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Original article

Timing of insulin basal rate reduction to reduce hypoglycemia during late post-prandial exercise in adults with type 1 diabetes using insulin pump therapy: A randomized crossover trial

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ABSTRACT

Aims. – To compare the efficacy of three timings to decrease basal insulin infusion rate to reduce exercise-induced hypoglycaemia in patients with type 1 diabetes (T1D) using pump therapy.
Methods. – A single-blinded, randomized, 3-way crossover study in 22 adults that had T1D > 1 year and using insulin pump > 3 months (age, 40 ± 15 years; HbA_{1c}, 56.3 ± 10.2 mmol/mol). Participants practiced three 45-min exercise sessions (ergocyle) at 60% VO_{2peak} 3 hours after lunch comparing an 80% reduction of basal insulin applied 40 minutes before (T-40), 20 minutes before (T-20) or at exercise onset (T0).
Results. – No significant difference was observed for percentage of time spent < 4.0 mmol/L (T-40: 16 ± 25%; T-20: 26 ± 27%; T0: 24 ± 29%) (main outcome) and time spent in target range 4.0–10.0 mmol/L (T-40: 63 ± 37%; T-20: 66 ± 25%; T0: 65 ± 31%). With T-40 strategy, although not significant, starting blood glucose (BG) was higher (T-40: 8.6 ± 3.6 mmol/L; T-20: 7.4 ± 2.5 mmol/L ; T0: 7.4 ± 2.7 mmol/L), fewer patients needed extra carbohydrates consumption prior to exercise for BG < 5.0 mmol/L (T-40: *n* = 3; T-20: *n* = 5; T0: *n* = 6) as well as during exercise for BG < 3.3 mmol/L [T-40: *n* = 6 (27%); T-20: *n* = 12 (55%); T0: *n* = 11 (50%)] while time to first hypoglycaemic episode was delayed (T-40: 28 ± 14 min; T-20: 24 ± 10 min; T0: 22 ± 11 min).
Conclusion. – Decreasing basal insulin infusion rate by 80% up to 40 minutes before exercise onset is insufficient to reduce exercise-induced hypoglycaemia.

Introduction

Because of its association with lower risk of premature mortality, reduced cardiovascular risk, reduced insulin requirements, and improved overall well-being [1–3], exercise is an integral part of type 1 diabetes (T1D) treatment. Nonetheless, inactivity is highly prevalent among this population and is associated with a poor cardiovascular risk profile [4].

In people without diabetes, endogenous insulin levels fall with physical activity to maintain normoglycaemia. However, matching subcutaneous insulin delivery to reduced insulin requirements of exercising patients with T1D remains a therapeutic challenge [5–7]. Thus, patients frequently face excessive active exogenous insulin increasing muscle glucose uptake and decreasing endogenous hepatic glucose production. In a context of frequent

Abbreviation: CSII, continuous subcutaneous insulin infusion, insulin pump; CHO, carbohydrates.

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insufficient counter-regulatory hormones secretion, this contributes to an increased risk of hypoglycaemia [8,9]. Consequently, despite the numerous benefits of exercise, fear of hypoglycaemia has been identified by this population as the main barrier against the practice of physical activity [4].

Different strategies, used alone or in combination, have been studied to reduce the risk of exercise-induced hypoglycaemia in patients with T1D [10]. When exercise is anticipated, and undertaken within 90 minutes after a meal, pre-meal insulin bolus reduction proportional to exercise duration and intensity is the most frequently recommended method to reduce risks of exercise-induced hypoglycaemia [11–13]. Unfortunately, it is not always possible for patients to anticipate the exact timing, type, intensity, and duration of an exercise session to apply the appropriate insulin bolus reduction. For unanticipated or long duration exercise, consumption of extra carbohydrates (CHO) is, most often, required [14,15]. This strategy can, on one side, help enhance performance, but can offset weight loss and/or glucose lowering objectives. A third strategy, available only for patients using insulin pump therapy [continuous subcutaneous insulin infusion (CSII)], is to temporarily reduce basal insulin infusion rate for the exercise period.

Some studies have managed to reduce hypoglycaemia by suspending or decreasing basal insulin rate at exercise onset. In an adult population with T1D exercising in a late post-prandial state (e.g. > 3 hours post-meal), no hypoglycaemia, measured with a continuous glucose monitoring system (glucose < 3.3 m-.3 mmol/L), was observed when basal insulin was reduced by 50% or 80% at the start of a 30-min moderate aerobic exercise (50% Vo_{2peak}) or by 80% or pump stopped for a more intense exercise (75%VO_{2peak}). Moreover, hypoglycaemia risk in the afternoon following the exercise was comparable to the risk during rest interventions when 80% basal rate reduction was applied or insulin stopped for moderate and intense exercise intervention [16]. In a paediatric study (n = 10), researchers found no difference in hypoglycaemia episodes between pump on vs. pump off and no significant difference in the drop in glycaemia during a 40–45-min physical activity, but children were offered a 20 g complex CHO snacks before and after exercise [17]. In 49 children (8–17 years old) with T1D, the DirecNet Trial demonstrated a hypoglycaemia risk reduction from 43% to 16% by suspending insulin infusion at the onset of a 60-min aerobic exercise performed 4 hours after lunch [18]. This hypoglycaemic risk reduction was however obtained at the expense of an increased risk of post-exercise hyperglycaemia. Although modifying basal rate at exercise onset seems to help in reducing hypoglycaemia risk, earlier timings might be more beneficial to further prevent this risk. Considering the pharmacodynamics of short acting insulin analogs, the timing of basal rate reduction could range from exercise onset to 90 minutes before exercise when practiced in a late post-prandial state [16,19,20]. The optimal and practical timing of this reduction remains to be determined [10,21,22].

Hence, the objective of this single-blinded, randomized, 3-way crossover study was to compare the efficacy of three practical basal rate reduction timing strategies to reduce time spent in hypoglycaemia during a 45-min exercise performed at 60% VO_{2peak} (moderate intensity), starting 3 hours after a standardized meal in adults with T1D using CSII. The three tested strategies consisted of reducing insulin basal rate by 80% either 40 minutes prior to exercise (T-40), 20 minutes prior to exercise (T-20), or at the onset of exercise (T0). We hypothesized that the longest delay of basal rate reduction (T-40) would be the most beneficial to reduce time spent in exercise-induced hypoglycaemia.

Materials and methods

Study design and participants

Subjects invited to participate in this trial were ≥ 18 years old, had T1D for at least 1 year, were using CSII for at least 3 months with a recent (< 3 months) HbA_{1c} result ≤ 108 mmol/mol (12%). Exclusion criteria included clinically significant microvascular complications, recent (< 3 months) acute macrovascular events, abnormal blood panel and/or anaemia, ongoing pregnancy and recent (< 2 weeks) severe hypoglycaemia episodes.

Participants were recruited through the diabetes clinic at the Institut de recherches cliniques de Montréal (IRCM), Canada and through the local diabetes association's website. The study protocol was approved by the IRCM Ethics Committee and conducted according to the declaration of Helsinki. All participants signed a consent form and the trial was registered with ClinicalTrials.gov (NCT02631265).

Procedures and interventions

During the admission visit, a medical evaluation, HbA_{1c} level and anthropometric measurements were obtained. Records of insulin therapy over the past three days were collected. Physical fitness was assessed using a graded exercise test adapted from Storer et al. [23] on an ergocycle (Ergoline 900, Bitz, Germany) until voluntary exhaustion with the power output increased by 10 to 20 Watts every minute. During the test, expired gas samples were analyzed through a mixing chamber using a Moxus (AEI Technologies Inc, Napierville, IL, USA) cardiorespiratory test station. VO_{2peak} was determined as the highest 30-sec average value obtained during the exercise test.

A computer-generated block balanced randomization was used to determine the order of the interventions for each participant and a sealed envelope opened at admission visit. Participants were instructed to refrain from drinking alcohol and from exercising the day before and the days of the interventions and to avoid installing pump catheter in leg.

On intervention days (Fig. 1), participants consumed a standardized lunch (70 g of CHO for men and 50 g CHO for women) around 12:30, were instructed to take their insulin bolus as per their usual carbohydrate-to-insulin ratio and were admitted to the research facility at 14:00. Capillary blood glucose (BG) was measured at 14:30 and 15:15. At 14:50, 15:10 and 15:30, the participant's insulin pump was manipulated by the team to implement the basal insulin reduction according to randomization. At 15:30, participants performed a 45-min exercise on an ergocycle at 60% of VO_{2peak} (moderate intensity). The participant's insulin pump (Medtronic, Animas or Omnipod) and usual insulin (Aspart or Lispro) were used throughout the trial. For the exercise period, capillary BG was measured at 15:30 (exercise onset), 15:45 and then every 5 minutes until the end of exercise.

Safety measures

For safety considerations, a 21 g of carbohydrates snack (juice) was given 15 minutes prior to exercise if capillary BG was < 5.0 mmol/L. Blood ketones were checked if BG was > 18.0 mmol/L and intervention was postponed if ketones were > 1.5 mmol/L. Exercise was initiated only if BG ≥ 4.0 mmol/L. Patients were blinded to BG measurements during exercise. The participant's basal insulin rate was set back to usual rate at the end of exercise.

During exercise, if capillary BG dropped below 3.3 mmol/L, 21 g of carbohydrates were given in the form of juice. When capillary BG was between 3.3 and 4.0 mmol/L, juice was given only if

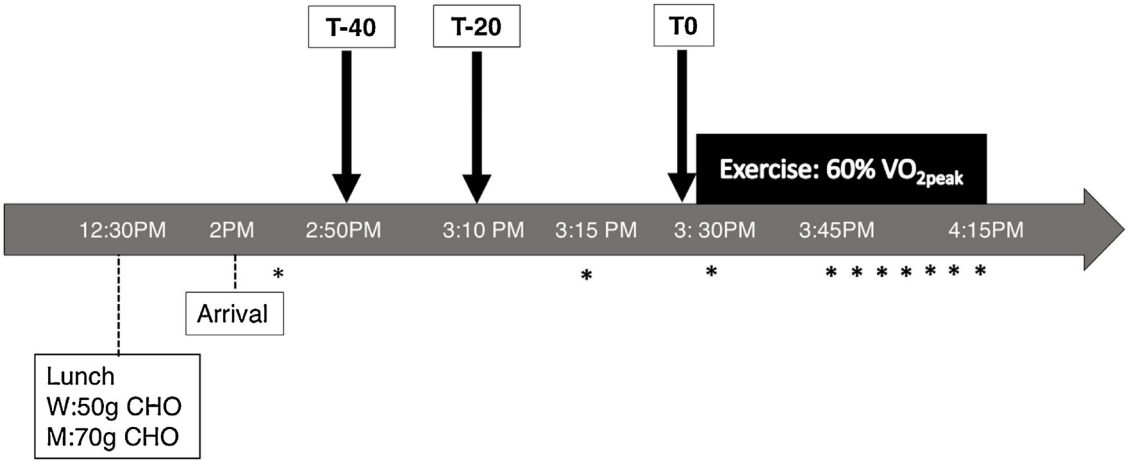

Fig. 1. Description of study procedures. * indicates when capillary blood glucose was measured.

participants expressed symptoms of hypoglycaemia. Exercise was stopped for 10 minutes if:

- the participant presented significant symptoms of hypoglycaemia;
- or if capillary BG level dropped < 3.0 mmol/L.

Then, exercise was resumed for a total of 45 min. Otherwise, carbohydrate replacement treatment was given without stopping exercise.

Outcomes

The primary outcome was the percentage of time spent in hypoglycaemia (< 4.0 mmol/L) during exercise. Secondary outcomes included percentage of time spent in target range (4.0–10.0 mmol/L) during exercise, decrease of BG during exercise and during the second half of exercise, the number of patients requiring oral treatment for hypoglycaemia during exercise and requiring CHO 15 minutes prior to exercise to reach a safe BG value to start exercise as well as time until first hypoglycaemia treatment during exercise.

Statistical analysis

Analysis was performed on interpolated values to every minute of the exercise session. For the primary outcome, a multivariate linear mixed effect model (LMEM), with intervention, sequence period, carbohydrates consumption 15 minutes prior to exercise, and glycaemia at patient's arrival (60 minutes before exercise) (as fixed effects) and subject nested within sequence (as random effect), entered as covariates, was applied.

A similar statistical strategy was used for the analysis of all secondary endpoints to compare intervention's effects using either a LMEM with binomial family and logit link, Gaussian family with identity link, or Poisson (or negative binomial) family and log link for dichotomous, continuous and counts endpoints, respectively. *P*-value from Tables 2 and 3 are obtained from 2 × 2 comparisons using Tukey method (unadjusted *P*-values were presented given the relative small sample size) from the LMEM models. Because glycaemic data has positive values (e.g., time below a threshold) that follow a non-normal distribution and often has zero values, non-parametric bootstrap procedures were used to evaluate statistical significance and 95% confidence intervals of those endpoints differences between intervention. Time to first treated hypoglycaemic event were derived using survival analysis from a multivariate cox-regression model. Statistical significance was set at a *P*-value < 0.05.

Based on previous data [24], we supposed that the T0 strategy would have the highest percentage of time < 4 mmol/L, and that the T-20 strategy would decrease percentage of time < 4 mmol/L by 25%, and that the T-40 strategy would decrease percentage of time < 4 mmol/L by 50% compared to T0. Therefore, we assumed that the percentage of time < 4 mmol/L for T0 would be around 39.3%. Our sample size (n = 22) was chosen to detect a reduction of 50% between T0 and T-40 strategies (primary outcome) at 5% significance level, and 80% power, assuming a correlation of 0.25 between the two strategies.

Results

Twenty-six participants were initially enrolled but 4 dropped out due to time constraints. Twenty-two participants (11 males and 11 females) completed the study from January 2016 to May 2017, with a mean age of 40 ± 15 years, type 1 diabetes duration of 23 ± 13 years, HbA_{1c} level of 56.3 ± 10.2 mmol/mol (7.3 ± 1.0%) and VO_{2peak} 32.6 ± 7.05 mlO_2 kg^{-1} min^{-1} (Table 1).

While the mean percentage of time spent at glucose levels < 4.0 mmol/L during exercise was lower for T-40 (16 ± 25%) compared to T-20 (26 ± 27%) and T0 (24 ± 29%), differences did not reach statistical significance (*P* = 0.21, *P* = 0.19; respectively). As for the percentage of time spent in target glucose levels (4.0–10.0 mmol/L) during exercise, no differences were observed among the 3 strategies; 63 ± 37% at T-40, 66 ± 25% at T-20 and 65 ± 31% at T0. Primary outcomes for the three strategies are presented in Table 2 and BG profiles during exercise are shown in Fig. 2.

A favourable trend for the T-40 strategy was observed with lower areas under the curve (AUC) for hypoglycaemia (BG < 4.0 mmol/L) and higher decremental AUC's in comparison with T-20 and T0 without being statistically significant (Table 2). BG decline during

Table 1
Baseline characteristics of study participants (n = 22).

Characteristic	Mean ± SD	Min–Max
Age (years)	40 ± 15	19–70
Body mass index (kg/m^2)	25.4 ± 3.3	20.5–33.2
HbA_{1c} (mmol/mol)	56.3 ± 10.2	33.3–80.3
(%)	7.3 ± 1.0	5.2–9.5
Duration of diabetes (years)	23 ± 13	2–45
Total daily insulin dose (U)	42.8 ± 14.8	16.2–74.5
Total daily insulin dose (U/kg)	0.57 ± 0.17	0.30–0.98
VO_{2peak} (mL kg^{-1} min^{-1})	32.6 ± 7.05	18.2–51

Table 2
Comparison of the three-basal insulin rate reduction strategies.

Outcome	Reduction at −40 minutes	*P*-value (T-40 vs. T-20)	Reduction at −20 minutes	*P*-value (T-20 vs. T0)	Reduction at exercise onset	*P*-value (T-40 vs. T0)
Glucose value at exercise onset (mmol/L)	8.6 ± 3.6	0.15	7.4 ± 2.5	0.93	7.4 ± 2.7	0.21
Time spent at glucose levels (%)						
< 4.0 mmol/L[a]	16 ± 25	0.19	26 ± 27	0.68	24 ± 29	0.22
4.0–10.0 mmol/L	63 ± 37	0.65	66 ± 25	0.96	65 ± 31	0.71
Decrease in glucose levels (mmol/L)						
From start to end of exercise	−2.9 ± 1.5	0.009	−3.5 ± 1.7	0.09	−2.8 ± 2.0	0.61
For the last 22 min of exercise	−1.4 ± 0.9	0.16	−1.7 ± 1.0	0.33	−1.4 ± 1.0	0.64
AUC of glucose levels < 4 mmol/L (mmol/L × min)	23.9 ± 38.0	0.28	38.0 ± 39.8	0.86	37.6 ± 44.9	0.21
Decremental AUC (mmol/L × min)	263.8 ± 176.0	0.50	221.7 ± 102.1	0.43	199.7 ± 113.3	0.10

[a] Primary outcome. AUC is area under the curve. *P*-value < 0.05 is regarded as significant. *P*-values are from bootstrap. Data is presented as means ± SD.

exercise was comparable between the T-40 strategy (−2.9 ± 1.5 mmo/L) and the T0 strategy (−2.8 ± 2.0 mmol/L; $P = 0.58$) but lower than the decline with the T-20 strategy (−3.5 ± 1.7 mmol/L; $P = 0.01$ for T-40 vs. T-20 and $P = 0.10$ for T-20 vs. T0). However, the decline during the second half of exercise was comparable among the three strategies (−1.4 ± 0.9 mmol/L for T-40, −1.7 ± 1.0 mmol/L for T-20, −1.4 ± 1.0 mmol/L for T0).

Although basal insulin rate reduction 40 minutes prior to exercise is not sufficient to reduce the occurrence of hypoglycaemia, a few non-significant trends emerged. Starting glucose value was numerically higher for T-40 (8.6 ± 3.6 mmol/L) than for T-20 (7.4 ± 2.5 mmol/L) and for T0 (7.4 ± 2.7 mmol/L). Moreover, fewer patients needed extra carbohydrates consumption 15 minutes prior to exercise for BG < 5.0 mmol/L [3 (14%) with T-40 vs. 5 (23%) with T-20 and 6 (27%) with T0]. Interestingly, close to 50% reduction in the number of participants requiring CHO treatment for exercise-induced hypoglycaemia was observed with the T-40 strategy ($n = 6$) in comparison with T-20 ($n = 12$) and T0 strategies ($n = 11$). Time to first hypoglycaemic episode (< 3.9 mmol/L) was also numerically delayed with the T-40 strategy (28 ± 14 min for T-40 vs. 24 ± 10 min with T-20 and 22 ± 11 min with T0). Details of the hypoglycaemic events are presented in Table 3 and survival curve of hypoglycaemic treatment in Fig. 3.

Overall, hypoglycaemia was frequently observed with only six of the 22 participants (27%) never requiring any hypoglycaemia correction during all three interventions.

Discussion

In patients with T1D, the clinical benefits are well established for regular physical activity practice, which is nevertheless often avoided due to the challenges of glucose management during and after exercise [4]. Several strategies to tackle this issue have been suggested [10–12,14,15] but systematic evaluation of these recommendations is still required. Accordingly, this trial considered one of the pending questions related to the best timing to reduce basal insulin infusion rate in CSII users. Three practical time points (i.e. without large anticipation) were randomly tested to reduce basal insulin infusion by 80%: 40 minutes before exercise, 20 minutes before and at exercise onset, aiming to reduce exercise-induced hypoglycaemia in patients with T1D. Our results show that, despite lowering the basal insulin infusion rate by 80% up to 40 minutes prior to a 45-min submaximal aerobic exercise, hypoglycaemic risk remains considerable. There is, however, a trend for less time spent in hypoglycaemia when insulin infusion is reduced the longest. Other favourable trends observed when the T-

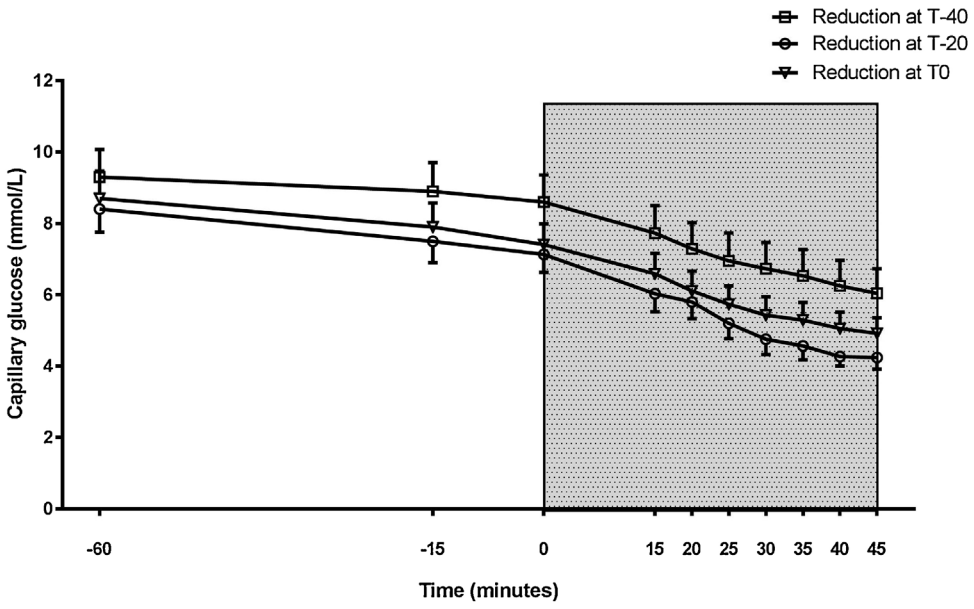

Fig. 2. Blood glucose profiles for the threeinsulin basal rate reduction strategies. The grey zone represents the exercise period.

Table 3
Comparison of hypoglycaemic events for the threebasal insulin rate reduction strategies.

Outcome	Reduction at −40 minutes	*P*-value (T-40 vs. T-20)	Reduction at −20 minutes	*P*-value (T-20 vs. T0)	Reduction at exercise onset	*P*-value (T-40 vs. T0)
Time to first hypoglycaemic event (minutes) (< 3.9 mmol/L)	28 ± 14	0.37	24 ± 10	0.43	22 ± 11	0.63
Time to first treated hypoglycaemic event (minutes)	35 ± 7	0.37	32 ± 11	0.43	31 ± 10	0.63
Number of hypoglycaemia treatments	6	0.13	14	0.53	11	0.32
Number of patients with hypoglycaemic treatment (%)	6 (27)	0.24	12 (55)	0.81	11 (50)	0.34
Number of patients requiring CHO 15 min prior to exercise	3	0.37	5	0.79	6	0.24

CHO is carbohydrates. *P*-value < 0.05 is regarded as significant.

40 strategy was applied were: higher blood glucose at exercise onset, less required CHO before and during exercise and a delayed time before the first hypoglycaemic episode. Despite the clinical relevance of these trends, our findings suggest that either a greater basal rate reduction is required (i.e. by up to 100%) or an earlier start time for basal rate reduction should be tested.

Previous studies have looked at basal insulin reduction to prevent hypoglycaemia during aerobic exercise [16–18,25–27]. Despite the different timings, percentages of basal rate reductions tested and hypoglycaemia definitions, hypoglycaemia remained common, as seen in our study. While studies testing basal suspension at exercise onset report reduced hypoglycaemia occurrence, they still showed frequent hypoglycaemic rates. For example, hypoglycaemia still occurred in 16% of cases of a 1-h late-post prandial exercise (estimated at 55% $V0_{2peak}$) in paediatric patients with pump stopped [18]. Others have tested basal reduction rather than suspension. Based on continuous glucose monitoring (CGM) readings, Franc et al. [16] suggested a reduction of insulin basal rate by 80% at exercise onset to limit the post-exercise hypoglycaemic risk associated with a shorter 30-min late post-lunch exercise at 50% VO_{2max}. Despite this reduction, 9 of their 20 participants (45%) presented at least one hypoglycaemic event (CGM glucose < 3.3 mmol/L) following the exercise. Some hypoglycaemic events might have been detected earlier during the exercise if plasma or capillary BG were considered, given that CGM frequently overestimates BG values when they are dropping during exercise [28,29]. In comparison, our present study, based on capillary BG values and testing a longer exercise protocol (45 minutes), showed a higher rate of hypoglycaemia (i.e. 50%) when an 80% basal rate reduction occurs at exercise onset (T0) or 20 minutes prior to exercise start time (T-20). With our earliest basal insulin infusion rate reduction (i.e. 40 minutes prior to exercise), hypoglycaemic rate was reduced to 27% and the timing of the first hypoglycaemic event was also delayed (Table 3 and Fig. 3), albeit these differences failed to reach statistical significance.

Literature is scarce when it comes to comparing different timings to reduce or suspend basal insulin infusion for exercise in T1D. Since prolonged insulin suspension can lead to hyperglycaemia [18], it is generally advised that pump suspension should not last more than 2 hours to reduce the risk of hyperglycaemia with ketosis [10,20,21]. Available literature is providing contradictory observations as, on one hand, some authors showed a benefit with an important 80% basal rate reduction at the onset of a 30-min exercise [16] while, on the other hand, a recently published study [26] reported that a 50% basal rate reduction 1 hour prior to a 30 min exercise was insufficient to prevent hypoglycaemia. Published consensus guidelines suggests reducing basal rate 60 to 90 minutes before exercise [10,20] but are not providing optimal percentage of basal rate reduction. In short, data is still needed to determine the best timing and percentage of reduction for different types and durations of exercise. We thus investigated if more practical timings, closer to exercise onset (20 minutes and 40 minutes prior to exercise), for basal rate reduction would impact hypoglycaemic risk during a 45-min moderate intensity exercise with the added option of carbohydrate intake 15 minutes before exercise if blood glucose level was low (< 5 mmol/L).

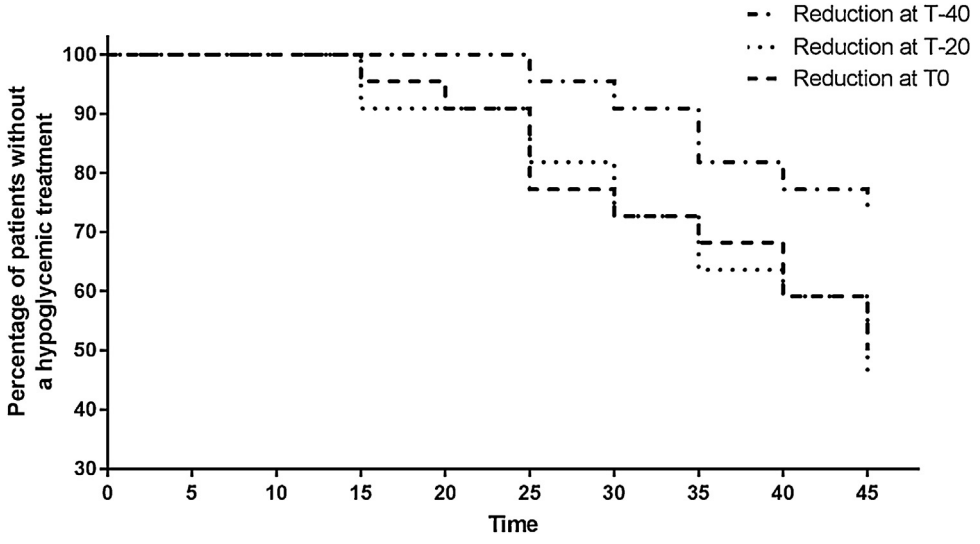

Fig. 3. Survival curve of hypoglycaemic treatments for the threeinsulin basal rate reduction strategies.

As for the magnitude of BG decrease during exercise observed in the present study (−2.8 to −3.5 mmol/L) with the various basal rate strategies tested, these declines in glycaemia compare to results of previous studies with similar exercise protocols [16,17]. When testing different insulin reduction strategies, exercise timing and intensities, Franc et al. reported a mean decrease in BG of 3.6 mmol/L during the 30-min exercise [16]. A similar decrease was published by Admon et al. [17] who reported no significant difference between the decrease in BG during a 45-min exercise on ergometer at 60% $V0_{2peak}$ executed 2 hours after breakfast when comparing reduction of basal rate by 50% (−4.1 ± 2.8 mmol/L) with pump suspension (−3.3 ± 3.2 mmol/L) at exercise onset.

Although circulating insulin levels were not measured in the present study, we postulate that the three time points for lowering basal insulin tested might not have allowed sufficient time to adequately reduce circulating insulin levels. It has been suggested that 30 to 60 minutes are needed before a decrease in plasma insulin levels can be detected when lowering basal insulin infusion at rest [19], but a more recent study (n = 14 adults) published after the initiation of our study showed that lowering basal insulin infusion by 50% at 60 minutes before a 30 min moderate exercise performed in a fasting state did not significantly lower circulating insulin levels [26]. An increase in insulin levels may even be observed in the early exercise period possibly secondary to increased blood flow in subcutaneous adipose tissue [26,30]. These observations might explain the shortcoming of the T-40 strategy to completely prevent hypoglycaemia and the similarity between the results of T0 and T-20 interventions.

Apart from lowering basal insulin delivery, other strategies have been studied to minimize the risk of exercise-induced hypoglycaemia: lowering the pre-meal bolus for exercise performed in closer proximity to meals [12], adding supplementary carbohydrates [15], or a combination of strategies [10,25]. In a study conducted with men using CSII and performing 60 minutes of moderate aerobic exercise 90 minutes after breakfast, hypoglycaemia could only be prevented when the pre-meal bolus was decreased by 50% and the basal insulin infusion was suspended during exercise [25]. Another option used by patients is combining a reduction of basal insulin with the consumption of additional carbohydrates. In a survey conducted by Roberts et al. [31] 68% of youth (10–18 years) reported decreasing or suspending basal insulin infusion during exercise and 70% reported a food intake in the hour preceding exercise, 26% of which contained mainly carbohydrates. Thus, even in a late post-prandial state (i.e. without significant impact of meal insulin bolus), the combination of a basal rate reduction and increased carbohydrate feeding might be needed. In our trial, carbohydrates were only given if BG was < 5.0 mmol/L 15 minutes prior to exercise or if glucose levels dropped to hypoglycaemic values during the activity. None of the time points for basal rate reduction were sufficient to completely avoid the need for supplementary carbohydrates 15 minutes prior to exercise and this intake (21 g) did not always protect against subsequent exercise-induced hypoglycaemia, given that hypoglycaemic treatment was still needed in 10 out of 14 (71%) exercise sessions.. Similar to insulin reduction, the optimal amount and timing of carbohydrate intake remain to be established.

Glucose level at exercise onset can be one determinant of exercise-induced hypoglycaemia [17]. McAuley et al. [26] suggested that reducing insulin infusion rate by 50% 60 minutes before a 30-min aerobic exercise at moderate intensity in the fasting state helps reduce hypoglycaemia in most participants. However, if BG at onset of exercise was lower than 5.0 ± 0.01 mmol/L this measure was not efficient. In the present study, mean BG levels at onset of exercise was 5.9 ± 1.4 mmol/L for the pooled interventions needing hypoglycaemia treatment and 9.1 ± 3.1 mmol/L for interventions without treatment ($P < 0.001$). This suggests the mild pre-exercise hyperglycaemia somewhat protects against hypoglycaemia during the activity. Nevertheless, we could not identify a starting BG level protective of hypoglycaemia even if our results do suggest that some favourable trends observed with the T-40 strategy might be due to the higher starting BG level. Different study designs might explain differences observed with McAuley's proposed threshold: patient population (adolescent vs. adults), exercise timing (fasting vs. late post-prandial), and longer duration (30 vs. 45 minutes). Moreover, the important intra- and inter-individual variations observed for blood glucose decrease during exercise might hinder the establishment of a safe pre-exercise blood glucose threshold [8,32,33].

Strengths and limitations

Our study has several strengths including the crossover design and the standardization of meals and snacks with testing of 3 practical timings for basal rate reduction. The use of capillary BG levels as compared to CGM is also an advantage giving a more precise picture of BG profile during exercise [28]. Nevertheless, some limitations are also acknowledged. In the calculation of our sample size, we assumed a difference in the primary outcome between T-20 and T0 strategies which proved not to be the case reducing our power with the enrolled sample size. Moreover, the great diversity in subjects' profiles (i.e. age, BMI, HbA1c, duration of diabetes and total daily insulin dose) may have reduced the statistical power of our study, but results of exploratory sub-group analysis are in line with our initial results. Conversely, such diversity should increase external validity of our findings. Additionally, this trial tested only a single percentage of basal rate reduction and we did not explore other exercise modes which can have a less pronounced hypoglycaemic effect (e.g. resistance or interval training), durations or intensities. All these variables are thought to affect the glycaemic responses to exercise in patients living with T1D [10,34]. Moreover, this paper does not address the issue of delayed post-exercise glucose control including delayed hypoglycaemic risk, another great challenge for patients with T1D [35].

Conclusion

Our study reiterates the fact that exercise-induced hypoglycaemia is frequent and could not be reduced with an 80% basal insulin infusion rate reduction applied up to 40 minutes prior to exercise. Some non-significant favourable trends observed with the T-40 strategy; however, suggest that earlier or larger basal insulin reductions prior to exercise need to be tested. This study also suggests that, if basal rates were to be reduced between exercise onset and 40 minutes before exercise, consumption of supplementary carbohydrates may still frequently be required to prevent hypoglycaemia. The timing, amount, and glucose threshold for this preventive strategy warrant further investigation in future studies. It is probable that insulin adjustment and carbohydrate feeding strategies need to be individualized based on each of these key factors and perhaps even the unique metabolic responses of a given patient. A combination of different approaches is, most probably, required to provide an optimal glucose control with physical activity.

Authors' contribution

Funding: RR-L.
Study design: RR-L, VM, NT, LL & A R-F.
Data collection: A R-F, VM, CC, SE and CS.
Data analysis: A R-F, ML, RR-L, LL, VM, MRS, NT.
Manuscript: A R-F (1st draft), NT, VM, CS, CC, SE, MRS, ML, LL, RR-L.

Disclosure of interest

RR-L has received consultant's or speaker's honorariums or grants from AstraZeneca, Becton Dickinson, Boehringer Ingelheim, Eli Lilly, Janssen, Lifescan, Medtronic, Merck, Novartis, Neomed, Novo Nordisk, Roche, Sanofi-Aventis and Valeant.
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The other authors declare that they have no competing interest.

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