Automated insulin delivery around exercise in adults with type 1 diabetes: A pilot randomised controlled study

Olivia M. McCarthy [1,2*], Merete B. Christensen [2], Kasper Birch Kristensen [2], Signe Schmidt [2], Ajenthen G. Ranjan [2,3], Stephen C. Bain [4], Richard M. Bracken [1], Kirsten Nørgaard [2,5]

Affiliations:

[1] Applied Sport, Technology, Exercise and Medicine Research Centre, Swansea University, UK.

[2] Copenhagen University Hospital – Steno Diabetes Center Copenhagen, Herlev, Denmark.

[3] Danish Diabetes Academy, Odense, Denmark.

[4] Medical School, Swansea University, UK.

[5] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

Shot running title: Automated insulin delivery and exercise.

***Author for correspondence**: Olivia.McCarthy@swansea.ac.uk.

Word count: 3750

 # Figures: 2

 # Tables: 3

Keywords: Exercise, type 1 diabetes, automated insulin delivery system, artificial pancreas.

Clinical Trials Register: NCT05134025

Abstract

Aim: To assess the effectiveness of an automated insulin delivery (AID) system around exercise in adults with type 1 diabetes (T1D).

Methods: This was a three-period, randomised, crossover trial involving ten adults with T1D (HbA_{1c}: 8.3±0.6% [67±6 mmol/mol]) using an AID system (MiniMed 780G, Medtronic USA). Participants performed 45 minutes of moderate intensity continuous exercise 90 minutes after consuming a carbohydrate-based meal using three strategies: (i) a 100% dose of bolus insulin with exercise announcement immediately at exercise onset 'spontaneous exercise' (SE) or a 25% reduced dose of bolus insulin with exercise announcement either (ii) 90 minutes (AE90) or (iii) 45 minutes (AE45) before exercise. Venous-derived plasma glucose (PG) taken in 5- and 15-minute intervals over a 3-hour collection period was stratified into the percentage of time spent below (TBR [<3.9 mmol/L]) within (TIR [3.9-10 mmol/L]) and above (TAR [>10 mmol/L]) target range. In instances of hypoglycaemia, PG data were carried forward for the remainder of the visit.

Results: Overall TBR was greatest during SE (SE: 22.9±22.2, AE90: 1.1±1.9, AE45: 7.8±10.3%, p=0.029). Hypoglycaemia during exercise occurred in four participants in SE but one in both AE90 and AE45 (χ^2 [2] = 3.600, p=0.165). In the one-hour post-exercise period, AE90 was associated with higher TIR (SE: 43.8±49.6, AE90: 97.9±5.9, AE45: 66.7±34.5%, p=0.033), lower TBR (SE: 56.3±49.6, AE90: 2.1±5.9, AE45: 29.2±36.5%, p=0.041) with the greatest source of discrepancy observed relative to SE.

Conclusion: In adults using an AID system and undertaking post-prandial exercise, a strategy involving both bolus insulin dose reduction and exercise announcement 90 minutes before commencing the activity may be most effective in minimising dysglycaemia.

Introduction

Recent progress in the field of diabetes technology has led to the development of automated insulin delivery (AID) systems for the glycaemic management of people with type 1 diabetes (T1D). These devices combine (i) insulin pump infusion, (ii) continuous glucose monitoring and (iii) a dosing algorithm that dynamically controls the insulin infusion rate in accordance with ambient glucose concentrations.

Research has demonstrated superiority in clinical glycaemic outcomes when using AID systems compared to conventional insulin therapy in various interventional and real-world studies (1–5). However, little is known about their effectiveness when challenged with intense metabolic stressors such as physical exercise (6). Indeed, data supporting the ability of these technologies to manage glycaemia during exercise is not a pre-requisite for market approval, and clinical guidance is primarily based on experience with first generation AID technologies (7).

The heightened bioenergetic demands of exercise induce large increases in intramuscular glucose disposal (8). In the context of T1D, the synergistic glucose lowering effects of exercise and active on-board exogenous insulin (which is not liable to endogenous feedback control) accentuate the risk of exercise-related hypoglycaemia (9–11). This is particularly evident when exercise is performed post-prandially (10), at a time when circulating insulin levels are raised due to the pharmacokinetics of the concomitant bolus insulin dose (12), leaving little to no room for spontaneity. Worryingly, many of the symptomatic traits of hypoglycaemia are analogous to the physiological responses induced by exercise (i.e., elevated heart rate, sweating, dizziness). Hence, differentiating between these two altered states of physiology is difficult, and in situations where endogenous glucose counter-regulation is compromised, the

sensitivity and safety of exogenous therapy aids to prevent and/correct against hypoglycaemia is magnified.

Existing insulin pump-specific glucose management strategies that attempt to mitigate the risk of hypoglycaemia during exercise i.e., heavy basal and bolus insulin dose reductions, often come at the cost of pre-exercise hyperglycaemia. However, elevated glucose levels at exercise onset are associated with a greater decline in glucose during exercise, typifying a 'catch 22' situation in which dysglycaemia often prevails (13). Thus, exercise unfortunately continues to represent a challenge for many, with fears of hypoglycaemia and uncertainty in how to modulate insulin reported as major barriers to frequent engagement (14). With the commercial introduction of AID systems with new technological features, we are left with important questions of how to optimise their use around exercise to minimise dysglycaemia and maximise safety.

As such, we sought to compare the effectiveness of three different insulin delivery strategies around exercise in adults with T1D treated with one of the newest AID systems (the MiniMed^{TM} 780G).

Methods and Materials

Study design and ethical approval

This was a three-period, randomised, cross-over, in-patient study involving ten adults with T1D. The study was carried out in accordance with the Helsinki Declaration, EU Directive on good clinical practice and ICH-GCP guidelines after approval by the Regional Scientific Ethical Committee and the Capital Region's Videnscenter for Dataanmeldelser. All participants were provided with a full written and verbal description of the study and gave informed consent prior to taking part. The study was registered as a clinical trial (Clinical Trials Register; NCT05134025)

Screening procedures

Participants in the present study were recruited from a separate but simultaneously conducted and ongoing randomised, crossover trial during which the following inclusion and exclusion criteria applied: aged 18-75 years; T1D ≥2 years; HbA_{1c}; 7.5 – 7.9% (58 - 63 mmol/mol) (maximum 40% of participants) *or* ≥8% (64 mmol/mol [minimum 60% of participants]); use of insulin pump treatment for ≥12 months; use of a continuous, or an intermittently scanned, glucose monitoring system for ≥6 months; use of insulin Aspart (Novo Nordisk A/S, Bagsværd, Denmark) for ≥14 weeks. Main exclusion criteria were: females who were pregnant, breast-feeding, or planning to become pregnant during the course of the study period; use of glucose-lowering medicines (other than insulin), corticosteroids and/or other drugs affecting glucose metabolism during the study period or within 30 days prior to study start; daily use of acetaminophen; alcohol or drug abuse; severe cardiac disease or retinopathy contraindicating HbA_{1c} <7% (53 mmol/mol); other concomitant medical or psychological condition that,

according to the investigator's assessment, classified the person unsuitable for study participation.

After confirmation of suitability for the main study, participants were asked whether they would also like partake in the present exercise sub-study. Interested participants then attended the laboratory and undertook an exercise screening visit during which they performed a graded exercise test to volitional exhaustion on a workload-controlled cycle ergometer (Corival, Lode©, Groningen, The Netherlands). The results were used to determine the individualised workload (watts) required to complete the moderate intensity (~60% $\dot{V}O_{2peak}$) exercise bout incorporated in each of the exercise trial experimental visits. The randomisation schedule for the exercise trials was conducted via sealedenvelope.com by a person not otherwise involved in the study.

The automatic insulin delivery system

Participants were treated with the MiniMed^{TM} 780G system (Medtronic, Northridge, Ca, USA) and had been using the system for at least 4 weeks prior to study entry (average duration of pump use: 11±5 weeks). The technology includes an advanced hybrid closed loop algorithm with automatic basal insulin adjustments made every 5 minutes based on continuous glucose monitoring (CGM) input, adjustable glucose targets of: 100 (5.5), 110 (6.1), and 120 (6.7) mg/dL (mmol/L), and an automatic correction bolus delivery every 5 minutes. User-initiated meal announcements are required for optimal glycaemic results. A temporary glucose target of 150 (8.3) mg/dL (mmol/L) can be set in case of for example exercise, and by doing this the auto-correction feature will be suspended and the automatic basal insulin delivery will aim for the temporary target glucose. Participants used Guardian 3 link or Guardian 4 transmitters

connected to the MiniMed^{TM} 780G system. Participants were advised to change their sensor 24 hours before the trial visit.

Preparatory procedures prior to experimental trail days

Participants were asked to avoid caffeine for 12 hours as well as alcohol and atypical and/or vigorous physical exercise for 24 hours prior to experimental trial days. Participants were also encouraged to be vigilant in the avoidance of severe hypoglycaemia (defined as a capillary fingertip blood glucose value of <3.0 mmol/L) in the 24 hours before their arrival. Participants were instructed to avoid taking bolus insulin 4 hours prior to their scheduled arrival time.

Experimental trial day procedures

In a randomised, cross-over fashion, participants attended the laboratory on three separate occasions and performed a 45-minute bout of exercise 90 minutes after consuming a carbohydrate-based meal under three insulin strategies: (i) 'Spontaneous exercise' a 100% dose of bolus insulin with exercise announcement (i.e., setting a temporary target glucose 150 mg/dL [8.3 mmol/L]) immediately at exercise onset (SE), (ii) a 25% reduced dose of bolus insulin with exercise announcement 90 minutes prior to exercise commencement (AE90) and (iii) a 25% reduced dose of bolus insulin with exercise announcement 45 minutes prior to exercise commencement (AE45) (Figure 1).

Participants arrived at the research centre following an overnight fast (≥10 hours) from food with water *ad libitum*. Following successful completion of trial day inclusion criteria, participants adopted a bed-rest position and were fitted with an indwelling canula ahead of the beginning of the interventional period (t=-90 min). Following the first sample draw (baseline), participants consumed a standardised low-glycaemic index, carbohydrate-based drink

([Isomaltulose, BENEO GmbH, Mannhein, Germany] equating to 0.75 grams of carbohydrates per kg body mass) with one of three insulin dosing strategies according to randomisation. In arms (ii) and (iii), meal-time bolus insulin dose reductions were selected in accordance with exercise consensus documents i.e., a 25-75% bolus insulin dose reduction ahead of exercise within 3 hours of ingesting a meal (7) (10).

15 minutes before the anticipated exercise start time, plasma glucose (PG) concentrations were checked in accordance with safe starting concentrations (10). If PG was <5.5 mmol/L, participants were given 15 grams of oral glucose (Dextro Energy GmbH & Co. KG, Krefeld, Germany) as a safety precaution. Only on two occasions (in the same individual) was this approach necessary. If PG was ≥15.0 mmol/L and blood ketones levels were <0.6 mmol/L, exercise went ahead but only at the discretion of the participant with frequent monitoring for ketone body formation. If ketone levels were ≥1.5 mmol/L, the visit was cancelled and rescheduled. No such issues were encountered.

After 90 minutes of bed rest (t=0 min), participants commenced a bout of moderate intensity (~60% $V\dot{O}_{2peak}$) exercise on a workload-controlled cycle ergometer (Corival, Lode©, Groningen, The Netherlands). The exercise session lasted for 45 minutes (t=+45 min), or until hypoglycaemia (PG <3.9 mmol/L). In the case of the latter, exercise was stopped immediately, and a standardised hypoglycaemia treatment protocol was initiated i.e., provided 15 grams of oral carbohydrates (Dextro Energy GmbH & Co. KG, Krefeld, Germany, waited 15 minutes, repeated if necessary. With the exception of continued exercise, the experimental schedule continued as normal, but participants readopted their pre-exercise bed-resting position.

During exercise, breath by breath data were measured using a pulmonary gas analyser (Vyntus^{TM} ONE, Vyaire medical, Illinois, USA) calibrated using certified gases (Gas 1:

Ambient Air, Gas 2: 15% O_2, 5% CO_2) with data displayed for standardised temperature and pressure for dry air. Integrated heart rate data were recorded continuously via chest belt telemetry (Polar Electro, Finland). Raw cardiopulmonary data were exported in 5-second intervals (SentrySuite^{TM} software, Vyaire medical, Illinois, USA) and subsequently averaged in 30-second segments for statistical processing.

Following exercise, participants remained within the laboratory for a further 60 minutes of observational bed rest. After the final sample draw which concluded the experimental period (t=+105 min), participants were provided with a standardised carbohydrate-based meal (equating to 0.75 grams of carbohydrates per kg body mass) to consume within the laboratory. Participants were free to administer their usual, individualised bolus insulin dose but were advised to take a 25% dose reduction if plasma glucose was <5.5 mmol/L for safety purposes. Thereafter, participants were discharged from the laboratory and maintained their habitual lifestyle practices. Sensor glucose (SG) data were collected from laboratory departure until the following morning (~20-hour home period).

Blood sampling procedures

Venous-derived whole blood samples were obtained in 15-minute intervals from -90 to -15 min, 5-minute intervals from -15 to +60 minutes and 15-minute intervals from +60 to +105 minutes (Please refer to figure 1 for a pictorial overview of the timeline on experimental visits). At each timepoint, 300 µL of whole blood was dispensed into individual microtubes and immediately centrifuged at 3000 rpm for 30 seconds. The resultant supernatant (plasma) was processed via the YSI 2500 (YSI Inc. Ohio, USA) to determine point concentrations of PG.

Statistics and computation of glycaemic parameters

As this was the first study of its kind, we had no prior data on the topic to inform a power calculation, thus an n=10 enrolled individuals was chosen for feasibility. Data were collected from Sep 2021 to Aug 2022. Unless otherwise stated, data are presented as mean±SD. Time spent within a specific glucose zone was calculated as the number of PG readings that fell within that zone divided by the total number of glucose readings from the participant represented as a percentage i.e., time below range ([TBR] <3.9 mmol/L [<70 mg/dL]), time in range ([TIR] 3.9–10 mmol/L [70-180 mg/dL]), time above range ([TAR] >10 mmol/L [>180 mg/dL]) (15). Evaluated glycaemic variability measures included standard deviation (SD [mmol/L]) and coefficient of variation (CV [%]). To account for the confounding effect of rescue carbohydrate provision on subsequent PG concentrations, the first point at which a hypoglycaemic event occurred was carried forward for the remainder of the experimental trial day. Differences in PG concentrations between experimental arms were assessed via repeated measured ANOVA with Bonferroni adjustment used for pairwise comparisons in post hoc analyses. Cochran's Q test was used to identify differences in the prevalence of hypoglycaemia as a categorical variable between arms. The depth, and time to onset, of hypoglycaemia was assessed via one-way ANOVA. Alpha was set at 0.05 and significance was accepted when p values were ≤ alpha. All statistical analyses and descriptive statistics were performed via SPSS (IBM®, SPSS Inc. Chicago, USA).

Results

Participant characteristics

Data from ten adults with T1D (6 females) were included in this study. Baseline characteristics of the included cohort are displayed in Table 1.

Participants had a high HbA1c (8.3% [67 mmol/mol]) at inclusion into the main study. To ensure glycaemic stability before entry into the exercise trial, participants were provided with adequate familiarisation time (79±34 days) after transitioning from their usual pump to the AID system.

The mean duration of study participation was 41±19 days with an equal distribution in the number of days between the first and second visits as the second and third (i.e., the final) visits (25±21 versus. 16±14 days, respectively, p=0.399).

There was no change in body weight throughout trial participation (First visit: 83.1±2.5 kg, Second visit: 83.7±2.9 kg, Third visit: 83.3±3.0 kg, p=0.440).

Plasma glucose responses during the in-clinic period

Pre-exercise period

Fasting PG levels were comparable between arms (SE: 7.0±2.4, AE90: 7.2±2.2, AE45: 7.5±2.3 mmol/L, p=0.777). The individualised dose of meal-time bolus insulin differed between SE and both AE90 and AE45, but not between the latter two (SE: 7.0±2.4*, AE90: 5.5±2.5, AE45: 5.3±2.8 units, p<0.001, * p<0.01 between SE and AE90 & AE45 but not AE90 and AE45, [p=1.00]). The meal-induced rise in PG over the 90-minute pre-exercise period was comparable

between conditions (SE: +1.2±2.6, AE90: +2.2±2.3, AE45: +1.4±3.2 mmol/L, p=0.536) with no observable differences in time spent in each glycaemic range (Table 2).

Exercise period

PG concentrations immediately at exercise onset were similar between arms (SE: 8.2±2.6, AE90: 9.0±2.6, AE45: 9.2±2.8 mmol/L, p=0.666). Though there was a tendency for a shorter time spent cycling in SE, exercise duration was similar between arms (SE: 36.9±3.8, AE90: 45.0±0.0, AE45: 45.0±0.0 mmol/L, p=0.068) as was the relative intensity at which participants cycled on each occasion (SE: 56±2.5, AE90: 55±5.0, AE45: 58±12 % $\dot{V}O_{2peak}$, p=0.903). There were no differences in the change in PG over exercise when expressed in magnitude (SE: -3.5±1.7, AE90: -3.4±2.6, AE45: -3.9±2.6 mmol/L, p=0.872) or rate of decline (SE: -0.1±0.0, AE90: -0.1±0.1, AE45: -0.1±0.1 mmol/L/min, p=0.653).

Hypoglycaemia during cycling occurred in four participants in SE and one in both AE90 and AE45 (χ^2 [2] = 3.600, p=0.165) resulting in considerably more TBR in the former (SE: 21.3±25.9, AE90: 1.3±3.5, AE45: 1.3±3.5%, p=0.031, table 2). In those who experienced exercise-induced hypoglycaemia, the event tended to be earlier (SE: 28.8±9.5, AE90: 0.0±0.00, AE45: 45.0±0.0 minutes, p=0.090) and deeper in depth (SE: 3.42±0.22, AE90: 3.85±0.00, AE45: 3.77±0.00 mmol/L, p=0.084) in SE, but did not reach statistical significance. The singular hypoglycaemic events recorded in AE90 and AE45 occurred immediately at the start (minute 0) and end (minute 45) of cycling, respectively. Hence, despite both events being registered as hypoglycaemia within the exercise period, the full 45 minutes of dynamic exercise was performed. In the person who briefly registered hypoglycaemic (PG = 3.85 mmol/L) at exercise onset in AE90, 15 grams of oral carbohydrates had been given 15 minutes before

starting to cycle and the rechecked value was euglycaemic, thus exercise continued in accordance with the safety plan.

Though no main effect was detected (p=0.136), pairwise comparisons revealed that PG concentrations at the end of the designated exercise period (t=+45min) were notably lower in SE compared to AE90 (SE: 4.5±1.1, AE90: 5.6±0.8, AE45: 5.3±1.4 mmol/L, p=0.049, [figure 2]).

Post-exercise period

Mean PG concentrations were lowest in SE at each timepoint during the post-exercise period, with the source of statistical significance found relative to the AE90 arm (figure 2). In the one-hour post-exercise period, AE90 was associated with higher TIR (SE: 43.8±49.6, AE90: 97.9±5.9, AE45: 66.7±34.5%, p=0.033) and lower TBR (SE: 56.3±49.6, AE90: 2.1±5.9, AE45: 29.2±36.5%, p=0.041) with the greatest discrepancy observed against SE (table 2). The prevalence of hypoglycaemia during the acute post-exercise period was proportionate between arms (SE: n=1, AE90: n=1, AE45: n=3, (χ^2 [2], = 2.000 , p=0.368) as was the amount of treatment carbohydrates required to restore euglycaemia (SE: 5±11, AE90: 0±0, AE45: 7±11 mmol/L, p=0.157).

Overall period

Overall TBR was highest during SE (SE: 22.9±22.2, AE90: 1.1±1.9, AE45: 7.8±10.3%, p=0.029) with significantly higher CV in PG relative to AE90 (SE: 32.9±5.2, AE90: 25.6±6.9, AE45: 29.2±9.8%, p=0.032). In total, five people experienced hypoglycaemia in SE, two in AE90 and four in AE45 (χ^2 [2], = 2.000, p=0.368). Both the time it took to reach hypoglycaemia from baseline (SE: 128.0±22.2, AE90: 142.5±74.2, AE45: 161.3±18.9 minutes, p=0.365) as

well as the mean PG concentration when it occurred (SE: 3.35±0.33, AE90: 3.87±0.02, AE45: 3.36±0.59 mmol/L, p=0.218) were similar between conditions.

Sensor glucose responses during the home period

Except from a higher maximal sensor glucose in SE, no significant differences were observed in any other CGM-derived glucose metrics between experimental arms during the 20-hour home period including the designated nocturnal period (table 3).

Discussion

This study assessed the performance of an advanced automated insulin delivery system around moderate intensity continuous exercise in adults with type 1 diabetes. Our findings demonstrated that when using one of the newest AID systems, post-prandially performed exercise can be undertaken with impressive e glycaemic stability, but *only* when prudent pump preparation is in place. Failure to do so notably increases the risk of hypoglycaemia both during and acutely after exercise.

The amount of time spent in hypoglycaemia was consistently and considerably higher in the spontaneous exercise arm during: (i) The exercise period, (ii) the post-exercise period, (iii) the combined exercise and post-exercise period, and (iv) the overall period. Nearly half (40%) of participants stopped cycling prematurely due to exercise-induced hypoglycaemia when exercise was initiated spontaneously, whilst this was completely avoided in the two strategies involving some form of forward thinking i.e., reducing bolus insulin by 25% and entering exercise mode well in advance of commencing cycling.

In both the spontaneous exercise arm and the strategy in which exercise announcement was set 45 minutes before cycling, there were episodes of level 2 (<3.0 mmol/L) hypoglycaemia. Yet, this threshold was never breached in the arm in which exercise was announced 1.5 hours in advance (χ^2 [2] = 2.00, p=0.368). Indeed, in the latter strategy the lowest registered hypoglycaemia event was considered ‘mild’ (3.85 mmol/L), perhaps a point with clear clinical if not ‘statistical’ significance. Despite the implementation of a standardised carbohydrate rescue protocol (provide 15 grams of glucose, wait 15 minutes, repeat if necessary) throughout the study, it was insufficient to counterbalance the elevated rate of decline in PG in the two arms where the time frame of exercise announcement was curtailed. The physiological and

psychological implications of hypoglycaemia rationalise the fears associated with its occurrence around exercise in many people with T1D (14). With this in mind, the importance of prudent preparation in insulin therapy management well in advance of post-prandially performed exercise is underscored. A caveat is that this study tested one AID system in response to a standardised exercise stimulus in a relatively heterogenous cohort with little scope to discern possible sex-specific differences and/or influences e.g., the menstrual cycle. Hence, whether these observations apply to other AID systems, exercise modalities, and/ cohorts remains to be established.

Irrespective of hypoglycaemia *per se*, the mean, minimum and maximum plasma glucose concentrations acutely after cycling were all higher in the strategy where bolus insulin was reduced, and exercise was declared most in advance (AE90). These data emphasise the necessity of pre-planned insulin therapy management for the better preservation of glucose at a time when intramuscular fuel requirements persist (16) and muscle tissue insulin sensitivity remains enhanced (17).

On each occasion, the intensity at which participants cycled (~60% $\dot{V}O_{2peak}$) primarily draws on oxidative metabolism to support fuel provision, where the insulin: glucagon ratio is the main driver for endogenous glucose production. This may explain the clear weightiness in the distribution of hypoglycaemia in the spontaneous exercise arm, where the ratio was likely disproportionately skewed to favor insulin due to the pharmacokinetics of the preceding bolus dose, which was quantifiably higher (~+1.6 units). Typically, catecholamine responses are relatively small until exercise intensity exceeds >60% $\dot{V}O_{2max}$ or lasts >2 hours (18). Hence, their contribution to endogenous glucose production was likely modest in our cycling model and insufficient in magnitude to counteract the synergistic glucose lowering effects of exercising muscle tissue and active on-board exogenous insulin.

We have shown that exercising whilst in a post-prandial state, which constitutes a particularly problematic period for those with T1D, can be done with quite remarkable glycaemic stability (~90% TIR during the exercise and post-exercise period in AE90) using AID therapy providing adequate preparation is in place. Our results are consistent to work by Paldus et al., who noted 91% TIR during 40-minutes of moderate intensity cycle ergometry when using the previous generation, MiniMed 670G system (19). However, their design involved exercise in the post-absorptive state (four hours after consuming a mixed meal with regular bolus) with exercise declaration two-hours prior to commencing cycling. The current study provides not only an updated account of the newest generation of the device, but also assurance as to its use during post-prandial exercise when consensus guidelines are adhered to. However, some degree of prudent preparation and patient-driven due diligence is still needed. Failure to 'think in advance' notably increases the risk of acute hypoglycaemia around exercise with a clear trend for lower glucose concentrations acutely after the activity. Thus, spontaneity to engage in unplanned or unforeseen activities remains a problem, even for the newest generation of automated insulin pumps.

Of particular interest was the similarity in time spent above range ([TAR] >10 mmol/L) between arms throughout trial days. Hence, the AE90 strategy was not only most effective in reducing the risk of hypoglycaemia during and after exercise, but also managed to do so without the concomitant cost of *hyper*glycaemia. In all arms of our study, the pre-exercise period was very tightly controlled, with an appreciable amount of time spent with plasma glucose in range (≥ 65%) during the 1.5-hour post-prandial phase. This resulted in most people (≥70% of participants) starting exercise with euglycaemic concentrations (mean: ~8.8 mmol/L). This falls neatly in alignment with consensus recommendations for: a) post-prandial glycaemic targets (i.e., <10.0 mmol/L in the 1-2 hours after a meal (20)) and b) safe starting

glucose levels for exercise in T1D (i.e., between 7-10 mmol/L). Overt and prolonged hyperglycaemia was a noted limitation of a recent study using a closed-loop system based on a predictive model (13), where implementation of a strategy exercise announcement (resulting in an increase in target sensor glucose levels from 6.0 to 9.0 mmol/L) and a 33% reduction in bolus insulin 90-minutes prior to a 60 minute bout of moderate intensity continuous exercise led to elevated starting glucose levels (12.8 mmol/L) and proportionately more TAR during cycling than observed in our study (56% *vs.* our data: 14%).

Previous reports have shown that pre-exercise blood glucose has a major influence on both carbohydrate requirements (21) and the degree of decline in glycaemia (22) during moderate intensity exercise. Clearly, attaining good glycaemic levels in the lead up to exercise remains a key factor in maintaining it thereafter. Hence, the automation and individualisation features of the new AID pumps confer great benefit in reducing the potential for pronounced glycaemic excursions whilst simultaneously minimising the burdens of self-management.

Our data showed no statistical differences in any sensor glucose derived glycaemic parameter during the 20-hour home phase which spanned the nocturnal period. Though mostly apparent acutely during the activity, the heightened risk of hypoglycaemia induced by exercise often endures for several hours after its cessation (16). Due to the difficulties and/or inconveniences of frequent self-monitoring during sleep, there is an increased reliance on the effectiveness of technological aids to support optimal glycaemia. Hence, the proportionately low TBR and commendable TIR during the out-patient phase provides encouragement as to the sensitivity of these devices at times where the legacy effects of exercise-related dysglycaemia may persist.

Study strengths limitations and future research directives

This study assessed the performance effectiveness of an advanced AID system in adults with T1D around sustained, moderate intensity cycling. Although the current data pertains only to moderate intensity continuous exercise, these data may help provide a foundational basis from which patients and their health care providers can formulate prudent exercise management strategies aimed at maximising safety and minimising glycaemic disturbance. Though an inherent limitation of this pilot study is the small sample size with homogeneity in diabetes and physical fitness characteristics, the novelty of this work provides new information with important clinical relevance. Expansion of this work to a larger, more heterogenous population with investigation of possible sex differences and/or influences should be considered in future research. There remains a need to develop strategies that support the performance of spontaneous exercise and promising candidates include better algorithms, shorter acting insulins and/or adding glucose elevating hormones to the system.

Conclusion

Our findings demonstrate that when using one of the newest AID systems, exercising whilst in a post-prandial state can be done with glycaemic stability. However, prudent preparation and adherence to consensus guidelines for optimal exercise management are necessary. Failure to pre-plan so notably increases the risk of hypoglycaemia both during and acutely after exercise. Hence, spontaneity to engage in unplanned activities remains a limiting factor for people living with T1D. As we continue to move forward with technological developments in diabetes care, it is imperative that we remember to consider exercise in their evolution.

Acknowledgements

The authors would like to thank the participants for their willingness to contribute and commit to the study protocol. We would also like to thank the Diabetesforeningen (Denmark) for their financial contributions to the project as well as BENEO GmbH (Mannhein, Germany) for supplying the pre-exercise carbohydrate source used in this research (Palatinose^{TM}). Finally, we would like to thank the study biomedical scientist, Sandra Tawfik, for her help in performing trial-day activities.

Conflicts of interest and source of funding

The ongoing randomised controlled trial on the MiniMed 780G from which participants in the current exercise study were recruited, was an investigator-initiated study funded by Medtronic diabetes, USA. SS is an employee of Novo Nordisk A/S as of May 1st, 2022. SS has received speaker's fee from Novo Nordisk. KN received funding to her institution for participating in advisory boards from Medtronic, Novo Nordisk, and Convatec and for lecturing from Sanofi, Novo Nordisk, Medtronic, and Dexcom. Her institution received funding for studies she performed from Zealand Pharma, RSP Systems, Novo Nordisk, Medtronic, and Dexcom. The remaining authors report having no relevant conflicts of interest to disclose.

Author contributions

OMM, MBC, SS, RMB, SCB and KN contributed to the conception and design of the study. OMM, KBK, MBC, SS, KN, and AGR contributed to the acquisition of data. OMM was responsible for data analyses. All authors were responsible for data interpretation. OMM wrote the original draft of the manuscript. All authors contributed to revising the article. All authors provided final approval of the version to be published.

References

1. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med [Internet]. 2019 Oct 31 [cited 2022 Oct 31];381(18):1707–17. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1907863

2. Silva J Da, Lepore G, Battelino T, Arrieta A, Castañeda J, Grossman B, et al. Real-World Performance of the MiniMed™ 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Ther [Internet]. 2022 Feb 1 [cited 2022 Oct 31];24(2):113–9. Available from: https://pubmed.ncbi.nlm.nih.gov/34524003/

3. Breton MD, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. Diabetes Technol Ther [Internet]. 2021 Sep 1 [cited 2022 Oct 31];23(9):601–8. Available from: https://www.liebertpub.com/doi/10.1089/dia.2021.0097

4. Pintaudi B, Gironi I, Nicosia R, Meneghini E, Disoteo O, Mion E, et al. Minimed Medtronic 780G optimizes glucose control in patients with type 1 diabetes mellitus. Nutr Metab Cardiovasc Dis [Internet]. 2022 Jul 1 [cited 2022 Oct 15];32(7):1719–24. Available from: https://pubmed.ncbi.nlm.nih.gov/35599092/

5. Choudhary P, Kolassa R, Keuthage W, Kroeger J, Thivolet C, Evans M, et al. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. Lancet Diabetes Endocrinol [Internet]. 2022 Oct 1 [cited 2022 Oct 15];10(10):720–31. Available from: http://www.thelancet.com/article/S2213858722002121/fulltext

6. Sherr JL, Heinemann L, Fleming GA, Bergenstal RM, Bruttomesso D, Hanaire H, et al. Automated Insulin Delivery: Benefits, Challenges, and Recommendations. A Consensus Report of the Joint Diabetes Technology Working Group of the European Association for the Study of Diabetes and the American Diabetes Association. Diabetes Care [Internet]. 2022 Oct 6 [cited 2022 Oct 20]; Available from: https://diabetesjournals.org/care/article/doi/10.2337/dci22-0018/147674/Automated-Insulin-Delivery-Benefits-Challenges-and

7. Phillip M, Nimri R, Bergenstal RM, Barnard-Kelly K, Danne T, Hovorka R, et al. Consensus Recommendations for the Use of Automated Insulin Delivery Technologies in Clinical Practice. Endocr Rev [Internet]. 2022 Sep 6 [cited 2023 Jan 4]; Available from: https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818

8. Rose AJ, Richter EA. Skeletal muscle glucose uptake during exercise: How is it regulated? Physiology [Internet]. 2005 [cited 2022 Oct 14];(4):260–70. Available from: https://journals.physiology.org/doi/10.1152/physiol.00012.2005

9. McCarthy O, Deere R, Churm R, Dunseath GJ, Jones C, Eckstein ML, et al. Extent and prevalence of post-exercise and nocturnal hypoglycemia following peri-exercise bolus insulin adjustments in individuals with type 1 diabetes. Nutr Metab Cardiovasc Dis. 2020 Aug;

10. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;8587(17):1–14.

11. García-García F, Kumareswaran K, Hovorka R, Hernando ME. Quantifying the Acute Changes in Glucose with Exercise in Type 1 Diabetes: A Systematic Review and Meta-Analysis. Sport Med 2015 454 [Internet]. 2015 Jan 24 [cited 2022 Oct 14];45(4):587–99. Available from: https://link.springer.com/article/10.1007/s40279-015-0302-2

12. Heise T, Hövelmann U, Brøndsted L, Adrian CL, Nosek L, Haahr H. Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart. Diabetes Obes Metab [Internet]. 2015 Jul 1 [cited 2022 Oct 15];17(7):682. Available from: /pmc/articles/PMC5054830/

13. Tagougui S, Taleb N, Legault L, Suppère C, Messier V, Boukabous I, et al. A single-blind, randomised, crossover study to reduce hypoglycaemia risk during postprandial exercise with closed-loop insulin delivery in adults with type 1 diabetes: announced (with or without bolus reduction) vs unannounced exercise strategies. Diabetologia [Internet]. 2020 Nov 1 [cited 2022 Jan 16];63(11):2282–91. Available from: https://pubmed.ncbi.nlm.nih.gov/32740723/

14. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to Physical Activity Among Patients With Type 1 Diabetes. Diabetes Care [Internet]. 2008 Nov [cited 2022 Jan 16];31(11):2108. Available from: /pmc/articles/PMC2571055/

15. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019 Aug;42(8):1593–603.

16. McMahon SK, Ferreira LD, Ratnam N, Davey RJ, Youngs LM, Davis EA, et al. Glucose

requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. J Clin Endocrinol Metab [Internet]. 2007 [cited 2022 Oct 15];92(3):963–8. Available from: https://pubmed.ncbi.nlm.nih.gov/17118993/

17. Holloszy JO. Exercise-induced increase in muscle insulin sensitivity. https://doi.org/101152/japplphysiol001232005 [Internet]. 2005 Jul [cited 2022 Oct 15];99(1):338–43. Available from: https://journals.physiology.org/doi/10.1152/japplphysiol.00123.2005

18. Galbo H. Hormonal and metabolic adaptation to exercise. New York: Thieme-Stratton Inc.; 1983.

19. Paldus B, Lee MH, Morrison D, Zaharieva DP, Jones H, Obeyesekere V, et al. First Randomized Controlled Trial of Hybrid Closed Loop Versus Multiple Daily Injections or Insulin Pump Using Self-Monitoring of Blood Glucose in Free-Living Adults with Type 1 Diabetes Undertaking Exercise. J Diabetes Technol [Internet]. 2021;15(6):1399–401. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8655292/

20. Holt RIG, Devries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care [Internet]. 2021 Nov 1 [cited 2022 Sep 29];44(11):2589–625. Available from: https://diabetesjournals.org/care/article/44/11/2589/138492/The-Management-of-Type-1-Diabetes-in-Adults-A

21. Moser O, Eckstein ML, Mueller A, Birnbaumer P, Aberer F, Koehler G, et al. Pre-

exercise blood glucose levels determine the amount of orally administered carbohydrates during physical exercise in individuals with type 1 diabetes—a randomized cross-over trial. Nutrients. 2019 Jun;11(6).

22. Riddell MC, Zaharieva DP, Tansey M, Tsalikian E, Admon G, Li Z, et al. Individual glucose responses to prolonged moderate intensity aerobic exercise in adolescents with type 1 diabetes: The higher they start, the harder they fall. Pediatr Diabetes. 2018 Dec;20(1):pedi.12799.

Tables

Table 1. Baseline characteristics of study participants.

Characteristic	Mean±SD	Range (min – max)
Age (years)	55±12	35 (37 – 72)
BMI ($kg.m^{-2}$)	27.8±4.5	12.8 (21.0 – 33.8)
HbA_{1c} (mmol/mol)	67±6	17 (59 – 76)
HbA_{1c} (%)	8.3±0.6	1.6 (7.5 – 9.1)
Diabetes duration (years)	33±12	38 (13 – 51)
Age of diabetes onset (years)	22±8	26 (19 – 45)
Total daily insulin dose (U/kg)	0.6±0.2	0.5 (0.4 – 0.9)
Average daily CHO intake (g/kg)	1.9±0.9	2.8 (0.7 – 3.5)
Average 14-day SG (mmol/L)	8.3±0.6	2.0 (7.2 – 9.2)
Average 14-day SG CV (%)	34.8±4.4	15.7 (26.0 – 41.7)
Average 14-day SG TBR (%)	2.3±2.1	6.0 (0.0 – 6.0)
Average 14-day SG TIR (%)	73.7±5.9	19.0 (66.0 – 85.0)
Average 14-day SG TAR (%)	23.8±6.0	18.0 (15-0 – 33.0)
Systolic blood pressure (mmHg)	134±8	25 (121 – 146)
Diastolic blood pressure (mmHg)	82±11	36 (58 – 94)
Mean arterial pressure (mmHg)	100±9	31 (79 – 110)
Resting heart rate (bpm)	73±12	32 (56 – 88)
HDL (mmol/L)	2.0±0.4	1.2 (1.4 – 2.6)
LDL (mmol/L)	2.4±0.5	1.6 (1.9 – 3.5)
VLDL (mmol/L)	0.4±0.1	0.4 (0.3 – 0.7)
Triglycerides (mmol/L)	0.9±0.3	1.0 (0.5 – 1.4)
Total cholesterol (mmol/L)	4.8±0.6	1.9 (3.9 – 5.8)
$\dot{V}O_{2peak}$ (mL/min/kg)	27.8±8.0	26.1 (18.9 – 45-0)
$Power_{peak}$ (watts/kg)	2.6±0.8	2.7 (1.4 – 4.1)

Table 1. Baseline characteristics of study participants. BMI: body mass index. HbA1c: Haemoglobin A1C, CHO: carbohydrates. SG: sensor glucose. CV: coefficient of variation. TBR: time spent with sensor glucose values below the target range (<3.9 mmol/L). TIR: time spent with sensor glucose values within the target range (3-9 to 10.0 mmol/L). TAR: Time spent with sensor glucose values above the target range (>10.0 mmol/L). HDL: high density lipoprotein. LDL: low density lipoprotein. VLDL: very low-density lipoprotein. $\dot{V}O_{2peak}$: the highest value of $\dot{V}O_2$ attained during graded exercise testing to volitional exhaustion. Data are presented as mean±SD as well as the range (minimum to maximum) in values.

Table 2. Glycaemic parameters during each pre-defined time-period on experimental trial days.

Glycaemic parameter	**SE**	**AE90**	**AE45**	**p-value**
Pre-exercise period(-90min to -5min)				
Mean PG (mmol/L)	8.5±1.9	8.9±2.2	9.1±2.2	0.736
Minimum PG (mmol/L)	6.6±2.1	7.1±2.2	7.1±2.0	0.843
Maximum PG (mmol/L)	9.8±1.9	10.1±2.2	10.4±2.6	0.822
TBR PG (%)	0.0±0.0	0.0±0.0	0.0±0.0	-
TIR PG (%)	73.4±39.2	65.6±35.2	67.2±43.3	0.922
TAR PG (%)	26.6±39.2	34.4±35.2	32.8±43.3	0.922
CV PG (%)	14.9±8.3	13.6±7.6	13.4±7.5	0.540
Exercise period(0min to +45min)				
Mean PG (mmol/L)	6.4±2.0	7.8±1.5	7.3±1.8	0.205
Minimum PG (mmol/L)	4.6±1.1	5.4±1.0	5.2±1.4	0.260
Maximum PG (mmol/L)	8.2±2.4	9.5±2.1	9.3±2.5	0.416
TBR PG (%)	21.3±25.9	1.3±3.5	1.3±3.5	*0.031**
TIR PG (%)	72.5±21.9	85.0±20	87.5±21.9	0.426
TAR PG (%)	6.3±10.6	13.8±20.7	11.3±22.3	0.687
CV PG (%)	21.4±6.9	19.0±7.1	19.9±8.5	0.738
Post-exercise period(+50min to +105min)				
Mean PG (mmol/L)	4.1±0.6	5.5±0.9	5.5±1.9	*0.033**
Minimum PG (mmol/L)	3.9±0.4	5.1±1.1	5.0±1.6	*0.045**
Maximum PG (mmol/L)	4.4±0.9	6.0±1.0	6.1±2.2	*0.042**
TBR PG (%)	56.3±49.6	2.1±5.9	29.2±36.5	*0.041**
TIR PG (%)	43.8±49.6	97.9±5.9	66.7±34.5	*0.033**
TAR PG (%)	0.0±0.0	0.0±0.0	4.2±11.8	0.393
CV PG (%)	3.7±4.6	6.9±4.4	8.5±6.7	0.207
Exercise + Post-exercise period(0min to +105min)				
Mean PG (mmol/L)	5.6±1.4	6.9±1.0	6.7±1.5	0.083
Minimum PG (mmol/L)	3.9±9.4	4.9±1.1	4.8±1.3	0.086
Maximum PG (mmol/L)	8.2±2.4	9.7±1.8	9.6±2.4	0.337
TBR PG (%)	34.4±33.3	1.6±2.9	11.7±15.5	*0.029**
TIR PG (%)	61.8±29.6	89.9±12.0	79.7±17.3	0.073
TAR PG (%)	3.9±6.7	8.6±12.9	8.6±13.8	0.634
CV PG (%)	27.5±10.3	25.3±8.5	26.1±10.5	0.870
Overall period(-90min to +105min)				
Mean PG (mmol/L)	6.5±1.5	7.6±1.3	7.5±1.4	0.213
Minimum PG (mmol/L)	3.9±0.4	4.5±0.6	4.6±1.1	0.191
Maximum PG (mmol/L)	9.8±1.9	10.3±1.9	10.9±2.1	0.523
TBR PG (%)	22.9±22.2	1.1±1.9	7.8±10.3	*0.029**
TIR PG (%)	65.6±17.1	81.8±18.8	75.5±22.1	0.289
TAR PG (%)	11.5±16.5	17.2±19.6	16.7±20.0	0.811
CV PG (%)	32.9±5.2	25.6±6.9	29.2±9.8	*0.032**

Table 2. Glycaemic parameters during each pre-defined time-period on experimental trial days. PG: plasma glucose. TBR: Time spent with plasma glucose below the target range (<3.9

*mmol/L). TIR: time spent with plasma glucose levels within the target range (3.9 – 10 mmol/L). TAR: time spent with plasma glucose above the target range (>10 mmol/L). CV: Coefficient of variation. *p≤0.05 between SE and AE90.*

Table 3. Glycaemic parameters obtained via CGM during the 20-hour home period including the nocturnal period (2300 to 0700) for each experimental trial arm.

Glycaemic parameter	**SE**	**AE90**	**AE45**	**p-value**
Overall period(20 hours post laboratory)				
Mean SG (mmol/L)	8.8±1.7	7.8±1.0	8.2±1.4	0.181
Minimum SG (mmol/L)	3.8±1.5	3.7±0.7	3.7±0.8	0.992
Maximum SG (mmol/L)	17.4±3.7	14.0±2.8	14.9±3.4	*0.013*
TBR SG (%)	4.5±3.7	1.3±1.4	3.5±5.3	0.224
TIR SG (%)	68.7±18.2	78.7±12.5	74.0±13.3	0.277
TAR SG (%)	26.8±19.1	20.0±11.7	22.6±15.6	0.513
CV SG (%)	39.2±13.4	33.5±7.5	32.5±5.9	0.158
Nocturnal period(2300 to 0700)				
Mean SG (mmol/L)	8.3±2.3	7.3±1.8	7.1±0.8	0.278
Minimum SG (mmol/L)	5.1±1.2	5.1±1.2	4.8±1.1	0.609
Maximum SG (mmol/L)	13.4±4.2	11.0±3.0	9.8±1.6	*0.042*
TBR SG (%)	2.3±2.0	0.0±0.0	2.1±1.5	0.491
TIR SG (%)	78.0±23.7	88.0±18.9	95.6±5.4	0.090
TAR SG (%)	19.7±22.9	12.1±18.9	2.3±4.5	0.093
CV SG (%)	28.0±12.8	20.9±11.1	18.5±7.1	0.165

Table 3. Glycaemic parameters obtained via continuous glucose monitoring during the 20-hour home period including the nocturnal period (2300 to 0700) for each experimental trial arm. SG: sensor glucose. TBR: Time spent with sensor glucose below the target range (<3.9 mmol/L). TIR: time spent with sensor glucose levels within the target range (3.9 – 10 mmol/L). TAR: time spent with sensor glucose above the target range (>10 mmol/L). CV: Coefficient of variation.

Figures legends

Figure 1. Study schematic. AE90: a 25% reduced dose of bolus insulin with exercise announcement 90-minutes prior to exercise commencement. AE45: a 25% reduced dose of bolus insulin with exercise announcement 45-minutes prior to exercise commencement. SE: 'Spontaneous exercise' a 100% dose of bolus insulin with exercise announcement immediately at exercise onset.

*Figure 2. Plasma glucose concentrations on experimental visits when data are expressed as A) the absolute concentrations at each timepoint and B) the change from fasted starting values at each timepoint. AE90: a 25% reduced dose of meal-time insulin with exercise announcement 90-minutes prior to exercise commencement. AE45: a 25% reduced dose of meal-time insulin with exercise announcement 45-minutes prior to exercise commencement. SE: 'Spontaneous exercise' a 100% dose of meal-time insulin with exercise announcement immediately at exercise onset. Filled in black boxes denote a significant change in plasma glucose concentrations relative to immediately pre-exercise values (minute 0). *$p \leq 0.05$ in the point concentration of plasma glucose between SE and AE90. Data are presented as mean±SEM.*