity was after or within 3 hours, respectively. Additional adjustments for the amount of both basal and bolus insulin were made on daily basis in response to the blood glucose/FSL information.

Nutritional requirements for activities: a skilled dietitian calculated for each participant the daily energy and carbohydrate (CHO) intake, adjusted for the physical activity at the camp. Participants ate three meals a day with a mean of 1-1.2 g pro Kg of low glycemic index carbohydrate, and 2 snacks of 0.5 g pro Kg of CHO.

Hypoglycemia prevention and treatment protocol

- BGLs before exercise commencement had to be >7 mmol/mol (126 mg/dL) otherwise 10 to 20 g of high glycemic index CHO was ingested.

- In case of hypoglycemia <3.9 mmol/L (<70 mg/dL) detected by FSL scan, capillary BG was done as suggested by the instrument technical sheet. If BG was <70 mg/dL, the hypoglycemic event was corrected and the subject remained at rest until the BG was checked again after 15 minutes.

Subjects have been randomized into three different groups (1, 2, 3) on respect of level of physical activity, age and sex (Table 2). All the patients were educated to correct hypoglycemia < 3.9 mmol/L (<70 mg/dl) with 0.3 g/Kg of rapid acting CHO: group 1 with a glucose preparation (Glucosprint Plus®); group 2 used fondant candies (Perugina®); group 3 used fruit juice. Patients had to stay still for 15 minutes, afterwards they took 30 g of longer acting carbohydrates in the form of biscuits to maintain BGLs following hypoglycemia treatment during ongoing activity.

The glycemic index (GI) of the hypoglycemia treatments were influenced by structure and form, and were: 100 for the glucose preparation; 70 for sugar fondant candies; 57 for the fruit juice (12, 13).

Measurements

BMI was expressed as standard deviation score (SDS) according to the Italian Standards (14). SDS

Table 2. Characteristics of subjects divided into 3 different groups (1, 2, 3). Data are reported as mean (range)

	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	P value
Gender F	3	3	3	
M	4	4	4	
Pubertal stage (pre/pubertal)	1/6	0/7	0/7	
Age (years)	13.6 (12.0-15.9)	14.1 (13.2-15.8)	13.5 (12.0-15.0)	0.41
BMI SDS	+0.2	-0.8	-0.2	0.62
HbA1c (mmol/mol)	58 (53-60)	60 (55-66)	58 (51-62)	
HbA1c (%)	7.5 (7.0-7.6)	7.6 (7.2-8.2)	7.5 (6.8-7.8)	0.85
Diabetes duration (years)	4.8 (1.4-9.2)	5.2 (2.2-8.0)	6.0 (1.8-12.4)	0.90
Insulin per day (IU/Kg)	0.74 (0.55-0.93)	0.81 (0.56-1.07)	0.90 (0.62-1.17)	0.058
Treatment model				
MDI Degludec	3	3	4	
MDI Glargine	3	3	2	
CSII	1	1	1	
Level of PA low	2	2	2	
medium	4	3	4	
high	1	2	1	

was calculated with the formula: (measurement – mean)/standard deviation. The patients were classified as prepubertal or pubertal, by physical inspection, according to the standard Tanner's criteria (15). Mean annual glycated hemoglobin (HbA1c) was calculated as the mean of venous HbA1c level measured every 3 months. Level of physical activity was assessed by the International physical activity questionnaires (IPAQ-last 7 day format). Capillary blood glucose (BG) was measured by our pediatric nurses (BM, DS) using an Accu-chek Guide BG monitor (Roche Diagnostics).

Data analysis

Quantitative data were normally distributed and expressed as mean \pm SD; differences among groups 1, 2 and 3 were evaluated by Anova test. The SAS Enterprise Guide® statistical software (SAS Institute Inc. Cary, NC, 27513, USA) was used for these analyses.

Results

All 21 patients completed the 5 stages of the camp. No severe hypoglycemia occurred.

The FSL device worked without disruption in all but two patients during the trip.

In 2 patients the sensor stick failed in the evening and was promptly substituted in 2 hours time.

During the camp we documented by capillary BG, 126 episodes of hypoglycemia <3.9 mmol/L (70 mg/dL) in all cohort, ranging from 2 to 13 episodes for child, on average 1.3 episodes per child per day. During the camp FSL detected 7 more events of hypoglycemia <70 mg/dL on the 21 subjects, that showed no symptoms. These were not confirmed by capillary blood check, but FSL did not miss any symptomatic episode of hypoglycemia.

In Table 3 results are compared along with the 3 groups. No significant differences were recognized among the three treatments in terms of number of hypoglycemic events and time spent in hypoglycemia. We did not find treatment failure (<3.9 mmol/L) after 15 minutes, while repeated hypoglycemia occurred before the following meal in a few subjects as reported in Table 3.

Compared to starting insulin dosing (reduced according to the protocol), additional adjustments were made but at the end of the camp the difference pre/

Table 3. Results along with the 3 groups in 5 days. Mean \pm SD

	Group 1 Glucose (n=7)	Group 2 Sugar fondant (n=7)	Group 3 Orange Juice (n=7)	P value
Mean glucose value (mmol/L) (mg/dL)	8.59 \pm 3.70 154.6 \pm 66.7	8.94 \pm 3.31 160.9 \pm 59.7	9.71 \pm 3.36 174.8 \pm 60.62	0.43
Time in range (%): 70-180 mg/dL	52.43 \pm 15.35	48.67 \pm 9.50	47.0 \pm 8.60	0.29
Mean individual hypoglycemic events (n°)	6.85 \pm 1.28	5.8 \pm 1.80	5.7 \pm 1.59	0.55
BG levels before treatment of hypoglycemia (mmol/L) (mg/dL)	3.35 \pm 0.42 60.30 \pm 7.56	3.12 \pm 0.50 56.1 \pm 9.0	3.22 \pm 0.49 57.9 \pm 8.8	0.09
BG levels 15 minutes after treatment (mmol/L) (mg/dL)	7.14 \pm 1.47 128.5 \pm 26.6	6.64 \pm 0.96 119.5 \pm 17.3	6.9 \pm 0.83 124.2 \pm 15.0	0.82
BG rise 15 minutes after treatment (mmol/L) (mg/dL)	2.71 \pm 2.11 48.78 \pm 38.0	3.19 \pm 1.86 57.4 \pm 33.5	2.86 \pm 1.71 51.5 \pm 30.8	0.60
Mean individual time spent in hypoglycemia after treatment (minutes)	9.3 \pm 5.7	11.0 \pm 3.3	10.9 \pm 3.8	0.66
Rate of insulin reduction Total dosage (%)	-22.16 \pm 3.37	-24.0 \pm 2.09	-25.01 \pm 4.46	0.34
Basal dosage (%)	-27.39 \pm 5.23	-30.08 \pm 3.56	-32.23 \pm 3.20	0.17
N° of repeated hypoglycemia	5	7	3	0.43

post as well as differences among the three groups (Table 3) were not significant.

Discussion

Thanks to this study we had the opportunity to explore the impact of different types of rapid acting CHO for the hypoglycemia treatment in children with T1DM during the prolonged aerobic activity of a 70 km trekking camp. The aim was to know which type of fast acting CHO is better to use. We tried to prevent hypoglycemia during and after exercise, by suggesting frequent BG checks, additional carbohydrate intake and insulin reductions. All patients were subjected to the same physical effort, the food intake was established by a skilled dietician and the insulin reduction followed a protocol. We used flash glucose monitoring (FSL) as an adjunct of capillary glucose test to monitor glycemic response to exercise and to measure time spent in hypoglycemia. Nevertheless each patient experimented a mean of 1.3 episodes per day. The 21 subjects were randomized to the three types of rapid acting CHO to correct hypoglycemia and we did not find any difference among the groups in terms of rise in BGLs at 15 minutes, time spent in hypoglycemia, number of hypoglycemia episodes, number of repeated hypoglycemia and mean BG. During this trekking camp none of the three different types of rapid acting CHO was superior to the others. We did not compare glucose, sucrose and fructose, but glucose preparation with foods used “in real life” to correct hypoglycemia with different structure and form.

Our conclusions are different from the two previous studies on which the ISPAD 2018 recommendations are based (2): authors found that glucose acts faster and gives higher blood glucose (BG) than sucrose and orange juice (3,4). Instead our results are similar to the ones reported by two more recent studies. McTavish et al. (6) studied 39 children during a 5 days diabetes camp, randomized to one of the four treatments: glucose tablets, jellybeans, orange juice, and sugar mints (containing oligosaccharides). Jellybeans were the less effective treatment. Glucose tablets, sugar mints and orange juice at 0.3 g pro Kg carbohydrate had similar efficacy in resolving hypoglycemia in 15 minutes time. The setting was a diabetes camp, but physical activ-

ity was not quantified and time spent in hypoglycemia could not be reported because participants had only capillary BG checks (4). Husband AC et al. studied 33 children at home with a randomized crossover design. They compared glucose, sucrose and fructose. Effectiveness for fructose was significantly lower and no differences between glucose and sucrose were detected; only capillary BG measurements were performed (5). In another study 100 physically trained adults with T1DM reported in a questionnaire that a mean dose of 12 g of glucose recovered from exercise/sport associated hypoglycemia within 8-15 minutes during physical activity (10). Moreover, 40 g liquid glucose supplement, taken 15 minutes before exercise, helped to maintain safe BG in the aforementioned adults that perform 60 min of exercise 180 minutes after breakfast without modification of their insulin regimen (16).

According to our knowledge no data comparing hypoglycemia treatment in children during prolonged aerobic physical activity are available.

We expected that glucose preparation could act faster than the other foods containing rapid acting CHO, because the glycemic index of glucose is 99, of sugar fondant candies is 70 and of peach fruit juice is 57 (12,13). Differences in the form and composition of the three treatments could influence the effectiveness of hypoglycemia treatment: glucose preparation is in a liquid form, instead fruit juice contains soluble fiber and sucrose is in the form of solid tablets, that could really delay the absorption.

The main strength of our work lies in its real world applicability and the usefulness of the author experience with insulin dose adjustment to minimize hypoglycemia in the camp setting following a precise study protocol. All but one children were in puberty and probably the increased growth hormone secretion, typical of this period, could have mitigated differences in the response to the three types of treatment. As a secondary outcome of the study, we found that the rate of total and basal insulin reduction we established in the protocol before starting the camp was confirmed within the groups along the camp. At the end of the camp, additional insulin adjustments were not of significant value compared to the starting point.

Although the number of subjects in the study was limited, it is important to remember that there is lit-

the published data regarding this important issue in T1DM children and clearly further investigations are required to confirm the results.

To conclude, we do suggest that 0.3 g/Kg of rapidly acting CHO in the form of glucose or sugar fondant or fruit juice effectively resolve hypoglycemia in children in 15 minutes, during aerobic prolonged physical activity.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

- Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. *Diabetes Care* 2010;33:17-22
- Ly TT, Maahs DM, Rewers A, Dunger D, Oduwole A, Jones TW. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2014;15:180-192
- Brodows RG, Williams C, Amatruda JM. Treatment of insulin reactions in diabetics. *JAMA* 1984;28:252:3378-3381
- Georgakopoulos K, Katsilambros N, Fragaki M et al. Recovery from insulin-induced hypoglycemia after saccharose or glucose administration. *Clin Physiol Biochem* 1990;8:267-272.
- Husband AC, Crawford S, McCoy LA, Pacaud D. The effectiveness of glucose, sucrose, and fructose in treating hypoglycemia in children with type 1 diabetes. *Pediatr Diabetes* 2010;11:154-158
- McTavish L, Krebs JD, Weatherall M, Wiltshire E. Weight-based hypoglycaemia treatment protocol for adults with Type 1 diabetes: a randomized crossover clinical trial. *Diabet Med* 2015;32:1143-1148
- Riddell MC, Iscoe KE. Physical activity, sport, and pediatric diabetes. *Pediatr Diabetes* 2006;7:60-70
- Pivovarov JA, Taplin CE, Riddell MC. Current perspectives on physical activity and exercise for youth with diabetes. *Pediatr Diabetes*. 2015;16:242-55
- Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol* 2017;5:377-390
- De Fazio C, Gentile S, Strollo F, Russo V, Corigliano G. Treatment of exercise related hypoglycemia in people with type 1 diabetes mellitus by a liquid supplement containing glucose, thiamine and manganese. *J AMD* 2016;19:179-186
- Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan D, Scaramuzza AE, Hasnani D, Hofer SE. Exercise in children and adolescents with diabetes. *Pediatric Diabetes* 2018;19:205-226
- Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 2002;76:5-56.
- Atkinson FS, Foster-Powell K, Brand Miller JC. K. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008 Dec;31(12):2281-2283
- Cacciari E, Milani S, Balsamo A, Spada E et al. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). *J Endocrinol Invest* 2006;29:581-593
- Tanner JM. *Growth of Adolescents*. Oxford, Blackwell Scientific Publications, 1962
- Dubé MC, Weisnagel SJ, Prud'homme D, Lavoie C. Exercise and newer insulins: how much glucose supplement to avoid hypoglycemia? *Med Sci Sports Exerc* 2005 Aug;37:1276-1282

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