Volume 1 • Issue 1 • 2017

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Scientia Ricerca

Research Article

Nutrition and Food Toxicology

ISSN: 2573-4946

Dextrose Supplementation against Exercise Related Hypoglycaemia in Athletes with Type 1 Diabetes Mellitus

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Received: March 17, 2017; **Published:** March 22, 2017

Abstract

Hypoglycaemia is a major diabetes complication and fear of it is a strong barrier against regular exercise and sports activities in people with insulin-dependent diabetes mellitus (T1DM). Poor management of exercise-related hypoglycaemic episodes in terms of quality, carbohydrate load and glycaemic index of ingested food often causes reactive hyperglycaemia and large glycaemic variability. The purpose of the study was to assess the ability of a commercially available product containing 10g glucose (GlucoSprint®, Harmonium, Italy) to reverse exercise-related hypoglycaemia in T1DM athletes. To do so we analysed 100 people with T1DM regularly practicing exercise or sports to verify

1. Blood glucose increase within 8' and 15' after product administration,
2. Eventually occurring rebound hyperglycaemia within 60'-75',
3. A series of hypoglycaemia awareness related items and
4. Subjective evaluation of product's features.

Participants were recruited during events of "diabetes and sports" organized by ANIAD (Italian National Association of Athletes with Diabetes). They proved to recover from exercise related hypoglycaemia within 8'-15' (mean glycaemic increase being 53.2 mg/dl) by using 1.2 vials - i.e. 12 grams glucose on average. 77% people considered ingestion to be easy and 89% to be burdened with no late hyperglycaemic rebounds. Tips provided by T1DM athletes were: try to

- Produce 3 different vial sizes (15, 20 and 30 gr),
- Associate glucose with slow-release carbohydrates,
- Produce squeezable gel packs too, and
- Added flavors (mint, citrus, cinnamon, etc).

As a result of the study, a liquid glucose containing vial like the one tested hereby may be the product of choice to stop exercise/sports related hypoglycaemia provided some changes are made to improve its organoleptic features.

Keywords: *Exercise/sports; Hypoglycaemia; T1DM*

Volume 1 Issue 1 March 2017

Introduction

Hypoglycaemia is one of the most threatening events pending on people with Type 1 Diabetes Mellitus (T1DM) in everyday life, who are known, indeed, to experience several thousand such episodes during their life [1].

It therefore heavily hampers treatment intensification meant at getting blood glucose and glycated haemoglobin (HbA1c) targets and in fact people mostly tend to "over-correct" glucose levels, i.e. fail to wait the expected time for blood glucose to get from low to consistently normal [2]. Moreover, fear of hypoglycaemia represents a major barrier against regular physical activity in people with T1DM [3].

In fact, according to the latest ADA Position Statement on Exercise [4], aerobic exercise decreases blood glucose levels if performed during postprandial periods with the usual insulin dose administered at the meal before exercise [5], and prolonged activity done then may cause exaggerated decreases [6-8]. Variable glycaemic responses to physical activity [9] make uniform recommendations for management of food intake and insulin dosing difficult. To prevent hypoglycaemia during prolonged (> 30 min), predominantly aerobic exercise, additional carbohydrate intake and/or reductions in insulin are typically required. For low- to moderate-intensity aerobic activities lasting 30 to 60 min undertaken when circulating insulin levels are low (i.e., fasting or basal conditions), some 15 g of carbohydrate may prevent hypoglycaemia [10]. For activities performed with relative hyperinsulinemia (after bolus insulin), 30 to 60g of carbohydrate per hour of exercise may be needed [11], which is similar to carbohydrate requirements to optimize performance in athletes with[12] or without [13] type 1 diabetes.

That's why ADA suggests that:

- Additional carbohydrate intake and/or insulin reductions are typically required to maintain glycaemic balance during and after physical activity;
- Frequent blood glucose checks are required to implement carbohydrate intake and insulin dose adjustment strategies;
- Continuous glucose monitoring during physical activity can be used to detect hypoglycaemia when used as an adjunct rather than in place of capillary glucose tests.

Indeed, factors most typically related to hypoglycaemia are inadequately high basal or bolus insulin dosages as compared to exercise induced glucose utilization, missed meal or late carbohydrate ingestion with respect to insulin administration, lower than needed carbohydrate intake, high energy expenditure during long term, unforeseen exercise sessions, and, finally, excess alcohol ingestion–which is known to often trigger hypoglycaemia [14].

The primary outcome of our study was the anti-hypoglycaemic effect of a commercially available glucose-containing liquid formula in exercising athletes with T1DM. Secondary outcomes were hypoglycaemia awareness, "overcorrection" behaviour and satisfaction with the product over time.

Materials and Methods

100 physically trained people with T1DM, 54 on multiple daily injections and 46 on continuous subcutaneous insulin infusion were analysed during sports events organized by the ANIAD (Italian National Association of Athletes with Diabetes), a voluntary patient organization dedicated to sports and diabetes within a six month period. Clinical characteristics of involved people are reported in Tables I and II.

	N	Age (years)	BMI (kg/m^2)	Duration (years)	HbA1c (%)
Total	100	38.8 ± 11.8	23.6 ± 2.7	20.7 ± 11.9	7.3 ± 0.8
M	77	38.8 ± 11.7	23.8 ± 2.4	20.5 ± 11.8	7.3 ± 0.7
W	23	39.0 ± 12.2	22.9 ± 3.4	21.5 ± 12.7	7.4 ± 0.9

Table I: *Clinical and anthropometric features of our athletes with T1DM. M = men; W = women*

% Exercise or Sports Activities	Walking	Soccer	Running	Triathlon	Aerobics	Others
	14.3	19.0	34.3%	3.8%	15.2%	13.4%

Table II: *Percent participant involvement in different sports activities. The term "Aerobics" includes swimming, trekking, cycling; the term "Others" includes rowing, sailing, boxing, basketball, volley and gym.*

The commercially available glucose-containing liquid formula under investigation was GlucoSprint® (Harmonium, Italy), a supplement meant at controlling hypoglycaemia [15,16] and advertised as being endowed with five main features:

- Fast-acting effect: peak blood glucose levels attained within 15 min of ingestion;
- User friendliness: easy to ingest, quickly absorbed;
- Long shelf-life thanks to its light-impermeable containers;
- Measurable effects: dose scaling along the vial wall allowing glucose dose selection;
- Reusability: multiple usage allowed by repeated recapping.

HbA_1c was measured by HPLC (upper reference limit <6%, namely 42 mmol/mol) in certified public laboratories commonly used by involved participants.

All participants filled in a questionnaire at enrolment, oriented at hypoglycaemia awareness and control modalities (Table III) and a product evaluation form including glucose recordings and personal considerations concerning product effectiveness after the exercise session (Table IV). One year after the intervention study every other participant (n = 50) was randomly asked to fill in a follow-up evaluation form within one week of invitation to assess his/her adherence to the product and associated metabolic control (Table V).

Questionnaire on Current Low Blood Glucose Correction Habits
1. How do you rate your hypoglycaemia awareness? a. Optimal (always aware) b. Good (almost always aware) c. Poor (hardly aware)

2. How many hypoglycaemic episodes did you experience during the last month and when mostly? a. Number …… b. Morning (7:01 – 13:00) …….. c. Afternoon (13:01 – 19:00) …….. d. Evening (19:01 – 24:00) ……..….. e. Night (24:01 – 7:00) ……..
3. Your glycaemic threshold (try to indicate the blood glucose level below which you generally experience symptoms of hypoglycaemia, if possible) a. 60-70 mg/dl b. 40-59 mg/dl c. < 40 mg/dl
4. What do you generally take to reverse hypoglycaemia? Please state type of food/beverage and best approximate amount (grams or millilitres) a. in everyday life …….. b. during/after exercise ……..
5. Do you happen to get rebound hyperglycaemia by overcorrecting hypoglycaemia? a. seldom (1-2 in 10 times) b. often (3-6 in 10 times) c. always

Table III: *Questionnaire designed to explore hypoglycaemia awareness and correction habits*

Low Blood Glucose Prevalence and Correction Evaluation Form

I myself ……., born in …….. on ……. accept to take part in the present study by taking GlucoSprint® 1 to 3 vials (each vial contains 10 grams glucose) to reverse hypoglycaemia as deemed needed and filling in the present form.

Date	Time	Starting blood glucose (mg/dl)	No. of ingested vials	Blood glucose (mg/dl) 8 min after ingestion	Blood glucose (mg/dl) 15 min after ingestion	Did you experience rebound hyper-glycaemia?	Notes

1. In my view hypoglycaemic episodes were mostly reversed as follows:
    a. fully
    b. partially
    c. not at all
2. Briefly describe your rating of the product with respect to the following items:
    a. time needed to reach the target:
        i. short enough
        ii. longer than expected
3. notes: ……..……
    a. rebound late onset hyperglycaemia:
        i. absent
        ii. present
4. notes ……
    a. ease of use:
        i. optimal
        ii. to be improved
5. notes: ……..
    a. taste:
        i. pleasant
        ii. unpleasant
6. notes: ……
    a. price:
        i. fair
        ii. high
7. notes: ……

***Table IV**: Product evaluation form.*

Follow-Up Evaluation Form

1. Have you gone on with GlucoSprint® for one year?
    a. Yes
    b. Occasionally
    c. No (please state why ……..)
2. Have you experienced rebound hyperglycaemia within 60 to 75 min of its ingestion?
    a. Yes
    b. Occasionally
    c. No
3. Which was your lowest HbA1c level during the last year? ……
4. Which HbA1c level did you get during the last three months? ……..

***Table V**: Long-term adherence questionnaire.*

Neither the questionnaire nor the evaluation forms had been previously validated by other groups but both were based on a previous long-lasting Authors' analysis of needs explicitly perceived by the many athletes with T1DM followed up for up to 25 years.

They resulted from a thorough selection of useful information previously performed by CDF e GC in collaboration with 30 highly educated athletes with T1DM (unpublished data) and expected to allow athletes to easily and reliably fill in those forms.

Personal glucose meters compliant with ISO 2013 standards were allowed for use only after a thorough quality control check [17].

Rebound hyperglycaemia was arbitrarily defined as blood glucose levels higher than 250 mg/dl attained between 60 and 75 min after exercise as a result of the so-called "over-corrected" hypoglycaemia (excess carbohydrate ingestion aimed at correcting low blood glucose levels).

Blood glucose levels increases observed 8 and 15 min after Glucosprint® ingestion were calculated, expressed in mg/dl and referred to as "Δ8" and "Δ15", respectively. Such parameters were used to evaluate the primary outcome of the study, i.e. the product's anti-hypoglycaemic effects.

Secondary outcomes were explored by taking into consideration the following:

a. Anamnestic (i.e. questionnaire based) and observed hyperglycaemic spikes resulting from "overcorrected" hypoglycaemia;
b. Questionnaire and evaluation form based ability to perceive hypoglycaemia and number of recorded hypoglycaemic episodes during previous month, as well as, hypoglycaemia awareness threshold, usual low blood glucose control modalities (glucose ingestion) and product acceptability. The latter, in turn, took into considerations various items including taste and price, as well as, improvement suggestions.
c. Adherence to the product and metabolic control attained within one year of the end of our study.

Statistical analysis was based on repeated measures ANOVA for quantitative data (reported as means ± SDs) and on chi-square for distribution differences of questionnaire-derived qualitative percent data.

Results

1015 hypoglycaemic episodes were recorded throughout the study, with a mean individual rate of 7.1 ± 5.0 episodes.

Table VI summarizes blood glucose level changes obtained 8 and 15 min after glucose intake and mean ingested amounts and Table VII depicts the utilized amount of dextrose vials and grams.

Blood glucose mg/dl	0 min	8 min	15 min
	54.3 ± 7.4	90.6 ± 10.8*	108 ± 12.9*

***Table VI**: Blood glucose levels at different time points with respect to product ingestion*
** stays for p < 0.001.*

Product n/gr	Vials	grams
	1.2± 0.4	12.1± 4.2

***Table VII**: Amount of vials and dextrose used to overcome hypoglycaemia.*

Table VIII refers to percent changes as reported through the questionnaire. In greater detail only 7% subjects underwent late hyperglycaemic rebound events when using GlucoSprint® as compared to 46% expected to occur based on the questionnaire (see Table IX; $p < 0.005$).

Hypoglycaemia 24h percent distribution	Morning	Afternoon	Evening	Night
Hypoglycaemia Awareness	25%	20%	28%	27%
	Optimal	Good	Poor	
Subjective Perception Threshold	54%	37%	9%	
	60-70 mg/dl	40–59 mg/dl	< 40 mg/dl	
	69.5%	24.8%	5.7%	
Previously Experienced Rebound Hyperglycaemia	Seldzom	Often	Always	
	54%	44 %	2%	

***Table VIII**: Percent answers to the anamnestic questionnaire on hypoglycaemia awareness.*

	Observed	Expected	
60–75 min Rebound Hyperglycaemia (%)	93	54	No
	7	46	Yes

***Table IX**: Percent observed vs. expected (i.e. questionnaire-based) rebound hyperglycaemic events ($p < 0.005$). Expected = percent of "often" plus "always" answers given in the questionnaire.*

Time Need to Reach the Target	Short Enough	Longer than Expected
Ease of use	94%	6%
	Optimal	**To be improved**
	77%	23%
Taste	**Good**	**Unpleasant**
	26%	74%
Price	**Fair**	**High**
	31%	69%

***Table X**: Athlete ratings of product's anti-hypoglycaemic efficacy and other subjectively relevant factors.*

On the opposite, participating athletes rated as fully reversed 88% hypoglycaemic episodes, and only partially reversed 12% (no episode was rated as unopposed).

In Table X participants' suggestions (as derived from the evaluation form) are reported based on their own glycaemic (objective) and affective (subjective) experiences.

Features suggested by athletes to be improved can be summarized as follows:

- Vial dosage diversification, i.e. 15, 20 e 30 gr;
- Squeezable gel packs in addition to the present liquid formula to overcome stomach troubles typically expected in people involved in long lasting endurance sessions;
- Combined slow-release carbohydrates for:
- Long distance runners;
- Post prandial activities or any other conditions characterized by inappropriately high insulin levels;
- Taste improvement (sweet syrup-like taste was rated as unpleasant by some participants) through product aromatization by added flavours (mint, citrus, cinnamon, etc).

Only 40 out of 50 randomly selected participants accepted to fill in the follow-up evaluation form. In fact 10 refrained from collaborating for the following reasons: no time to do it within the tight proposed deadline (n = 8); unreachable due to address change (n = 2). This resulted into 32 men and 8 women contributing to the follow-up section of our study, which did not significantly differ from percent gender distribution observed in the original group (80% vs 77% men and 20% vs 23% women, respectively; n.s.). 14 (35.0%) went on using GlucoSprint® on a regular basis, 9 (22.5%) just occasionally, 17 (42.5%) did not use it any more. Only 1 of 14 (7.2%) consistent users and 2 of 9 (22.2%) occasional users reported on some rebound hyperglycaemia, while 12 of 17 (70.6%) non-users reported on at least one such phenomenon ($p < 0.05$). The lowest HbA1c levels attained during the following year were 7.1 ± 0.6% as a whole without any significant differences among the three subgroups (7.3 ± 0.7%, 6.9 ± 0.5% and 6.9 ± 0.4, respectively; n.s.). HbA1c levels attained within the last three months were 7.0 ± 0.6% as a whole without any significant differences among the three subgroups either (7.0 ± 0.5%, 7.1 ± 0.7% and 7.0 ± 0.8, respectively; n.s.) but significantly lower than baseline calculated within the same group (7.4 ± 0.7%).

Discussion

Fear of hypoglycaemia is a major problem hindering insulin treated patients' involvement in exercise or sports programs. Most often low blood glucose level control is left to single athlete's momentarily availability of carbohydrate-rich food/products. Many of the latter do not allow people to recover from hypoglycaemia within an short time: sucrose, for instance, has to be split into two molecules, one only of which is glucose; cakes or biscuits, in turn, contain starches rich in long-chain carbohydrates and even in various fats further retarding glucose absorption by slowing down stomach-emptying. Easy to use alternatives like coke or fruit juices somehow interfere with best sports performance because of either associated gas gut filling or of low-glycaemic index, gut-engulfing fructose content, respectively [18]. Moreover none of the above is able to provide athletes with any well-defined glucose amounts and therefore might cause rebound hyperglycaemia through excess slow release carbohydrate supply.

Also psychological and behavioural factors contribute to that, including fear of hypoglycaemia both per se and as a source of deep humiliation in front of trainers and team mates, as well as, the intimate will to complete the session at any cost, and concerns about personal ability to recognize alerting symptoms early enough. The consequence of that is a trend to ingest much more carbohydrate rich foods and beverages than needed with consequent relevant blood glucose peaks and high glycaemic variability.

The product we used in our study proved to solve most of the above problems by

1. Allowing recovery from exercise-related hypoglycaemia within 8-15 min through a mean 53.2 mg/dl blood glucose increase ($p < 0.001$) and
2. Dramatically reducing the risk for "over-correction" ($p < 0.005$) as reported in Table 4.

The fast effects observed on blood glucose levels are expected to depend on the fact that the tested product contains only D-glucose (i.e. dextrose), i.e. a fast absorbed molecule which

- Does not need to be split down into any further energy sources and
- Is the 100%, reference compound for glycaemic index tables (where bread is 75%, sucrose 70%, Coke 65% and fructose 23%) [19].

The association of dextrose with manganese and Vitamin B1 is another relevant feature of GlucoSprint®. In fact, manganese is required to activate Vitamin B1 and is also a strong antioxidant expected to protect cells from free radicals continuously generated during high intensity and long duration sports activities; Vitamin B1, in turn, contributes to multiple glycolysis related enzymatic processes leading to fast and full glucose utilization and consequent immediately available energy production required for best sports performance [20,21]. From a subjective standpoint the product was mostly appreciated as comfortable, despite some improvement being suggested by utilizers in terms of formulation and palatability.

In fact, the only reason why people refrained from using Glucosprint® during the follow-up period was price: they admitted not to feel like paying extra money for glucose after doing so for fruit or any other available food. However, in this case they had to face a significantly higher rate of rebound hyperglycaemic episodes that consistent or occasional users.

Conclusions

Consistent utilization of GlucoSprint® at a mean daily dose of 1.2 vials (i.e. 12 gr dextrose) fully reversed exercise-related hypoglycaemia within a very short time in most regularly exercising people with T1DM participating in our study and seldom caused late hyperglycaemic rebound events. The overall one-year long educational effect of product's utilization for a while was witnessed by the lower HbA1c attained by the whole group at the end of follow-up independent of still being GlucoSprint® users or not.

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