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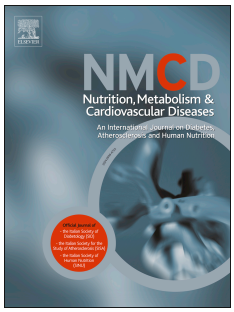

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Extent and prevalence of post-exercise and nocturnal hypoglycemia following peri-exercise bolus insulin adjustments in individuals with type 1 diabetes

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Abstract

Aim: To detail the extent and prevalence of post-exercise and nocturnal hypoglycemia following peri-exercise bolus insulin dose adjustments in individuals with type 1 diabetes (T1D) using multiple daily injections of insulins aspart (IAsp) and degludec (IDeg).

Methods: Sixteen individuals with T1D, completed a single-centred, randomised, four-period crossover trial consisting of 23-hour inpatient phases. Participants administered either a regular (100%) or reduced (50%) dose (100%; 5.1±2.4, 50%; 2.6±1.2 IU, $p<0.001$) of individualised IAsp one hour before and after 45-minutes of evening exercise at 60±6% $\dot{V}O_{2max}$. An unaltered dose of IDeg was administered in the morning. Metabolic, physiological and hormonal responses during exercise, recovery and nocturnal periods were characterised. The primary outcome was the number of trial day occurrences of hypoglycemia (venous blood glucose $\leq$3.9 mmol.L $^{-1}$).

Results: Inclusion of a 50% IAsp dose reduction strategy prior to evening exercise reduced the occurrence of in-exercise hypoglycemia ($p=0.023$). Mimicking this reductive strategy in the post-exercise period decreased risk of nocturnal hypoglycemia ($p=0.045$). Combining this strategy to reflect reductions either side of exercise resulted in higher glucose concentrations in the acute post-exercise ($p=0.034$), nocturnal, ($p=0.001$) and overall ($p<0.001$) periods. Depth of hypoglycemia ($p=0.302$), as well as ketonic and counter-regulatory hormonal profiles were similar.

Conclusions: These findings demonstrate the glycemic safety of peri-exercise bolus dose reduction strategies in minimising the prevalence of acute and nocturnal hypoglycemia following evening exercise in people with T1D on MDI. Use of newer background insulins with current bolus insulins demonstrates efficacy and advances current recommendations for safe performance of exercise.

Keywords; Type 1 diabetes, exercise, insulin aspart, insulin degludec, hypoglycemia.

Introduction

Individuals with type 1 diabetes (T1D) on multiple daily injection (MDI) regimens are reliant on insulin replacement therapy for managing blood glucose. However, exogenously administered insulin is not subject to autoregulation, thus hyperinsulinemia [1,2], and therefore hypoglycemia [3,4], remain major limitations in the current therapeutic management of diabetes. This becomes particularly relevant around physical exercise, which can rapidly increase intramuscular glucose uptake through mechanisms mediated by, but also independent of, insulin [5–10]. Thus, the additive effects of peripheral hyperinsulinemia and exercise in promoting tissue permeability and uptake of glucose [11–14], accentuate the risk of exercise-related hypoglycemia in people with T1D. Beyond these acute effects, exercise-induced increases in tissue sensitisation to insulin may persist for many hours following cessation [15–20], with evidence of a second peak occurring several hours later [21]. In the case of evening exercise, this may bring an already chronically hyperinsulinemic individual with T1D into a nocturnal period in a supra-insulin-sensitised state. As such, the window of hypoglycaemic risk is often expanded to include the nocturnal hours [22–25], at a time when self-blood glucose monitoring is understandably difficult [26]. In appreciation of these factors, careful adjustments in bolus insulin therapy around physical exercise are advised for individuals with T1D, and general recommendations across many diabetes associations and peer-reviewed outlets are available [27–29]. However, intra-individual variation in blood glucose responses to the same exercise is large [30], which only adds to the complexity of developing an effective glycemic management strategy around physical activity in those with T1D. Furthermore, despite the endorsed integration of insulin dose reduction strategies, research continues to demonstrate that individuals with T1D frequently begin exercise hyperinsulinemic [25,31–33], a situation worsened by the apparent rise in systemic insulin concentrations during aerobic activities [12,25,34], likely due to the associated subcutaneous insulin washout, hyperaemia and blood/interstitial volume redistribution [35]. A key source of variance in research pertaining to recommended MDI alterations around exercise is the diversity of bolus and basal insulins employed within and between studies [34,36–40], most of which have relied on home-based interstitial glucose monitoring for confirmation of hypoglycemia leading into and throughout the nocturnal hours, a method with its own inherent limitations due to device inaccuracy when glucose deviates from the physiologic range [41]. Given the distinct pharmacokinetic profiles of different insulins, the range used in existing research makes for difficulty in interpreting findings, particularly when now outdated

analogues have previously been used and overnight sampling is scarce. Modern insulin analogues are in clinical practice, and the incorporation of ultra-long acting insulin analogues as conventional basal therapies with established bolus insulins is common within primary and secondary healthcare. Therefore, there remains a need to explore combinations of current generation insulins as part of a basal-bolus glycemic management strategy that, not only strengthens the efficacy of current exercise strategy recommendations pertinent to those with T1D, but also encourages safe exercise performance by limiting the potential for post-exercise and nocturnal hypoglycemia.

Aim: To detail the extent and prevalence of post-exercise and nocturnal hypoglycemia following peri-exercise bolus insulin dose adjustments in individuals with type 1 diabetes (T1D) using multiple daily injections of insulins aspart (IAsp) and degludec (IDeg).

Methods and Materials

Study design

This study involved a primary analysis of a single-centre, randomised, open-label, four-period cross over clinical trial (German Clinical Trials Register; DRKS00013509). The study was performed in accordance with good clinical practice and the Declaration of Helsinki (1996). Approval was granted by both the national research ethics committee (16/WA/0394) and the local health authority (EudraCT number: 2017-004774-34; UTN: U1111-1174-6676).

Screening visit

Ahead of trial inclusion, participants were screened for anthropometric, cardiovascular and T1D specific markers prior to the performance of a cardio-pulmonary exercise test on a semi-recumbent cycle ergometer (Corival Recumbent, Lode, NL) [42]. After successful completion against the reference inclusion criteria, participants were switched from their usual basal/bolus insulin therapies (*n=8*; glargineU100/aspart, *n=1*; glargineU300/aspart, *n=1*; degludec/aspart, *n=6*; detemir/aspart) to ultra-long-acting insulin degludec ([IDeg], Tresiba®, NovoNordisk, Denmark) in 3 mL pre-filled investigational pens (PDS290) and rapid-acting insulin aspart ([IAsp], NovoRapid® NovoNordisk, Denmark) in 3 mL pre-filled investigational pens (FlexPen®). Once titrated, the total daily basal insulin dose (TDBD) was 20% less for the once-daily-morning dosing for IDeg than detemir, glargineU100 and

glargineU300. Participants were required to achieve a mean overnight-fasted morning capillary blood glucose (cBG) value of 4.4 – 7.2 mmol.L^{-1} over 3 consecutive days within 4 weeks after first trial basal insulin dose. If glycemic instability persisted for ≥3 days following titration, a dose adjustment alteration was made until criteria was met. A run-in period of >7 days was required to assure optimal adaptation to IDeg prior to the experimental period. All participants were using IAsp ahead of trial inclusion, thus were instructed to maintain their usual bolus insulin regime in accordance with their individualised meal-time insulin dose requirements (Mean insulin: carbohydrate [CHO] ratio = 1 IU :10±4g).

Experimental trial visits

A schematic overview of experimental trial visits is illustrated in Figure 1. Between 08:00 and 16:00, participants undertook a standardised period during which they received set breakfast, brunch and lunch meals that were matched in macronutrient content to their habitual dietary preferences. Low glycaemic index (G1) meals were provided at each feeding timepoint to control the influence of high GI foods on blood glucose over the 23-hour in patient stays. With each of these meals, participants injected their routine dose of IAsp based on their individualised carbohydrate factor (CarbF) calculated by means of an algorithm (CarbF=5.7*kg/TDD)[43]. One hour before and after exercise (Ex), participants administered either a full (100%) or reduced (50%) dose (100%; 5.1±2.4 versus 50%; 2.6±1.2 IU, $p<0.001$) of individualised IAsp alongside the consumption of an identical low glycemic index (brown rice based vegetable dish), carbohydrate rich meal equating 1g.CHO.kg.bm^{-1} (Total energy; 496±62 kcals, Fat; 9±5g [20%], Protein; 19±11g [15%], CHO 80±10 [65%]). If pre-exercise fingertip cBG was <6 mmol.L^{-1}, the exercise test was delayed, and participants consumed a standardised 10g CHO gel (Glucogel®, BBI healthcare Ltd, UK) with subsequent 10-minutely monitoring until cBG was above a target threshold.

On the basis of block randomisation, trials were allocated the following identifiable codes; PreEx **F**ull – PostEx **F**ull (**FF**), PreEx **F**ull – PostEx **R**educed (**FR**), PreEx **R**educed – PostEx **F**ull (**RF**) and PreEx **R**educed – PostEx **R**educed dose (**RR**). The evening (17:00) exercise test consisted of 45 minutes (3-minute warm up @ 20 watts, 42-minutes @ target workload) of continuous cycling on a semi-recumbent ergometer at 60±6 % $\dot{V}O_{2max}$. The workload intensity was computed as the mid-point between the first and second lactate turn points as previously described [42]. During exercise, heart rate (HR [s410, Polar®, Finland]) respiratory

exchange ratios (METAMAX® 3B; Cortex Biophysik GmbH, GER) and power metrics were collected continuously. Respiratory exchange ratios were used to calculate the rates of carbohydrate and lipid oxidation via the principles of indirect calorimetry as described previously [44]. Prior to retiring to bed, participants consumed a small CHO-rich snack ($0.4 g.CHO.kg.bm^{-1}$) with omission of IAsp (21:00). Glycemia was determined via capillary (08:00-15:59) and venous (16:00-07:00) BG monitoring over the 23-hour inpatient stays. Venous derived samples were taken hourly leading into (16:00) and acutely post-exercise (17:45-21:00), then obtained two-hourly leading into, and throughout the nocturnal period (00:00-05:59). During exercise, 20µl capillary samples were collected every 6 minutes from the right earlobe and used for within-exercise metabolic analysis. Following obtention, BG was analysed immediately via an enzymatic-amperometric method (Biosen C-Line, EKF Diagnostic, GER). Hypoglycemia was identified as a venous BG (vBG) value of ≤3.9 mmol.L-1. Hypoglycemia was treated via the oral administration of a standardised 10g containing CHO gel (Glucogel®, BBI healthcare Ltd, UK). cBG was subsequently monitored every 10 minutes, and if necessary, the treatment procedure was repeated until cBG was restored to euglycemic concentrations.

Metabolic and counter-regulatory hormonal biomarkers

The Randox Daytona Plus RX series analyser (Randox Laboratories, Ltd, UK) was used for determination of ß-hydroxybutyrate ([β-OHB] RB4067). ELISA assays were used for the quantification of plasma glucagon (DGCG0, R&D Systems, Inc. Minneapolis, USA) and catecholamines (epinephrine [EPI] and norepinephrine [NE] ECT31-K02, Eagle biosciences, Inc. New Hampshire, USA]). Venous derived blood lactate (vBLa) concentrations were measured via the fully enzymatic-amperometric method (Biosen C-Line, EKF Diagnostic, GER).

Data analysis

All statistical analyses were carried out using SPSS 26.0 statistical software (SPSS, Chicago, Illinois, USA) and $p \leq 0.05$ (two sided) was considered statistically significant. Data were treated via repeated measures ANOVA and uni-or multi-variate analysis techniques with bonferroni-corrected pairwise comparisons used in post-hoc analysis to determine time and treatment effects. The total daily dose (TDD [inclusive of basal and bolus amounts] of insulin taken during the control period and exercise duration were accounted for as covariates in the

model where appropriate. Cross tabulation analysis was used to identify estimated risk ratios (ERR) between nominal variables, with fishers exact testing and chi-square values used to report significance. Data were stratified into distinct phases i.e. the day-time control period (08:00-15:59), the pre-exercise period (16:00-16:59), the exercise period (17:00-17:45), the post-exercise period (17:46-23:59), the nocturnal period (00:00 -05:59) and the fasted morning period (06:00–07:00).

Results

Participant characteristics and pre-intervention study standardisation

Baseline physiological and diabetes characteristics are displayed in Table 1. During the day-time control period (08:00-15:59), carbohydrate (CHO) intake ([inclusive of standardised and treatment amounts] **FF** 169.3±46.7, **FR** 168.6±43.6, **RF** 168.5±37.8, **RR** 165.3±34.3 g, p=0.993) and total daily insulin dosages (**FF** 0.50±0.22, **FR** 0.48±0.20, **RF** 0.50±0.20, **RR** 0.49±0.22 IU.kg.bm^{-1}, p=0.995) were identical between trials.

23-hour hypoglycemia

Trial day vBG concentrations were highest in the **RR** trial, which differed from all other arms (**FF** 8.0±3.6, **FR** 8.0±3.3, **RF** 7.8±3.3, **RR** 9.2±3.8 mmol.L^{-1}, p<0.001). Of a possible 832 sample draws, there were 66 (8%) confirmed vBG hypoglycemic events during the entire experimental period (**FF** = 21 events in 14 people, **FR** =16 events in 14 people, **FR** =15 events in 9 people, **RR** = 14 events in 10 people, p=0.593). During their study involvement, every participant experienced at least 1 hypoglycemic event, whilst 15/16 people experienced recurrent hypoglycemia (>1 event). There was no difference between trials in the probability of experiencing recurrent hypoglycemia (χ^2 = 1.834, *DF* = 3, p=0.608). The average depth of hypoglycemia during the experimental period was similar between trials (p=0.302, Table 4), with a mean concentration of 3.3±0.4 mmol.L^{-1} (range 2.2 to 3.9 mmol.L^{-1}).

Hypoglycemia during exercise

Baseline (**FF** 7.1±1.9, **FR** 6.7±1.3, **RF** 6.1±1.5, **RR** 6.3±2.0 mmol.L^{-1}, p=0.670) and immediate pre-exercise (Table 2, p=0.448) vBG concentrations were identical between experimental arms. In all trials, vBG decreased during exercise (p≤0.001). However, both the magnitude of the drop (**FF** Δ -3.45±2.94, **FR** Δ -4.41±2.29, **RF** Δ -3.37±1.4, **RR** Δ -

198 3.59±2.13 mmol.L^{-1}, p=0.444) and the rate of change in vBG were similar between trials (**FF**
199 -0.10±0.08, **FR** -0.13±0.06, **RF** -0.09±0.04, **RR** -0.08±0.05 mmol.L^{-1}.min^{-1}, p=0.278). Of 64
200 exercise sessions, 39 (61%) were terminated prematurely due to hypoglycemia (**FF** 11, **FR**
201 14, **RF** 8, **RR** 6 events, p=0.021 [Table 3]) with proportionality more hypoglycemia observed
202 in the **FR** versus **RR** dosing arm (p=0.023). The risk of hypoglycemia during cycling was 2-
203 fold higher in trials that incorporated a full dose of IAsp with the pre-exercise meal (ERR
204 2.00 [95% CI 1.234 - 3.259], p=0.005). The mean hypoglycemic value at the end of exercise
205 was 3.3±0.4 mmol.L^{-1} (ranging from 2.2 to 3.9 mmol.L^{-1}) and reached severe hypoglycemia
206 (<3.00 mmol.L^{-1}) in all except the **FR** dose-trial, in which the lowest vBG measurement was
207 3.0 mmol.L^{-1} (Table 4). There was no difference between trials in the end hypoglycemic
208 (p=0.659 [Table 4]) or overall (p=0.711 [Table 2]) vBG concentrations. Exercise duration did
209 not differ between trials (**FF** 37.0±10.2, **FR** 36.1±6.2, **RF** 39.3±8.7, **RR** 42.0±6.3 minutes,
210 p=0.175). As a result of a greater incidence of hypoglycemia, more rescue CHO were needed
211 in the pre-exercise unaltered insulin dosing trials (**FF** 6.9±4.8, **FR** 8.8±3.4, **RF** 5.0±5.2, **RR**
212 4.4±5.1 g, p=0.048).

213 ***Post exercise and nocturnal hypoglycemia***

214 The second largest incidence of trial-related hypoglycemia (13 of 66 events = 20% of trial
215 total) occurred in the immediate post-exercise period (17:46-23:59). The 13 events happened
216 in 12/16 people across all 4 trials (**FF**; 6 events in 6 people [38%], **FR**; 2 events in 2 people
217 [13%], **RF**; 2 events in 2 people [13%], **RR**; 3 events in 2 people [13%]). During the post-
218 exercise period, there were no differences between trials in either the occurrence (p=0.348,
219 Table 3), nor depth (p=0.527, Table 4), of hypoglycemia, neither was there any difference in
220 the risk of recurrent hypoglycemia (χ^2 =3.048, *DF*=3, p=0.384). Overall post-exercise (17:45–
221 23:59) vBG concentrations were highest in the **RR** trial (**FF** 7.49±3.76, **FR** 7.35±2.76, **RF**
222 7.45±2.78, **RR** 8.67±3.52, p=0.034). There was a greater need for post-exercise treatment
223 CHO in the **FF** trial (**FF** 9.7±8.7, **FR** 2.5±7.7, **RF** 5.6±9.6, **RR** 1.9 ± 5.4g, p=0.030).

224 Mean nocturnal (00:00-05:59) vBG concentrations were highest during the **RR** trial (**FF**
225 9.5±3.2, **FR**, 10.1±3.2, **RF** 9.2±3.7, **RR** 11.5±3.6 mmol.L^{-1}, p=0.001), which differed from
226 the two opposing unaltered post-exercise dosing other arms. Nocturnal hypoglycemia
227 occurred on 7 occasions (11% of trial total) with a mean hypoglycemic vBG value of
228 3.03±0.36 mmol.L^{-1}. The occurrence of nocturnal hypoglycemia was proportionately low

between conditions (**FF** 3, **FR** 0, **RF** 3, **RR** 1 events, p=0.558, Table 3) as was the likelihood of experiencing recurrent nocturnal hypoglycemia (χ^2 = 3.048, *DF* =3, p=0.384). The extent of hypoglycemia was also equivalent (p=0.238, Table 4) Of the 7 incidences of nocturnal hypoglycemia, 6 (86%) occurred in the trials that included a full dose of IAsp in the post-exercise period, which was associated with a near 4-fold increase in the risk of hypoglycemia during the night (ERR 3.81 [95% CI 0.611 – 23.734], p=0.045).

Physiologic, metabolic, and counter-regulatory hormonal responses to exercise

The cardiorespiratory, metabolic, and counter-regulatory hormonal responses to exercise are presented in Table 2. There were no differences between trials in any parameter at immediately prior to exercise, as an exercising mean, or at the end of exercise. The exercising energy expenditure from CHO (**FF** 83.8±10.7, **FR** 84.6±9.8, **RF** 79.4±13.1, **RR** 81.6±7.4%, p=0.752) and lipids (**FF** 16.2±10.7, **FR** 15.4±9.8, **RF** 20.6±13.1, **RR** 18.5±7.4%, p=0.752) was similar between trials. Cycling induced a significant increase in all cardio-respiratory variables (Table 2†). Catecholamines and glucagon remained unchanged by exercise in all conditions. There were no differences between trials in the magnitude of change ($_{delta}$) in response to exercise in any counter-regulatory hormonal or metabolic biomarkers (EPI_{delta}, p=0.142, NE_{delta}, p=0.443, $Glucagon_{delta}$, p=0.842, $v\beta\text{-}OHB_{delta}$, p=0.758, $vBLa_{delta}$, p=0.919). There were no recorded incidences of any trial related hyperketonemia or lactic acidosis at any timepoint throughout the entire experimental period.

Discussion

This study is the first to detail the extent and prevalence of post-exercise and nocturnal hypoglycemia, following peri-evening exercise bolus insulin dose alterations using specific multiple daily injections of insulins aspart (IAsp) and degludec (IDeg) in individuals with T1D over a 23-hour in-patient period. Our findings demonstrated that a 50% IAsp dose reduction prior to evening exercise reduces the occurrence of hypoglycemia during exercise and mimicking this strategy in the post-exercise period decreases the risk of nocturnal hypoglycemia. Combining this approach and reducing IAsp dose either side of exercise results in higher glucose concentrations in acute post-exercise, nocturnal and overall periods.

The significant reduction in IAsp units injected before exercise (PreEx50% 2.6±1.2 vs. PreEx100% 5.1±2.4 IU, p<0.001), resulted in a greater meal-induced rise in glucose

compared to the unaltered dose (PreEx50% Δ +2.1±2.1 vs PreEx100% Δ +1.2±2.0 mmol.L^{-1}, p=0.031). However, despite the small amount of insulin taken before exercise, and the consequent increase in post-prandial blood glucose, this acute relative reduction represented only ~6% of injected insulin up to this point. Similar to previous studies [12,25,31,34], participants were likely supra-hyperinsulinemic ahead of exercise commencement, which potentially evoked an inhibitory effect by inactivating phosphorylase, ultimately reducing the rate of glycogenolysis, yet accentuating peripheral glucose uptake [12]. Further, exercise induced increases in skeletal muscle blood flow, capillary perfusion and membrane permeability enhance the rate of delivery and absorption of blood borne substrates and hormones to working muscles during exercise [45,46]. The macronutrient composition of a pre-exercise meal also considerably influences patterns of fuel metabolism and utilisation during exercise, with shifts towards higher muscle glycogenolysis and carbohydrate oxidation observed following ingestion of a glucose load [47], particularly when superimposed with hyperinsulinemia [12]. Thus, that participants not only exercised within the peak effect of IAsp (time until peak onset of action = ~31 - 70 minutes [48]), but were also acutely post-prandial, having just consumed a high carbohydrate meal (~65% carbohydrate content), likely primed tissues to use glucose as the predominate energy source during exercise [49,50]. Indeed, irrespective of the pre-exercise insulin dose used, exercising rates of carbohydrate oxidation were high compared to lipid combustion (contribution of carbohydrates ~83±9%), and probably accounted for the significant drop in blood glucose concentrations during exercise (~Δ vBG 3.7±2.2 mmol.L^{-1}). Notably, 61% of all exercise tests were terminated prematurely due to hypoglycemia. As such, as an independent time phase, the 45-minute exercise period accounted for 59% of all hypoglycemic events recorded over 23 hours. This was most obvious when exercising with an unaltered dose of IAsp, which led to a two-fold increase in the risk of hypoglycemia relative to when a 50% dose reduction was incorporated.

Hypoglycemia defence mechanisms were challenged with our model of cycling, with pronounced drops in arterial blood glucose concentrations observed across all trial arms. However, glucagon and catecholamine concentrations remained unchanged from pre-exercise values in all conditions. Both glucagon and the catecholamines positivity regulate net hepatic endogenous glucose production via stimulating glycogenolysis and gluconeogenesis [51,52]. However, in addition to abnormalities in hepatic glucose production during exercise [53], individuals with T1D demonstrate attenuated counter-regulatory responses to hypoglycemia

[54], a situation worsened by hyperinsulinemia [55]. Thus, the small, and possibly blunted, counter-regulatory hormonal responses observed in our data, may be an additional factor owing to the high prevalence of within-exercise hypoglycemia.

The effects of exercise on enhancing tissue sensitivity to insulin and peripheral glucose uptake persist for several hours following exercise cessation, a situation intensified in the presence of hyperinsulinemia [15–18,56]. Our data reveal that overall acute post-exercise (~6 hours) glycemia was most supported in the peri-exercise dose reduction arm, whilst in direct contrast, the incorporation of an unaltered dosing strategy either side of exercise independently accounted for ~50% of all acute post-exercise hypoglycaemic events. These data support and advance research work by Campbell et al [57], who also demonstrated the glycemic preservation benefits associated with a 50% dose reduction to the post-exercise bolus insulin (IAsp or lispro used with background insulins glargineU100 and detemir) dose in the acute (~4 hours) but not extended (~8 hours) period after exercise [57]. The authors hypothesised that the observed similarity in the prevalence of hypoglycemia in the extended post-exercise window may have been due to the administration of additional, and indeed unaltered, bolus insulin doses in the post-laboratory home-phase. In heed of these discoveries, later work highlighted the protective effect of consuming a small carbohydrate based snack (0.4g.CHO.kg.bm^{-1}) ahead of the night-time period in minimising rates of nocturnal hypoglycemia subsequent to evening exercise in patients treated with insulins aspart and glargineU100 [25]. However, due to relatively short post-exercise in-patient monitoring phases (~3 hours), hypoglycemia was determined via interstitial glucose monitoring in both of these studies, and given the inherent flaws in device accuracy during hypoglycemia [41], may have misidentified events. Thus, using venous derived glucose values collated in laboratory-controlled conditions, our data confirm the effectiveness of these strategies in people with T1D using MDI consisting of insulins aspart and degludec.

A 50% dose reduction to mealtime insulin in the post-exercise period provided a near 4-fold decrease in the risk of nocturnal hypoglycemia compared to a full bolus insulin dose. Interestingly, in addition to the provision of a small carbohydrate based snack with bolus insulin omission 2 hours ahead of the night time hours, the nocturnal period in this study commenced ~5 hours following the last bolus insulin injection, hence, given its pharmacokinetic characteristics (time of duration of action; 3 - 5 hours [48]), it was unlikely that IAsp represented much of the total pool within the circulation. The enhanced sensitivity

to insulin following exercise has been shown to follow a biphasic trend, during which in addition to an initial increase immediately after exercise, a second peak occurs 7-11 hours later [22] .Thus, in addition to the direct effects of acute hyperinsulinemia in accelerating risk of in-exercise hypoglycemia, these data affirm the long-standing metabolic effects of antecedent exercise in increasing the risk of delayed onset of hypoglycemia in people with T1D [25]. Irrespective of hypoglycemia *per se*, employing 50% dose reductions either side of exercise led to the highest preservation in glucose throughout the night-time hours, thus reinforces the glycemic safety of prudent dose alterations alongside carbohydrate rich meals before and after exercise for this cohort. Though considerably higher following the administration of an unaltered insulin dose post-exercise, rates of nocturnal hypoglycemia in this study were minimal, and align with previous reports of a low prevalence of severe ($\leq$3.1 mmol.L^{-1}) nocturnal hypoglycemia following moderate intensity cycle exercise (~60% $\dot{V}O_{2max}$ for 30 minutes) in participants with T1D treated with insulins aspart and degludec [58]. However, in this study the pre-exercise mealtime bolus insulin manipulation was taken well in advance of exercise commencement (~3 hours), with an equivalent reduction in the carbohydrate amount. Critically this meant that the individualised carbohydrate :insulin ratio remained unaltered, which may explain the complete avoidance of hypoglycemia during exercise. Interestingly, when we re-examined our data against the threshold for severe hypoglycemia, the occurrence dropped to 3 events which happened similarly across trials (**FF**, 1 **FR** 0, **RF** 1, **RR** 1 events, χ^2 = 1.049, *DF* = 3, p=0.789) and provide some assurance for glycemic stability whilst using IDeg. In light of the potential obesogenic implications associated with an over reliance on additional carbohydrate intake and exogenous insulin administration [59], the increase in energy expenditure as a result of longer duration exercise, combined with a lesser need for treatment carbohydrates with insulin dose reductions, has important clinical undertones that stretch beyond those relating to dysglycemia. Finally, trial day β-OHB concentrations were below levels deemed hyper-ketonemic (>1.0 mmol.L^{-1}) [60], thus support previous work in displaying no adverse metabolic implications associated with bolus insulin reduction (or omission) concomitant with high carbohydrate intakes in individuals with T1D [61]. Therefore, from a clinical viewpoint, the integration of peri-exercise IAsp dose reductions with IDeg can be implemented safely with no risk of ketone body formation.

Study strengths, limitations, and future recommendations

The study design enabled intensive 23-hour monitoring including an overnight stay in a medically-supervised clinical research facility with frequent venous sample draws, standardised mealtime feedings and monitored insulin dose administrations. Collectively, these factors helped overcome the identified limitations of previous research whilst providing up-to-date information on the extent and prevalence of exercise-related hypoglycemia, using specific modern insulin analogue combinations in people with T1D. With mixed gender design of the study and a wide age range for trial inclusion, our participant cohort findings are applicable to the wider population and advance out understanding of insulin dose adjustments in T1D individuals treated with MDI.

Conclusion

These findings demonstrate improved glycemia with peri-exercise bolus dose reduction strategies which reduce the prevalence of acute and nocturnal hypoglycemia following evening exercise. Incorporation of newer background insulins with current bolus insulins demonstrates efficacy and advances current recommendations for safe performance of exercise in people with T1D using MDI.

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Author contributions

OM[c], OM, MLE, RD, JP and RMB were responsible for data collection, interpretation and analysis. JH, DMW and SCB provided to medical oversight. RC, GJD and CJ performed laboratory-based data analysis. OM[c] and RMB wrote the manuscript. SCB and RMB are the chief and principle investigators of the study. RMB wrote and secured funding for the study. All co-authors contributed to feedback and revisions for the final manuscript.

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Tables

Table 1. Baseline characteristics of study participants

Baseline characteristics of study participants	
Characteristic	**n=16**
Gender M versus F (n)	13 vs 3
Age (years)	34.5±13.9
BMI ($kg.m^2$)	26.0±3.4
Lean Mass (%)	23.4±3.3
HbA_{1c} (%)	7.2±1.3
HbA_{1c} (mmol/mol)	56±15
Diabetes Duration (years)	14.4±11.1
Pre study TDD ($IU.kg.bm^{-1}$)	0.6±0.3
Pre study TDBD ($IU.kg.bm^{-1}$	0.4±0.2
$\dot{V}O_{2max}$ ($ml.kg^{-1}.min.^{-1}$)	40.3±10.3

Table 1. Baseline characteristics of study participants. Data are presented as mean±SD. n; number of participants. M; Male. F; Female. BMI; body mass index. Kg; kilograms. M; meters. TDD; Total daily insulin dose (inclusive of basal and bolus amounts). TDBD; total daily basal insulin dose. Bm; body mass. ml; millimetres. Min; minutes.

607 Table 2. Metabolic, physiologic, and counter-regulatory hormonal responses to exercise

Parameter	Physiologic, metabolic, and respiratory responses				
	FF	**FR**	**RF**	**RR**	**p value**
a) Cardiorespiratory responses					
HR_{mean} (bpm)	133±11†	135±12†	134±11†	133±12†	0.904
$\dot{V}O_{2mean}$ ($l.min^{-1}$)	1.9±0.3†	1.9±0.4†	1.9±0.3†	1.9±0.3†	0.632
$\dot{V}CO_{2mean}$ ($l.min^{-1}$)	1.8±0.3†	1.8±0.4†	1.8±0.3†	1.8±0.3†	0.723
CHO $oxidation_{mean}$ ($g.min^{-1}$)	1.9±0.5†	1.9±0.5†	1.9±0.4†	1.9±0.4†	0.915
Lipid $oxidation_{mean}$ ($g.min^{-1}$)	0.2±0.1†	0.2±0.1†	0.2±0.2†	0.2±0.1†	0.455
TEE_{mean} ($kcals.min^{-1}$)	9.3±1.6†	9.1±1.8†	9.2±1.7†	9.3±1.5†	0.668
b) Metabolic responses					
$vBG_{pre\text{-}ex}$ ($mmol.L^{-1}$)	8.04±3.29	8.26±2.02	7.87±2.49	9.40±2.60	0.448
vBG_{end} ($mmol.L^{-1}$)	4.59±3.09†	3.69±1.19†	4.69±1.86†	4.98±2.18†	0.711
$vBLa_{pre\text{-}ex}$ ($mmol.L^{-1}$)	0.97±0.28	0.98±0.25	0.96±0.23	0.95±0.24	0.975
$vBLa_{end}$ ($mmol.L^{-1}$)	2.71±1.48	2.63±0.98†	2.61±1.23†	2.74±1.57	0.980
$v\beta\text{-}OHB_{pre\text{-}ex}$ ($mmol.L^{-1}$)	0.04±0.01	0.04±0.00	0.04±0.00	0.04±0.01	0.185
$v\beta\text{-}OHB_{end}$ ($mmol.L^{-1}$)	0.05±0.01	0.05±0.01	0.05±0.02	0.04±0.01	0.408
c) Counter-regulatory hormonal responses					
$EPI_{pre\text{-}ex}$ ($nmol.L^{-1}$)	0.03±0.03	0.06±0.10	0.06±0.12	0.05±0.05	0.773
EPI_{end} ($nmol.L^{-1}$)	0.09±0.11	0.09±0.12	0.05±0.78	0.08±0.11	0.887
$NE_{pre\text{-}ex}$ ($nmol.L^{-1}$)	0.65±0.85	0.63±1.01	0.79±0.90	1.01±1.09	0.605
NE_{end} ($nmol.L^{-1}$)	1.08±1.04	1.36±1.29	1.62±1.38	1.21±1.00	0.367
$Glucagon_{pre\text{-}ex}$ ($pg.mL^{-1}$)	14.9±34.8	21.1±33.5	50.5±83.4	15.6±26.8	0.191
$Glucagon_{end}$ ($pg.mL^{-1}$)	16.4±24.8	18.6±21.7	45.5±76.9	21.0±54.7	0.361

608 *Table 2. Physiologic, metabolic, and counter-regulatory responses to exercise. Data are reported as mean±SD (metabolic and counter-*
609 *regulatory hormonal data n=16. Cardiorespiratory data n=14). HR; Heart rate. bpm; beats per minute. $\dot{V}O_2$; Volume of inhaled oxygen.*
610 *$\dot{V}CO_2$; Volume of inhaled carbon dioxide. $l.min^{-1}$; liters per minute. $g.min^{-1}$; grams per minute. TEE; Total energy expenditure. Kcals;*
611 *kilocalories. vBLa; venous blood lactate. vβ-OHB; venous beta-hydroxybutyrate. End; end of exercise. Pre-exe; pre-exercise. †p≤0.05*
612 *compared with the corresponding pre-exercise value.*

613

614 Table 3. Prevalence of trial-day hypoglycemia

Prevalence of trial-day hypoglycemia					
Time	FF	FR	RF	RR	# hypos as % total (n=66)
Pre-Exercise (16:00-16:59)	1/1 (6%)	0/0 (0%)	1/1 (6%)	4/3 (19%)	6/5 (9% of total hypos) p=0.197
Exercise (17:00-17:45)	11/11 (69%)	14/14 (88%)*	8/8 (50%)	6/6 (38%)*	39/16 (59% of total hypos) p=0.021*
Post-Exercise (17:46-23:59)	6/6 (38%)	2/2 (13%)	2/2 (13%)	3/2 (13%)	13/12 (20% of total hypos) p=0.348
Nocturnal (00:00-05:59)	3/1 (6%)	0/0 (0%)	3/3 (19%)	1/1 (6%)	7/5 (11% of total hypos) p=0.558
Fasted a.m. (06:00-07:00)	0/0 (0%)	0/0 (0%)	1/1 (6%)	0/0 (0%)	1/1 (2% of total hypos) p=0.406
Overall (16:00-07:00)	21/14 (88%)	16/14 (88%)	15/9 (56%)	14/10 (63%)	Total = 66 in 16 people p=0.593

615 *Table 3. Prevalence of trial-day hypoglycemia (≤3.9 mmol.L^{-1}) with reference to distinct time phases. Data are reported as X/Y (Z%), where*
616 *X=number of hypoglycemic episodes, Y=number of people in which hypoglycemia occurred and Z=number of people in which*
617 *hypoglycemia occurred as a percentage of total number of participants (n=16). * p≤0.05 between the FR and RR trial (p=0.009) trial*
618

619 Table 4. Extent of trial-day hypoglycemia

Extent of trial-day hypoglycemia							
Time	Value	FF	FR	RF	RR	Overall	p value
Pre-Exercise	Mean	3.2±0.0	-	3.9±0.0	3.1±0.4	3.2±0.5	0.511
(16:00-16:59)	*Range*	*3.2-3.2*		*3.9-3.9*	*2.6-3.5*	*2.6-3.9*	
Exercise	Mean	3.3±0.4	3.3±0.3	3.4±0.3	3.2±0.6	3.3±0.4	0.659
(17:00-17:45)	*Range*	*2.5-3.9*	*3.0-3.8*	*2.9-3.8*	*2.2-3.8*	*2.2-3.9*	
Post-Exercise	Mean	3.4±0.3	3.5±0.1	3.0±1.1	3.3±0.3	3.3±0.4	0.527
(17:46-23:59)	*Range*	*3.2-3.9*	*3.4-3.6*	*2.2-3.8*	*2.9-3.4*	*2.2-3.9*	
Nocturnal	Mean	3.2±0.2	-	3.3±0.5	2.6±0.0	3.2±0.4	0.238
(00:00-05:59)	*Range*	*2.9-3.3*		*2.8-3.7*	*2.6-2.6*	*2.6-3.7*	
Fasted a.m.	Mean	-	-	2.7±0.0	-	2.7±0.0	-
(06:00-07:00	*Range*			*2.7-2.7*		*2.7-2.7*	
Overall	Mean	3.3±0.4	3.4±0.3	3.3±0.5	3.1±0.5	3.3±0.4	0.302
(16:00-07:00)	*Range*	*2.5-3.9*	*3.0-3.8*	*2.2-3.9*	*2.2-3.8*	*2.2-3.9*	

620 *Table 4. Extent of trial-day hypoglycemia (≤3.9 mmol.L^{-1}) with reference to the range in values in distinct time phases. Data are reported as*
621 *mean±SD (n=16).*

Figures

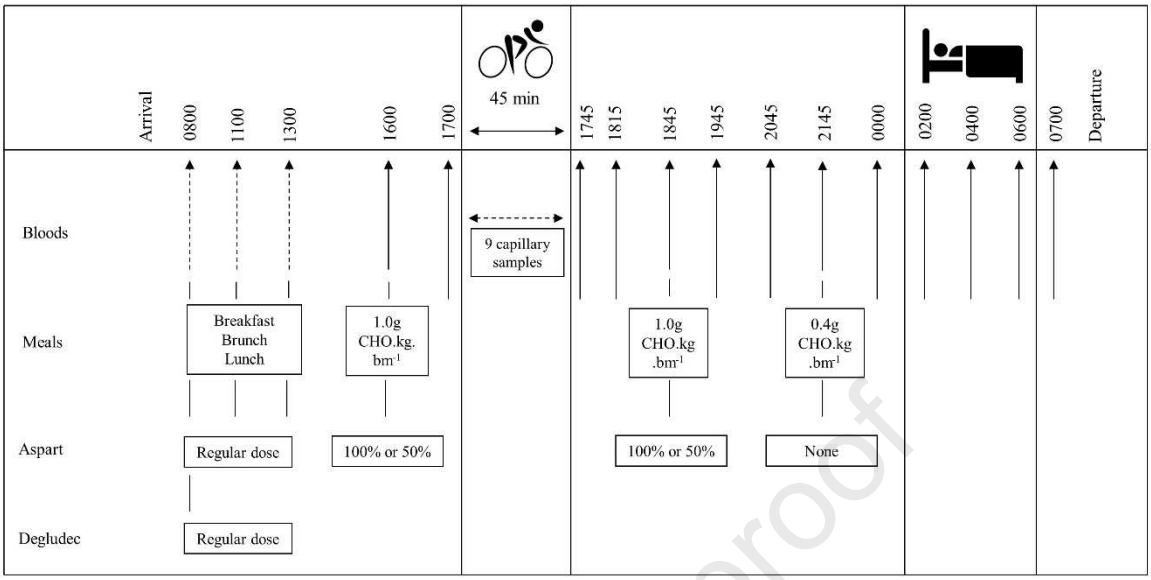
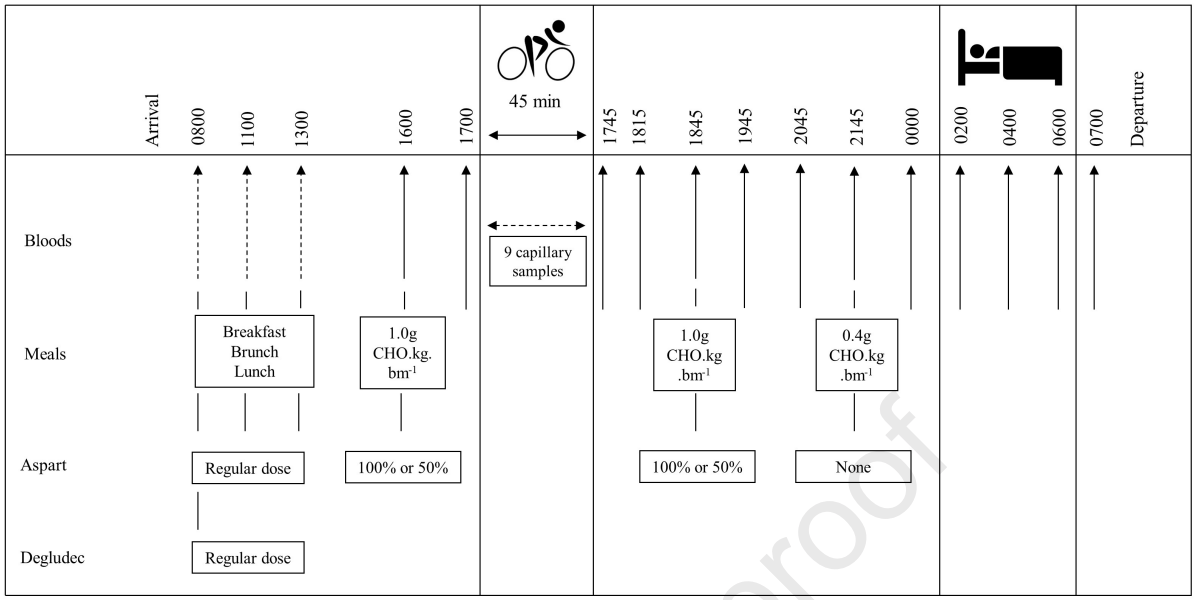


Figure 1. Experimental visit flow chart for each 23-hour in patient trial. Dashed black arrows indicate capillary blood glucose sampling. With the breakfast, brunch and lunch feedings, blood glucose was collected from the fingertip and assessed via the inbuilt glucometer (Freestyle libre, Abbott Laboratories Limited, UK). During exercise, capillary blood glucose sampling was collected from the right earlobe and analysed via the fully enzymatic-amperometric method ([FEA] Biosen C-Line, EKF Diagnostic, GER). Solid black lines represent venous sampling from which blood glucose was assessed via FEA. Solid black arrows with a gap indicate the provision of a meal and an accompanied insulin dose. Cycling icon indicates the 45-minute moderate intensity (@ 60% VO_{2max}) continuous exercise period. Bed icon indicates the night-time period during which venous blood glucose was sampled every two hours. 100%; Unaltered bolus dose. 50%; reduced bolus dose.



Highlights, research impact and clinical relevance

- Exercise-related hypoglycemia continues to represent a major clinical concern in the glycemic management of people with T1D.
- Though the integration of bolus insulin dose reductions around physical exercise is recognised as an integral component of an optimal glycemic management plan in people with T1D, less work has systemically investigated the extent and prevalence of venous blood confirmed hypoglycemia following specific peri-exercise bolus dose adjustments made on a background of ultra-long acting insulin degludec over an entire days' worth of in-patient monitoring under controlled, clinical laboratory environments.
- Using current generation insulin analogues, the results of this study provide up to date reaffirmation of the glycemic safety of integrating bolus insulin dose reductions around dynamic physical exercise in people with T1D treated with novel, ultra-long acting basal insulins. We detail the safe integration of modern basal-bolus insulins around exercise in people with T1D and demonstrate that failure to titrate bolus insulin appropriately in the hour leading into, or indeed after, exercise greatly increases the risk of hypoglycemia both during exercise and throughout the nocturnal hours subsequent to its performance.