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# Efficacy of carbohydrate supplementation compared to bolus insulin dose reduction around exercise in adults with type 1 diabetes: a retrospective controlled analysis

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Abstract:

Introduction

Individuals with type 1 diabetes try to manage the risk of exercise-induced hypoglycemia by means of pre-exercise/pre-meal bolus insulin dose reductions and/or consuming additional carbohydrates during exercise. Both strategies have proven to be effective in offsetting the occurrence against hypoglycemia, it is unclear as to which one is more beneficial. Consequently, the aim of this study was to assess the efficacy of carbohydrate supplementation in comparison to bolus insulin dose reduction to prevent hypoglycemia during moderate-intensity exercise in individuals with type 1 diabetes.

Methods

This was a retrospective controlled analysis of two independent clinical trials. All participants performed a continuous moderate-intensity cycle ergometer exercise session for ~45 minutes. Two different therapy management groups and a control group were compared: Group (A) supplemented 15 – 30 g carbohydrates at a glycemic threshold of 7.0 mmol/L during exercise, group (B) reduced their individual bolus insulin dose by 50% with their last meal prior to exercise and group (C) remained as a control.

Results

No hypoglycemic events occurred in group A, which differed to each four events recorded in groups B ($p = 0.02$) and C ($p = 0.02$).

Conclusion

Carbohydrate supplementation was superior to bolus insulin reductions in the prevention of hypoglycemia during exercise in people with type 1 diabetes.

Keywords: Physical Exercise, Type 1 Diabetes, Insulin Therapy, Carbohydrates

## Introduction

Physical exercise has become an important option in the adjuvant therapy and management of type 1 diabetes (T1D) [1]. Due to the specific nature of its pathology, individuals are reliant on exogenous insulin either via multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) [2]. In combination with intermittently scanned or continuous glucose monitoring measuring glucose, the management of T1D has advanced over the last decades. The induced improved glycemic management induce several benefits such as increased quality of life [3,4] and reduction of diabetes-specific comorbidities [5,6]. Nevertheless, the management of glycaemia around exercise is an intricately complex task, especially when considering the guidelines to achieve a blood glucose (BG) between 7.0 mmol/L to 10.0 mmol/L commencing exercise [7–9]. For most individuals with T1D the goal is the absolute avoidance of hypoglycemia around exercise. However, especially during physical exercise, the fear of hypoglycaemia is still understandable since hypoglycaemia can severely impact autonomic health which remains a major hurdle to regularly perform physical exercise safely [10,11].

Studies have introduced concepts to reduce the risk of exercise-induced hypoglycemia. Strategies include reductions to bolus or basal insulin dose prior to exercise [12–15] and/or threshold-based carbohydrate (CHO) supplementation during exercise for adults [16] and adolescents with T1D [17]. It is unclear which of these approaches are most efficacious in avoiding hypoglycemia and reducing glycemic disturbances during exercise in individuals with T1D. The aim of this analysis was to assess the efficacy of CHO supplementation versus bolus insulin dose reductions to prevent hypoglycemia during exercise in individuals with T1D.

## Methods

This retrospective analysis consisted of two clinical trials investigating insulin dose reduction strategies for moderate-intensity exercise [13,16]. Data from 18 adults with T1D on a stable basal insulin degludec- (Tresiba®, Novo Nordisk A/S, DEN) and bolus insulin aspart-therapy (Novo Nordisk A/S, DEN) were included. All procedures in this trial were performed according to Good Clinical Practice and the Declaration of Helsinki. Participants were divided into three groups, two of which were tested in a crossover design with a minimum washout period of one week between each exercise session (groups B and C). The remaining Group A supplemented 15 – 30 g of fluid CHO (72% glucose and 28% fructose) or glucose gel (67% glucose and 33% fructose) at a glycemic threshold of 7.0 mmol/L during exercise with no pre-exercise bolus insulin reduction. Blood and interstitial glucose was measured every 7 minutes during the exercise test. If a participant's BG was close to reaching the threshold of 7.0 mmol/L (within 1.0 mmol/L), then measurements were repeated at 3-minute intervals. Group A consumed their last carbohydrate-rich meal at least 2 hours prior to the moderate-intensity exercise session with their regular individual CHO to bolus insulin dose ratio which consisted of 1 g CHO per kg bodyweight [16]. Group B reduced their regular bolus insulin dose by 50% one hour prior to the start of exercise with their last meal (1 g CHO per kg bodyweight). Group C remained as a control group and did not perform a bolus insulin reduction prior to exercise nor did supplement additional CHO during the moderate-intensity exercise session [13]. However, they have also consumed their last meal 1 h prior to exercise (1 g CHO per kg bodyweight) with a regular bolus insulin dose. Prior to each exercise session, all participants in each group were introduced to the exercise procedure. Group A conducted a 3-minute passive warm-up, a 3-minute active warm-up at 20W, followed by 49 minutes at the individual target workload, a 3-minute active cool-down at 20W and 3 minutes of passive cool-down. Group B and C had very similar exercise

procedures: a 3-minute passive warm-up, a 3-minute active warm-up at 20W, followed by 42 minutes at target workload and 3 minutes of passive cool-down.

The maximum potential test duration for group A was 49 minutes, whereas group B and C had a maximum potential test duration of 42 minutes. The test duration at moderate-intensity for each group were due to the set-up of the previous trials according to the predetermined main outcome [13,16]. Tests were terminated prematurely in all groups if participants reached hypoglycemia (BG concentration ≤3.9 mmol/L).

At the beginning of each clinical trial, participants performed a cardio-pulmonary exercise test until volitional exhaustion to determine the individualized intensity for the moderate-intensity exercise sessions. The intensity was defined as the power (W) at the midpoint between the individual first (LTP1) and second (LTP2) lactate turn points [18]. During the moderate-intensity exercise sessions, capillary BG samples from fingertip were taken every 6 – 7 minutes for safety reasons. Decisions for treatment were made according to capillary BG measurements measured via the glucometer which is integrated in the reader of the FreeStyle Libre 1 in all groups. Capillary BG samples from the earlobe (Biosen C-Line system EKF Diagnostic, GER) were taken as a confirmatory glucose measurement.. In addition, all participants wore an intermittently scanned glucose monitoring (isCGM) (Freestyle® 1, Abbott Diabetes Care Inc, USA) system, which provided interstitial based glycemic responses during the exercise sessions.

Numbers of hypoglycemic episodes were counted. Furthermore, data were stratified for the time spent in glycemic ranges based on BG during exercise defined as: hypoglycemia (≤3.9 mmol/L), euglycemia (>3.9 – 10 mmol/L) and hyperglycemia (>10 mmol/L). Data were tested for normal distribution via Shapiro-Wilk test and then compared via student's t-test, one-way ANOVA or Kruskal-Wallis test with $p \leq 0.05$. If applicable, Tukey's multiple comparison test was applied (post-hoc). Data are expressed as means (SD) or median [interquartile range] if applicable. All statistical procedures were conducted via Prism version 7 (GraphPad, San Jose, USA).

## Results

All participants were on multiple daily injection therapy. Participant's characteristics for group A were: n = 9, 5 males, age 32.1 ± 9 years, diabetes duration 19 ± 11 years, HbA1c 55 ± 7 mmol/mol (7.2 ± 0.6% ) and BMI 25.5 ± 3.8 kg/m$^2$. Group B and C included the same participants, who performed the study related exercise sessions in a cross-over design: n = 9, 6 males, age 32.8 ± 10 years, diabetes duration 14 ± 9 years, HbA1c 56 ± 15 mmol/mol (7.3 ± 1.4% ) and BMI 25.9 ± 3.1 kg/m$^2$. Inclusion of participants was conducted following matching for age ($p = 0.88$), diabetes duration ($p = 0.46$), HbA1c ($p = 0.94$) and BMI ($p = 0.79$).

The number of hypoglycemic events was significantly higher in group B compared to group A ($p = 0.02$) as well as in group C compared to A ($p = 0.02$). There were no differences between groups B and C (Table 1). BG levels prior to the start of exercise were similar between groups (A; 9.9 ± 2.2 mmol/L vs. B; 10.1 ± 2.4 mmol/L vs. C; 10.1 ± 3.5 mmol/L) ($p = 0.98$). The median BG concentration during exercise was lower in group C (5.6 [4.2 – 8.6] mmol/L) compared to A (7.6 [6.1 – 9.8]) ($p = 0.01$) with no significant difference to group B (7.5 ± 2.9 mmol/L) ($p = 0.36$). Acute post-exercise BG taken at rest directly after exercise was similar between all groups (A, 7.7 [7.3 – 8.7] mmol/L vs. B; 7.5 ± 2.0 mmol/L vs. C; 6.8 ± 5.9 mmol/L) ($p = 0.25$). The nadir glucose between group B (4.1 [3.4 - 6.2] mmol/L) and group C (3.4 [3.2 - 4.5] mmol/L) was not significantly different ($p = 0.25$).

**Table 1 – Efficacy of different glycemic management concepts during exercise in type 1 diabetes**

| | A | B | C | p-value |
|---|---|---|---|---|
| Number of Events $_{Hypoglycemia}$ | 0/9*† | 4/9* | 4/9† | 0.05 |
| Time $_{Hypoglycemia}$ (min) | 0† | 0 [0 – 9] | 12 [0 – 12]† | 0.01 |
| Time $_{Euglycemia}$ (min) | 49 [28 – 49] | 30 [12 – 36] | 23 ± 12.2 | 0.10 |
| Time $_{Hyperglycemia}$ (min) | 0 [0 – 21] | 6 [0 – 9] | 0 [0 – 6] | 0.41 |
| Time $_{Hypoglycemia}$ (%) | 0† | 0 [0 – 27] | 22 ± 18† | 0.01 |
| Time $_{Euglycemia}$ (%) | 100 [57 – 100] | 71 [47 – 86] | 62 ± 27 | 0.37 |
| Time $_{Hyperglycemia}$ (%) | 0 [0 – 43] | 14 [0 – 21.5] | 0 [0 – 14.5] | 0.43 |
| Participants $_{consumed\ CHO}$ (n) | 7/9 | 0/9 | 0/9 | |
| Time $_{until\ reaching\ hypoglycemia}$ (min) | - | 33 ± 11.5 | 31.5 ± 9 | 0.83 |
| CHO $_{consumed\ per\ participant}$ (g) | 20.8 ± 6.7 | - | - | |
| N $_{Total\ CHO\ treatments}$ | 14 | - | - | |

Abbreviations: A Consumed carbohydrates during exercise at a predefined glucose threshold of 7.0 mmol/L; B: Reduced individual bolus insulin dose by 50% prior to exercise; C: No carbohydrates were consumed or bolus insulin reductions prior to exercise. min: Minutes; g: Gram; n: numbers; CHO: carbohydrates. p-value: Results of ANOVA. * indicates statistically significant difference between group A and B ($p \leq 0.05$). † indicates statistically significant difference between group A and C ($p \leq 0.05$) †* indicate statistical difference following post-hoc testing

## Discussion

Since adjustments of bolus insulin dose or basal rate need to be performed 60 to 90 min prior to the start of exercise, pre-exercise bolus insulin dose reductions might obstruct spontaneous exercise [8,19,20]. Furthermore, our data indicate that this therapy strategy may still lead to hypoglycemia during exercise. Our results demonstrated that CHO supplementation during moderate-intensity exercise was superior to bolus insulin dose reductions to prevent hypoglycemia. Therefore, glycemic threshold-based CHO supplementation might be a more prudent approach for reducing the risk of exercise-induced dysglycemia in individuals with T1D. We also found that the time spent in euglycemia (%) during exercise tended to be higher in the CHO group compared to the other groups ($p = 0.37$). Indeed, the relative time in euglycemia for the CHO group was 100% [57-100] in comparison to 71% [47-86] in the group that performed a bolus insulin dose reduction and to 62 ± 27% in the control group that further supports the glycemic threshold-based CHO supplementation approach for future studies. Hypoglycemia in group B and C occurred almost at the same time ($p = 0.83$) which is surprising, since a reduction of bolus insulin dose prior to exercise did not show superior effects compared to a regular bolus insulin dose as shown previously [14]. Especially for people with T1D starting to engage in physical exercise, shorter exercise duration (~30 min) might lower the risk of hypoglycemia as seen in the latter stage of an exercise session. However, after becoming more experienced to physical exercise and its therapy adaptations, longer-duration physical exercise (~60 min) can be recommended.

Moser et al. have shown that threshold-based CHO supplementation may lead to ~80% time in target range during moderate-intensity exercise on five consecutive days [16]. Since these results show the summary of multiple exercise sessions, these are probably more transferable for daily life (90 sessions). This study only showed the effects of basal-insulin dose reductions and not the effects of

bolus insulin reductions, which are easier to incorporate if unplanned exercise is conducted. However, in this aforementioned study with 90 exercise sessions, no hypoglycemic event occurred, which further supports our findings and encourages the use of threshold-based CHO supplementation during moderate-intensity exercise.

These findings support people with T1D to exercise spontaneously at a moderate-intensity without additional planning and changes to their insulin therapy. This can ease every-day life for people with T1D and lower the hurdle to perform exercise safely and more regularly. Another advantage of this approach is that hyperglycemia, induced via bolus insulin reductions in preparation to exercise would become a thing of the past. Although the results for time in range, (7.0 – 10.0 mmol/L) (TIR) were not statistically different between groups, a TIR of 100% in the CHO group represent a valuable approach that may lead to a more stable glycemic control in physically active people with T1D.

A limitation of this study is its small sample size from two independent trials. Groups were well matched and the exercise volume was similar between both trials and therefore remain comparable [13,16]. These findings cannot be necessarily transferred to all types of exercise; hence studies with larger sample sizes are needed to investigate different types of exercise. It should be mentioned that bolus insulin dose reductions must not necessarily lead to hypoglycemia, yet people with T1D should be vigilant during exercise. Corrections/adaptations of individual bolus insulin dosing should be performed dependent on the individual's response to exercise and also in response to planned type, duration and intensity of exercise [8]. Vigorous intensity exercise or resistance exercise prior to moderate-intensity exercise may also prevent hypoglycemia, yet demand more effort from the individual planning to conduct aerobic exercise [21]. It must also be mentioned that increased carbohydrate intake during moderate-intensity exercise may reduce its beneficial effects in regard to weight management. However, research by Pinsker et al. have shown that carbohydrate consumption still remains a necessity since it is the most commonly used option around exercise in individuals with T1D, which can also be combined with the application of an individualized algorithm by Francescato et al. to avoid glycemic imbalances induced by exercise [22,23].

In conclusion, our findings bear potential for the implementation of glycemic-based threshold CHO supplementation during moderate-intensity exercise in people with T1D. These data provide compelling evidence for long-term studies to investigate changes in glycemic control assessed by means of TIR in individuals with T1D.

## Author Contributions

MLE and OM wrote the manuscript. OMC, RMB, NJT, PNP, AM, PB and PH reviewed, edited and approved the final version of the manuscript. HS and OM provided critical edits to the manuscript. MLE and OM performed the data analysis.

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