Diabetologia (2020) 63:2282–2291
https://doi.org/10.1007/s00125-020-05244-y

ARTICLE

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

Sémah Tagougui[1,2,3] · Nadine Taleb[1,4] · Laurent Legault[1,5] · Corinne Suppère[1] · Virginie Messier[1] · Inès Boukabous[1] · Azadeh Shohoudi[6] · Martin Ladouceur[7] · Rémi Rabasa-Lhoret[1,2,8,9]

Received: 14 April 2020 / Accepted: 15 June 2020 / Published online: 1 August 2020

Abstract

Aims/hypothesis For individuals living with type 1 diabetes, closed-loop insulin delivery improves glycaemic control. Nonetheless, maintenance of glycaemic control during exercise while a prandial insulin bolus remains active is a challenge even to closed-loop systems. We investigated the effect of exercise announcement on the efficacy of a closed-loop system, to reduce hypoglycaemia during postprandial exercise.

Methods A single-blind randomised, crossover open-label trial was carried out to compare three strategies applied to a closed-loop system at mealtime in preparation for exercise taken 90 min after eating at a research testing centre: (1) announced exercise to the closed-loop system (increases target glucose levels) in addition to a 33% reduction in meal bolus (A-RB); (2) announced exercise to the closed-loop system and a full meal bolus (A-FB); (3) unannounced exercise and a full meal bolus (U-FB). Participants performed 60 min of exercise at 60% $\dot{V}O_{2peak}$ 90 min after eating breakfast. The investigators were not blinded to the interventions. However, the participants were blinded to the sensor glucose readings and to the insulin infusion rates throughout the intervention visits.

Results The trial was completed by 37 adults with type 1 diabetes, all using insulin pumps: mean±SD, 40.0 ± 15.0 years of age, HbA_{1c} 57.1 ± 10.8 mmol/mol (7.3 ± 1.0%). Reported results were based on plasma glucose values. During exercise and the following 1 h recovery period, time spent in hypoglycaemia (<3.9 mmol/l; primary outcome) was reduced with A-RB (mean ± SD; 2.0 ± 6.2%) and A-FB (7.0 ± 12.6%) vs U-FB (13.0 ± 19.0%; $p < 0.0001$ and $p = 0.005$, respectively). During exercise, A-RB had the least drop in plasma glucose levels: A-RB −0.3 ± 2.8 mmol/l, A-FB −2.6 ± 2.9 mmol/l vs U-FB −2.4 ± 2.7 mmol/l ($p < 0.0001$ and $p = 0.5$, respectively). Comparison of A-RB vs U-FB revealed a decrease in the time spent in target (3.9–10 mmol/l) by 12.7% ($p = 0.05$) and an increase in the time spent in hyperglycaemia (>10 mmol/l) by 21% ($p = 0.001$). No side effects were reported during the applied strategies.

Sémah Tagougui and Nadine Taleb contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-020-05244-y) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

✉ Rémi Rabasa-Lhoret
remi.rabasa-lhoret@ircm.qc.ca

[1] Montreal Clinical Research Institute (IRCM), 110 Pine Ave W, Montreal, QC H2W 1R7, Canada

[2] Department of Nutrition, Université de Montréal, Montreal, QC, Canada

[3] Université de Lille, Université d'Artois, Université du Littoral Côte d'Opale, ULR 7369 – URePSSS – Unité de Recherche Pluridisciplinaire Sport, Santé, Société (URePSSS), Lille, France

[4] Department of Biomedical Sciences, Université de Montréal, Montréal, QC, Canada

[5] Montreal Children's Hospital, McGill University Health Centre (MUHC), Montreal, QC, Canada

[6] Montreal Heart Institute, Montreal, QC, Canada

[7] École de Santé Publique de l'Université de Montréal, Montreal, QC, Canada

[8] Montreal Diabetes Research Center, Montreal, QC, Canada

[9] Endocrinology Division, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

Research in context

What is already known about this subject?

- Glucose management during physical activity is problematic for individuals living with type 1 diabetes, even with current closed-loop systems
- Postprandial exercise taken 2–3 h after a meal is particularly challenging and is associated with a high risk of hypoglycaemia
- Certain strategies added to closed-loop systems have been effective when exercise is not taken near mealtimes, but studies are lacking for postprandial exercise

What is the key question?

- Would exercise announcement to the closed-loop system at mealtime, with or without insulin bolus reduction, reduce hypoglycaemia during postprandial exercise in type 1 diabetes?

What are the new findings?

- Hypoglycaemia risk during postprandial exercise was reduced to a greater extent with the strategy of exercise announcement at mealtime, together with a 33% reduction in meal bolus, than with other treatment groups. This strategy, however, was associated with a higher percentage of time spent in hyperglycaemia

How might this impact on clinical practice in the foreseeable future?

- Individuals who experience exercise-induced hypoglycaemia and wish to exercise soon after a meal would benefit most from announcing exercise to their closed-loop system and reducing their meal bolus by one-third

Conclusions/interpretation Combining postprandial exercise announcement, which increases closed-loop system glucose target levels, with a 33% meal bolus reduction significantly reduced time spent in hypoglycaemia compared with the other two strategies, yet at the expense of more time spent in hyperglycaemia.
Trial registration ClinicalTrials.gov NCT0285530
Funding JDRF (2-SRA-2016-210-A-N), the Canadian Institutes of Health Research (354024) and the Fondation J.-A. DeSève chair held by RR-L

Keywords Closed-loop insulin delivery · Hypoglycaemia · Postprandial exercise · Type 1 diabetes

Abbreviations

A-RB	Announced exercise to closed-loop system with a 33% reduction in meal bolus
A-FB	Announced exercise to closed-loop system with full meal bolus
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
U-FB	Unannounced exercise with full meal bolus

Introduction

Closed-loop insulin delivery (or artificial pancreas) is, to date, the most advanced and promising technology to improve glucose control and reduce the risk of hypoglycaemia in individuals living with type 1 diabetes [1]. Closed-loop systems combine continuous subcutaneous insulin infusion (CSII), continuous glucose monitoring (CGM) and a dosing algorithm that dynamically controls the insulin infusion rate [2]. Closed-loop systems have demonstrated superior clinical efficacy (reduction in hyper- and hypoglycaemia) over conventional CSII therapy in most studies [3, 4]. Nevertheless, optimisation of closed-loop systems is challenging during exercise and meal consumption: both situations are associated with rapid changes in glucose levels and complex physiological effects [5–7].

During and after exercise, people with type 1 diabetes are unable to decrease their circulating plasma insulin levels in the setting of hypoglycaemia. This relative hyperinsulinaemia is exacerbated by increased insulin absorption from subcutaneous deposits that occurs in response to exercise [8]. Inappropriately elevated plasma insulin levels restrict hepatic glucose production, thus limiting counterregulatory responses to hypoglycaemia. At the same time, exercise enhances the rate of glucose disposal into skeletal muscle [9]. Therefore, physical activity is associated with a significant increase in hypoglycaemic risk in type 1 diabetes [9, 10]. Exercise is

typically undertaken in a postprandial state (within 2 h of eating a meal) or later (in a post-absorptive state). Glucose management is particularly challenging during the postprandial state given the combined challenges of minimising the prandial glucose rise and mitigating the risk of exercise-induced hypoglycaemia from insulin given as a mealtime bolus [9, 11, 12].

When diabetic individuals who use CSII or multiple daily injections choose to exercise in the postprandial period, guidelines suggest a 25–75% reduction in the insulin bolus for the preceding meal [10, 11]. The degree of bolus reduction should be proportional to exercise length and intensity [11]. Those who use CSII may also choose to temporarily reduce their basal insulin infusion rate. Most available studies investigating this option have been conducted in the post-absorptive state rather than the postprandial state. Data suggest that basal insulin reduction needs to be implemented at least 40 min before exercise onset to significantly reduce circulating insulin levels given the pharmacokinetics of available insulin formulations [13]. Zaharieva et al [14] even suggest that basal rate reduction needs to be applied 90 min before exercise, to improve glucose control and decrease hypoglycaemic risk during exercise.

In the context of closed-loop systems, most exercise trials have taken place in the post-absorptive state, and postprandial exercise has not been well studied. Most published closed-loop reports to date had hybrid closed-loop systems that required some intervention by the user. Research teams have attempted to alert a closed-loop system to physical activity by adding wearable sensors to detect exercise (e.g. heart rate, energy expenditure) [15–18] or by directly announcing the start of an exercise session [6] and/or adding glucagon, a counterregulatory hyperglycaemic hormone, to the closed-loop system [4]. By announcing or detecting exercise, the closed-loop system sets a higher glucose target for its algorithm, which reduces the basal insulin infusion rate [6, 19]. Nevertheless, even with closed-loop systems, detection or announcement at the beginning or during exercise may not be enough to prevent exercise-induced hypoglycaemic risk given current insulin pharmacokinetics. For example, using closed-loop insulin delivery for a post-absorptive exercise session, announcement 20 min before the start of exercise did not fully prevent hypoglycaemia, which still occurred in 23.5% of study participants [6]. It is expected that the hypoglycaemic risk would be exacerbated in the postprandial state.

To the best of our knowledge, clinical trials specifically designed to address and compare effective strategies for postprandial exercise using closed-loop systems have not been conducted. We could identify only two in silico studies that included postprandial exercise sessions taken 2 h after a meal. The first study found that reducing basal insulin delivery by 50% 90 min before exercise and by 30% during exercise was safe and effective (meal bolus was not modified) [20]. A more recent study suggested that the combination of carbohydrate consumption with closed-loop systems is an effective strategy to mitigate the risk of exercise-induced hypoglycaemia [21].

We therefore aimed to assess the efficacy of three strategies applied in the context of a single-hormone (insulin) closed-loop system, to prevent hypoglycaemia during postprandial moderate-intensity exercise. These strategies included exercise announcement to the algorithm to increase its glucose target 90 min prior to exercise, with or without meal bolus reduction, in comparison with unannounced exercise.

Methods

Participants and study design We conducted a single-blind, randomised, three-way crossover study with a single-hormone (insulin) closed-loop system, to compare three strategies applied during postprandial exercise in adults with type 1 diabetes: (1) announced exercise to the closed-loop system and a 33% reduction in meal bolus (A-RB); (2) announced exercise to the closed-loop system and a full meal bolus (A-FB); (3) unannounced exercise and a full meal bolus (U-FB). Exercise announcement and meal bolus reduction were applied at breakfast time, 90 min before the start of the exercise session. The study was registered at ClinicalTrials.gov (registration no. NCT02855307) and was approved by the ethics committee of the Montreal Clinical Research Institute.

Inclusion criteria were a diagnosis of type 1 diabetes for at least 1 year, age ≥18 years, use of CSII for at least 3 months and HbA_{1c} ≤107.7 mmol/mol (≤12%). Exclusion criteria included advanced microvascular complications, a recent (<3 months) acute macrovascular event, use of medication with effects on heart rate (e.g. β-blockers), abnormal blood panel and/or anaemia, ongoing or planned pregnancy, and a severe hypoglycaemic episode within 2 weeks of screening.

Randomisation and blinding Balanced randomisation was used to determine the order of the interventions (A-RB, A-FB or U-FB). A study coordinator conducted the randomisation and placed the results in sealed envelopes that were opened at the end of each admission visit. Participants were blinded to the sensor glucose readings and to the insulin infusion rates throughout the intervention visits.

Procedures During the admission visit, medical data, HbA_{1c} level, anthropometric variables and records of insulin therapy (basal and bolus doses) for the previous 3 days were collected. Physical fitness was assessed using a graded exercise test, adapted from Storer et al [22], on an ergocycle (ER 900; Ergoline, Germany) until voluntary exhaustion with power output increased by 10, 15 or 20 W/min. Expired gas samples were analysed via a mixing chamber using a Moxus

cardiorespiratory test station (AEI Technologies, USA). $\dot{V}O_{2peak}$ corresponded to the highest 30 s mean value reached.

Participants were told to avoid moderate- to high-intensity exercise the day before the intervention. A glucose sensor (Dexcom G4 Platinum; Dexcom, USA) was inserted 24 h before each intervention and calibrated by the study participant according to the manufacturer's recommendation.

For the intervention visits, participants arrived at the testing centre at 06:30 h and stayed for 5 h and 30 min. Closed-loop control was started at 07:00 h and a standardised breakfast (65 g carbohydrates) was given at 08:00 h, with or without exercise announcement and with or without a reduction in meal bolus, according to the randomisation. The individual's usual insulin/carbohydrate ratio was used to calculate the breakfast insulin bolus. At 09:30 h, participants performed exercise for 60 min on an ergocycle at 60% of $\dot{V}O_{2peak}$. Exercise intensity (60% $\dot{V}O_{2peak}$) was monitored by indirect calorimetry (O_2 and CO_2) using a face mask.

Intravenous blood samples were collected every 15 min from 07:00 h to 09:30 h, every 10 min from 09:30 h to 10:30 h (exercise period) and every 15 min from 10:30 h to 12:00 h (recovery period). Blood samples were immediately processed to measure plasma glucose levels, using a YSI 2300 STAT Plus analyser (Yellow Springs, OH, USA), and were stored for subsequent measurement of insulin levels in duplicates using an immunoassay (Millipore, USA). At 11:30 h, participants were switched back to their usual CSII settings, were served a standardised meal (65 g carbohydrate) and discharged at 12:00 h. The three intervention visits were separated by a median of 7 days (IQR 7–14 days).

The closed-loop system was based on a model predictive control algorithm, as previously described [4, 6, 23]. Details may be found in the appendix of our previous study [4]. The artificial pancreas system was initialised using records of participants' previous 3 days of insulin therapy (total daily dose, carbohydrate/insulin ratios and basal rates) and body weight obtained at the screening visit. Participants' usual fast-acting insulin analogue was used. Exercise announcement to the algorithm increased the target glucose level from 6.0 mmol/l to 9.0 mmol/l, which was directly set back to 6.0 mmol/l at the end of exercise, as previously described [6]. Real-time sensor readings were manually entered every 10 min into the dosing algorithm running on a laptop computer. Recommendations of insulin delivery were then generated by the algorithm and applied manually through the infusion pump.

Hypoglycaemia events, necessitating glucose consumption for correction, were defined as plasma glucose <3.3 mmol/l with symptoms or <3.0 mmol/l irrespective of symptoms, as in our previous closed-loop studies [4, 6, 24]. For correction, 50 ml 20% dextrose was infused intravenously (instead of oral glucose) because of the use of facial masks for gas exchange sampling to quantify exercise intensity. Hypoglycaemia correction was repeated every 15 min until glucose levels reached 4.0 mmol/l.

Outcomes and statistical analysis The primary outcome was the time spent with plasma glucose levels in the hypoglycaemic range (<3.9 mmol/l) during exercise and the following 1 h recovery period. Secondary outcomes were: (1) decrease in plasma glucose levels during exercise; (2) number of participants experiencing at least one exercise-induced hypoglycaemia event requiring treatment; (3) total number of exercise-induced hypoglycaemia events; (4) during the exercise period only, the percentage of time spent with plasma glucose levels <3.9 mmol/l, <3.3 mmol/l, 3.9–7.8 mmol/l, 3.9–10 mmol/l, >10 mmol/l and >13.9 mmol/l, and mean plasma glucose at the start of exercise, plasma insulin concentration and insulin delivery rate, and SD and CV of glucose values. These glucose ranges were chosen in accordance with the recommendations of the consensus about outcome measures reported in artificial pancreas studies [25].

The main comparisons were made between unannounced exercise and each of the two announced strategies separately. The sample size calculation for the primary outcome was estimated by assuming a mean percentage of time spent with glucose levels <3.9 mmol/l of 6.84% (SD 8.35%) from a previous closed-loop study [6]. A sample size of 37 participants was needed to provide 80% power to detect a reduction of at least 5% in the primary outcome (Cohen's medium effect size around 0.6) with announced strategies compared with the unannounced strategy.

Continuous variables were presented as mean±SD; medians with IQR (25th–75th percentile) were additionally reported when dealing with skewed data. Categorical variables were presented as frequencies and percentages. A multivariate linear mixed-effects model was used to compare continuous outcomes between different strategies, with strategy sequence, period and strategy type (fixed effect), and participant nested within sequence (random effect), entered as covariates. The effect of study strategies on the categorical outcomes was assessed using a random-effects generalised linear mixed model with logit link function for binary outcomes and log link function (assuming a Poisson distribution) for count outcomes. A bootstrap resampling method with no replacement using 500 samples was used to estimate the 95% CIs and p values, thus testing the model's parameters. Using this approach, there was no need to check for distributional assumptions such as normality. Two-tailed p values <0.05 were considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute, USA). All data were included in the analysis and no data imputation (last observation carried forward) or exclusion was performed after hypoglycaemia events.

Public and patient involvement No members of the public or patients were involved in the design, conduct or interpretation of the study.

Results

Between September 2016 and November 2018, adults living with type 1 diabetes were enrolled at the Montreal Clinical Research Institute. In total, 39 adults with type 1 diabetes using CSII were recruited of whom 37 (20 women) completed the study. Two participants dropped out: one because of scheduling problems and one because of a knee injury not related to the study. The baseline characteristics of the participants are summarised in Table 1.

During exercise and the following 1 h recovery period, the mean time spent in hypoglycaemia (<3.9 mmol/l) was lower during the exercise announcement strategies (A-RB 2.0 ± 6.2% and A-FB 7.0 ± 12.6%) compared with the unannounced strategy (U-FB 13.0 ± 19.0%) ($p < 0.0001$ and $p = 0.005$, respectively) (Table 2, Fig. 1). The comparison between the two announced exercise strategies yielded a p value of 0.06. Time spent in hyperglycaemia (>10 mmol/l) for the A-RB strategy was increased by 24.6% in comparison with the A-FB strategy ($p = 0.0001$), and by 21.0% in comparison with the U-FB strategy ($p = 0.001$) (Table 2). Time spent in target (3.9–10 mmol/l) was decreased by 12.7% during A-RB in comparison with U-FB ($p = 0.05$) (Table 2).

Exercise announcement reduced the proportion of participants who experienced at least one hypoglycaemia event during exercise requiring treatment to 5.4% with A-RB, 10.8% with A-FB vs 16.2% with U-FB. A similar trend was seen in the following 1 h recovery period (Table 2). During exercise, none of the participants required repeated correction of hypoglycaemia with the A-RB strategy, while one participant during the A-FB and two participants during the U-FB strategies received repeated correction.

Table 1 Baseline characteristics of the 37 study participants (17 men and 20 women)

Characteristic	Mean±SD	Range (minimum–maximum)
Age, years	40.0 ± 15.0	18.0–71.0
BMI, kg/m^2	25.3 ± 3.5	18.6–33.4
$\dot{V}O_{2peak}$, ml kg^{-1} min^{-1}	32.0 ± 8.1	18.8–50.2
HbA_{1c}, mmol/mol [%]	57.1 ± 10.8 [7.3 ± 1.0]	42.2–75.1 [5.4–9.6]
Diabetes duration, years	22.9 ± 14.2	4.0–55.0
Total daily insulin dose, U/kg	0.6 ± 0.2	0.2–0.9

Participants began the exercise session with a higher mean plasma glucose for the A-RB strategy (12.8 ± 2.9 mmol/l) compared with both the A-FB strategy (11.4 ± 3.3 mmol/l; $p = 0.009$) and the U-FB strategy (11.4 ± 3.8 mmol/l; $p = 0.008$). Over the whole exercise period, mean plasma glucose was higher for the A-RB strategy in comparison with the A-FB ($p = 0.01$) and U-FB strategies ($p = 0.001$) (Table 2). The mean decrease in plasma glucose (glucose level at the end of exercise minus glucose level at the beginning of exercise) was lower with the A-RB strategy (−0.3 ± 2.8 mmol/l) compared with the A-FB (−2.6 ± 2.9 mmol/l; $p < 0.0001$) and U-FB (−2.4 ± 2.7 mmol/l; $p < 0.0001$) strategies.

When exercise was announced to the closed-loop system, plasma insulin concentrations over the whole exercise period were lower (median, IQR) for the A-RB (157.2, 104.1–206.9 pmol/l) and A-FB (179.1, 128.6–251.7 pmol/l) strategies than for the U-FB strategy (193.3, 136.5–256.2 pmol/l; $p = 0.0008$ and $p = 0.09$, respectively). Differences in the rate of insulin delivery among the strategies during the exercise period did not reach statistical significance (Table 2). The electronic supplementary material (ESM Table 1) shows CGM-based outcomes of percentages of time spent at different glucose levels and thresholds. ESM Fig.1 can be consulted for individual plasma glucose curves superimposed for the three strategies (one graph for each of the 37 participants).

Discussion

We conducted the first closed-loop system trial that directly compared announced with unannounced strategies to reduce hypoglycaemia risk during postprandial exercise in individuals with type 1 diabetes. Our findings suggest that the A-RB strategy reduced hypoglycaemia risk compared with the A-FB and U-FB strategies, albeit with increased time spent in hyperglycaemia.

Previous studies that compared CSII with closed-loop systems during exercise have shown that closed loop was associated with an increase in the time spent in range and a decrease in the number of hypoglycaemia events [3, 19, 24, 26–28]. However, none of these studies have challenged closed-loop systems with exercise taken in the postprandial state. Postprandial exercise combines multiple challenges for a closed-loop system [9, 29, 30]: the difficulty to control postprandial glucose excursions [12, 30] and the inability to reduce circulating insulin levels secondary to insulin meal bolus during exercise-induced hypoglycaemia.

Thus, this closed-loop study investigated strategies to achieve adequate plasma insulin levels for postprandial exercise by taking into account the basal infusion rate and the meal bolus. Basal insulin rate adjustment in a closed-loop system was made by setting higher glucose targets. Accumulating data in CSII suggest that the basal insulin rate needs to be

Table 2 Summary and comparison of study outcomes for the three interventions

Outcome	A-RB	A-FB	U-FB	*p* value (A-RB vs U-FB)	*p* value (A-FB vs U-FB)	*p* value (A-RB vs A-FB)
Primary outcome (beginning of exercise to 1 h after end of exercise)						
Time spent at PG <3.9 mmol/l, %				<0.0001	0.005	0.06
Mean (SD)	2.0 (6.2)	7.0 (12.6)	13.0 (19.0)			
Median (IQR)	0 (0–0)	0 (0–7.4)	0 (0–26.4)			
Secondary outcomes (during exercise)						
Time spent at PG, %						
3.9–7.8 mmol/l	25.1 (27.4)	40.3 (30.2)	36.1 (26.3)	0.09	0.29	0.006
3.9–10 mmol/l	36.5 (33.5)	59.0 (0.3)	49.2 (31.5)	0.05	0.20	0.0008
<3.9 mmol/l				0.0001	0.002	0.35
Mean (SD)	1.6 (6.1)	4.8 (10.6)	12.9 (22.3)			
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–19.7)			
<3.3 mmol/l				0.001	0.009	0.53
Mean (SD)	0.5 (3.2)	4.8 (10.6)	5.4 (12.1)			
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–6.6)			
>10 mmol/l	55.6 (34.9)	31.0 (30.2)	34.6 (34.0)	0.001	0.449	0.0001
>13.9 mmol/l				0.03	0.871	0.02
Mean (SD)	16.8 (26.9)	7.4 (19.7)	7.7 (17.3)			
Median (IQR)	0 (0–31.1)	0 (0–0)	0 (0–0)			
>16.7 mmol/l				0.07	0.10	0.03
Mean (SD)	3.1 (10.3)	3.3 (12.2)	2.6 (8.6)			
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)			
PG at exercise start, mmol/l	12.8 (2.9)	11.4 (3.3)	11.4 (3.8)	0.008	0.90	0.009
ΔPG, mmol/l	−0.3 (2.8)	−2.6 (2.9)	−2.4 (2.7)	<0.0001	0.50	<0.0001
Mean PG, mmol/l	10.3 (2.9)	8.6 (2.7)	8.4 (3.1)	0.001	0.40	0.01
Mean SD of PG (SD)	1.9 (0.8)	1.9 (0.9)	2.0 (0.9)	0.52	0.76	0.75
Mean CV of PG, %	19.4 (9.1)	23.1 (11.0)	24.9 (11.1)	0.023	0.49	0.11
Plasma insulin concentration, pmol/l	157.2 (104.1–206.9)	179.1 (128.6–251.7)	193.3 (136.5–256.2)	0.0008	0.09	0.03
Insulin delivery rate, U/h	0.8 (0.6–1.0)	0.8 (0.5–1.1)	0.9 (0.6–1.2)	0.60	0.10	0.20
Summary of hypoglycaemia events						
Participants with at least one hypoglycaemia event, *n* (%)						
During exercise	2 (5.4)	4 (10.8)	6 (16.2)			
During recovery	0 (0)	3 (8.1)	2 (5.4)			
No. of hypoglycaemia events necessitating correction, *n*						
During exercise	2	5	7			
During recovery	0	3	2			

Data are expressed as *n* or mean (SD); median (IQR) are added on second line when data are not normally distributed

PG, plasma glucose; ΔPG, decrease in plasma glucose level at the end of exercise compared with pre-exercise level

reduced about 90 min before exercise. This strategy would allow enough time for plasma insulin levels to drop by the time of exercise start given the pharmacokinetics of currently used insulins [11, 13, 14, 17, 20, 31]. Bolus reduction obviously has to be done at the time of meal consumption. A 50% reduction in meal bolus was recommended for moderate-intensity, continuous exercise [10–12]. This 50% recommendation was nonetheless based on a study arm that did not include a change in basal insulin rate infusion [11]. In a closed-loop system setting that dynamically adjusts the insulin infusion rate, we assumed that a lower reduction in meal bolus would be sufficient and thus tested a reduction by one-third (33%) instead of one-half (50%).

The effect of these insulin adjustments in the announced strategies (A-RB and A-FB) may be observed in their corresponding glucose profiles, plasma insulin levels and rate of hypoglycaemia events. Exercise announcement resulted in higher mean glucose levels during the exercise session in comparison with the unannounced approach (Table 2, Fig. 2). However, glucose levels at the beginning of exercise, i.e. 90 min after the meal bolus, were only higher with the A-RB strategy and therefore appear to be mainly influenced by the bolus reduction. This is expected, as rapid insulin analogues peak at around 90 min. The insulin adjustments were reflected in the plasma insulin values (Fig. 3) of the different strategies. Previous studies of post-absorptive exercise and insulin adjustments have shown a modest exercise-related increase in circulating insulin, followed by a decline throughout the exercise session [31, 32]. In the current study, during the U-FB strategy, insulin concentration increased over the whole exercise period without any observed decline. This was due to the active meal insulin bolus and to higher insulin infusion rates in the U-FB arm. On the other hand, the lowest plasma insulin levels were seen with the A-RB strategy, and middle

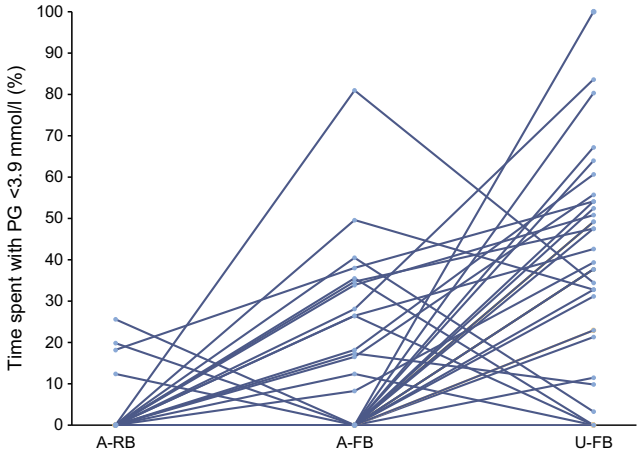

Fig. 1 Individual data points for the study primary outcome of time spent in hypoglycaemia (plasma glucose [PG] <3.9 mmol/l)

values with the A-FB strategy. Interestingly, some increases in plasma insulin concentrations towards the last 20 min in the A-RB strategy were observed, reflecting a closed-loop algorithm response to increased glucose values with this strategy. These observations will help to improve the design of the algorithms of closed-loop systems in relation to physical activity.

As a result of changes in plasma insulin levels, time spent in hypoglycaemia and the number of events requiring treatment for hypoglycaemia (using 50 ml 20% dextrose i.v. or carbohydrate intake) were minimised in A-RB and improved in A-FB in comparison with U-FB (control closed-loop arm). Our results highlight the limitations of available closed-loop systems using current CGM and CSII methods given the slow pharmacokinetics of insulin and the lag time of CGM readings when blood glucose declines rapidly during exercise [9, 33, 34]. A physiological lag time is needed to equilibrate glucose between the blood and the interstitial fluid compartments. If left without interference, adjustments of insulin infusion rates by the closed-loop algorithm based on changing CGM readings during exercise, as is the case with the U-FB strategy, carried higher risks of hypoglycaemia. CGM accuracy is key for optimal closed-loop algorithm operation; unfortunately, exercise is generally associated with glucose overestimation by CGM devices [34]. Such overestimation may lead to higher insulin infusion; even the A-RB strategy did not fully eliminate hypoglycaemia risk but significantly reduced it. Future CGM algorithms should reduce this overestimation by increasing sampling rates and adjusting readings according to trends in glucose changes or other techniques of glucose sensing than glucose oxidase [35].

Our results for the U-FB strategy agree with those of other studies that used exercise detection methods that proved to be insufficient to completely prevent hypoglycaemia during aerobic exercise [17]. The addition of carbohydrate snacks before or during exercise may be considered but can cause rebound hyperglycaemia. Diabetic individuals may also find it challenging to maintain or lose weight if frequently adding extra calories to their daily intake. There is insufficient data to guide the amount or timing of such snacks in the setting of postprandial exercise during closed-loop control.

During the A-RB strategy, a higher time in hyperglycaemia was noted in comparison with the full bolus strategies. Until further progress in insulin formulations and CGM technology is achieved, this mild hyperglycaemia during exercise may be an acceptable trade-off given the existing limitations of closed-loop components and the complexity of exercise-induced pathophysiological changes in type 1 diabetes. Other potential solutions could include testing a lower bolus reduction and/or faster acting new insulins and/or self-learning algorithms, because hypoglycaemia risk differs widely from one diabetic individual to another.

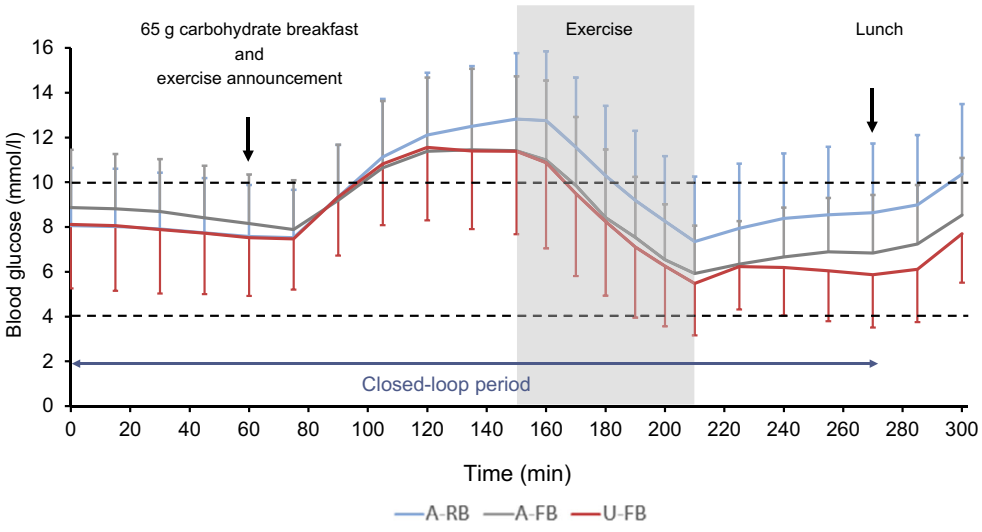

Fig. 2 Plasma glucose concentrations over the course of the three interventions. Shaded area corresponds to the exercise session. Data are expressed as mean (SD)

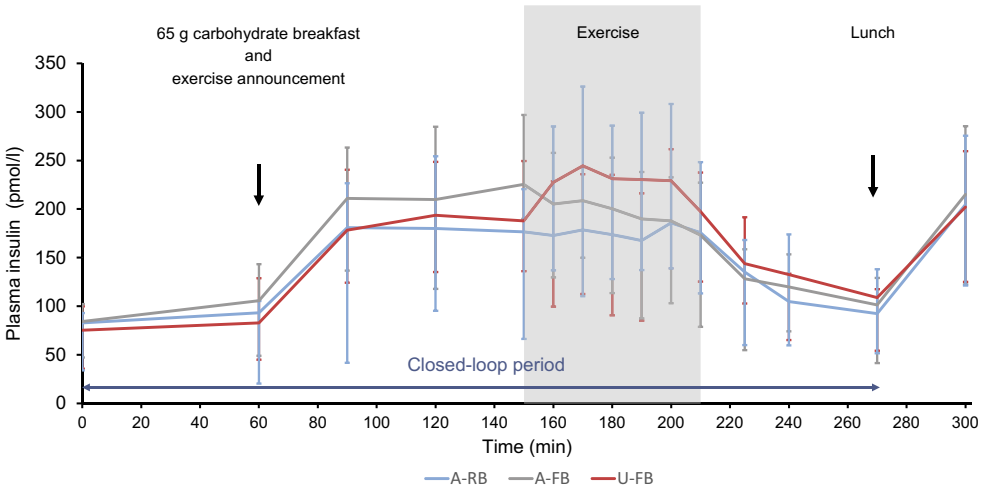

Fig. 3 Plasma insulin concentrations over the course of the three interventions. Shaded area corresponds to the exercise session. Data are expressed as median (IQR)

Multi-hormonal closed-loop systems with the addition of pramlintide and/or glucagon would be interesting options to investigate for postprandial exercise. Pramlintide is an analogue of amylin that is co-secreted with insulin to delay gastric emptying and prevent postprandial hyperglycaemia but is deficient in type 1 diabetes. Pramlintide has been shown to improve postprandial glucose control in dual-hormone closed-loop systems, but its efficacy has not been assessed during postprandial exercise [36, 37]. The beneficial effect of glucagon addition to closed-loop systems was shown during physical activity but has been mainly tested in post-absorptive exercise [6]. Both of these hormones might have a role in fine-tuning the balance between hyper- and hypoglycaemia in postprandial exercise.

The study had some limitations. It was conducted in a controlled setting with one testing per strategy; therefore, confirming the validity of the proposed approaches should be replicated in outpatient trials and during several exercise sessions. The closed-loop control was applied an hour before each intervention; one could argue that longer closed-loop use (≥24 h) might have brought participants to better control prior to the exercise intervention, but this would have made the study very burdensome to the participants (staying in the testing centre for a long time with an overnight stay). It is noteworthy that the participants were all using CSII and were relatively well controlled, with a mean HbA_{1c} that was close to the recommended target (56 mmol/mol; 7.3%). Intravenous glucose was used to correct hypoglycaemia events because the use of a face mask might not reflect the use of oral glucose in real-life settings. The lowest recommended dose for hypoglycaemia correction is 15 g using oral glucose and 10 g using i.v. dextrose [38]; hence, we chose the latter in our study. The type of exercise and its duration, intensity and timing are all factors that significantly influence blood glucose, so the proposed strategies of this study and other approaches would need to be tested in other exercise settings. Nevertheless, we started by testing a frequently chosen type of exercise (continuous exercise at moderate intensity) in type 1 diabetes and we picked convenient timing for most individuals (around 90 min would be needed on average to avoid exercising on a full stomach, and/or to reach a sports facility). The proposed strategy (A-RB) should be tested in multiple situations to ensure its applicability. On the other hand, the main strength of our trial is that it explored a clinical need under controlled conditions with a large number of participants and comparison of three scenarios.

In conclusion, in the context of moderate-intensity, continuous postprandial exercise undertaken 90 min after a meal, A-RB was superior in reducing the time spent in hypoglycaemia compared with the two other strategies. This approach was, however, associated with some increase in the time spent in hyperglycaemia during the exercise session. In the future, we plan to test whether the amount of reduction in meal bolus should be guided by the pre-meal blood glucose level, to mitigate the increased hyperglycaemia seen in our study. Future more advanced algorithms and/or multi-hormonal approaches could also be required to achieve the goal of preventing hypoglycaemia without inducing transient hyperglycaemia.

Acknowledgements We are thankful to all the participants who dedicated their time and effort to complete this study. We would like to thank A. Haidar (McGill University, Montreal, QC, Canada) for the algorithm conception and his contribution to the study. We would like to equally acknowledge the contributions of the diabetes nurses at Montreal Clinical Research Institute. We thank D. Mignault (Montreal Clinical Research Institute, Montreal, QC, Canada) for insulin dosages. We also thank K. Potter (Alberta Children's Hospital, Calgary, AB, Canada) for revising the English.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding ST is supported by a fellowship grant from the Société Francophone du Diabète and the Fondation pour la Recherche Médicale. NT is the recipient of a scholarship of scholarships from the Canadian Institutes of Health Research and Fonds de Recherche Santé Québec. This study was supported by funds from the JDRF (2-SRA-2016-210-A-N), the Canadian Institutes of Health Research (354024) and the Fondation J.-A. DeSève chair held by RR-L.

Authors' relationships and activities RRL has received research grants from the Canadian Diabetes Association, Astra-Zeneca, Eli Lilly, Cystic Fibrosis Canada, Merck, Novo-Nordisk and Sanofi-Aventis. He has been a consultant or member of advisory panels of Abbott, Amgen, Astra-Zeneca, Boehringer, Carlina Technology, Eli Lilly, Janssen, Medtronic, Merck, Neomed, Novo-Nordisk, Roche, Sanofi-Aventis and Takeda. He has received honoraria for conferences by Abbott, Astra-Zeneca, Eli Lilly, Janssen, Medtronic, Merck, Novo-Nordisk and Sanofi-Aventis. He has received in kind contributions related to closed-loop technology from Animas, Medtronic and Roche. He also benefits from unrestricted grants for clinical and educational activities from Eli Lilly, Lifescan, Medtronic, Merck, Novo Nordisk and Sanofi. He holds intellectual property in the field of type 2 diabetes risk biomarkers, catheter life and the closed-loop system. RR-L, LL and VM received purchase fees from Eli Lilly in relation with closed-loop technology. LL received consulting fees from Lilly and Dexcom, and received (to institution) research funding from Merck, Astra-Zeneca and Sanofi. The remaining authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement RR-L, LL, VM and ML contributed to the conception and design of the study. ST, IB and CS coordinated the study and acquired the data. ST, NT and AS analysed the data. NT, ST and RR-L interpreted the data. ST and NT drafted the manuscript. ST, NT, LL,CS, IB, VM, AS, ML, RR-L critically revised the manuscript for important intellectual content. All authors approved the final version of this manuscript. ST, NT and RR-L had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Taleb N, Tagougui S, Rabasa-Lhoret R (2019) Single-hormone artificial pancreas use in diabetes: clinical efficacy and remaining challenges. Diabetes Spectr 32(3):205–208. https://doi.org/10.2337/ds18-0094
2. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF (2006) Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes 55(12):3344–3350. https://doi.org/10.2337/db06-0419
3. Breton MD, Cherñavvsky DR, Forlenza GP et al (2017) Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study. Diabetes Care 40(12):1644–1650. https://doi.org/10.2337/dc17-0883
4. Haidar A, Legault L, Matteau-Pelletier L et al (2015) Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, randomised controlled trial. Lancet Diabetes Endocrinol 3(8):595–604. https://doi.org/10.1016/S2213-8587(15)00141-2
5. Zaharieva D, Yavelberg L, Jamnik V, Cinar A, Turksoy K, Riddell MC (2017) The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous versus circuit-based exercise in individuals with type 1 diabetes on continuous subcutaneous insulin infusion. Diabetes Technol Ther 19(6):370–378. https://doi.org/10.1089/dia.2017.0010
6. Taleb N, Emami A, Suppère C et al (2016) Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. Diabetologia 59(12):2561–2571. https://doi.org/10.1007/s00125-016-4107-0
7. Patel NS, Van Name MA, Cengiz E et al (2016) Mitigating reductions in glucose during exercise on closed-loop insulin delivery: the ex-snacks study. Diabetes Technol Ther 18(12):794–799. https://doi.org/10.1089/dia.2016.0311
8. Frank S, Jbaily A, Hinshaw L, Basu R, Basu A, Szeri AJ (2018) Modeling the acute effects of exercise on insulin kinetics in type 1 diabetes. J Pharmacokinet Pharmacodyn 45(6):829–845. https://doi.org/10.1007/s10928-018-9611-z
9. Tagougui S, Taleb N, Rabasa-Lhoret R (2019) The benefits and limits of technological advances in glucose management around physical activity in patients type 1 diabetes. Front Endocrinol 9:818. https://doi.org/10.3389/fendo.2018.00818
10. Riddell MC, Gallen IW, Smart CE et al (2017) Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol 5(5):377–390. https://doi.org/10.1016/S2213-8587(17)30014-1
11. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson JL (2001) Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). Diabetes Care 24(4):625–630. https://doi.org/10.2337/diacare.24.4.625
12. Gingras V, Bonato L, Messier V et al (2018) Impact of macronutrient content of meals on postprandial glucose control in the context of closed-loop insulin delivery: a randomized cross-over study. Diabetes Obes Metab 20(11):2695–2699. https://doi.org/10.1111/dom.13445
13. Roy-Fleming A, Taleb N, Messier V et al (2019) Timing of insulin basal rate reduction to reduce hypoglycemia during late postprandial exercise in adults with type 1 diabetes using insulin pump therapy: a randomized crossover trial. Diabetes Metab 45(3):294–300. https://doi.org/10.1016/j.diabet.2018.08.002
14. Zaharieva DP, McGaugh S, Pooni R, Vienneau T, Ly T, Riddell MC (2019) Improved open-loop glucose control with basal insulin reduction 90 minutes before aerobic exercise in patients with type 1 diabetes on continuous subcutaneous insulin infusion. Diabetes Care 42(5):824–831. https://doi.org/10.2337/dc18-2204
15. Turksoy K, Monforti C, Park M, Griffith G, Quinn L, Cinar A (2017) Use of wearable sensors and biometric variables in an artificial pancreas system. Sensors (Basel) 17(3):532. https://doi.org/10.3390/s17030532
16. Turksoy K, Hajizadeh I, Hobbs N et al (2018) Multivariable artificial pancreas for various exercise types and intensities. Diabetes Technol Ther 20(10):662–671. https://doi.org/10.1089/dia.2018.0072
17. Jacobs PG, Resalat N, El Youssef J et al (2015) Incorporating an exercise detection, grading, and hormone dosing algorithm into the artificial pancreas using accelerometry and heart rate. J Diabetes Sci Technol 9(6):1175–1184. https://doi.org/10.1177/1932296815609371
18. Castle JR, El Youssef J, Wilson LM et al (2018) Randomized outpatient trial of single- and dual-hormone closed-loop systems that adapt to exercise using wearable sensors. Diabetes Care 41(7):1471–1477. https://doi.org/10.2337/dc18-0228
19. Jacobs PG, El Youssef J, Reddy R et al (2016) Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. Diabetes Obes Metab 18(11):1110–1119. https://doi.org/10.1111/dom.12707
20. Schiavon M, Dalla Man C, Kudva YC, Basu A, Cobelli C (2013) In silico optimization of basal insulin infusion rate during exercise: implication for artificial pancreas. J Diabetes Sci Technol 7(6):1461–1469. https://doi.org/10.1177/193229681300700606
21. Bertachi A, Beneyto A, Ramkissoon CM, Vehí J (2018) Assessment of mitigation methods to reduce the risk of hypoglycemia for announced exercise in a uni-hormonal artificial pancreas.

Diabetes Technol Ther 20(4):285–295. https://doi.org/10.1089/dia.2017.0392
22. Storer TW, Davis JA, Caiozzo VJ (1990) Accurate prediction of $\dot{V}O_{2max}$ in cycle ergometry. Med Sci Sports Exerc 22(5):704–712. https://doi.org/10.1249/00005768-199010000-00024
23. Haidar A, Rabasa-Lhoret R, Legault L et al (2016) Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. J Clin Endocrinol Metab 101(1):214–223. https://doi.org/10.1210/jc.2015-3003
24. Haidar A, Legault L, Dallaire M et al (2013) Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. CMAJ 185(4):297–305. https://doi.org/10.1503/cmaj.121265
25. Maahs DM, Buckingham BA, Castle JR et al (2016) Outcome measures for artificial pancreas clinical trials: a consensus report. Diabetes Care 39(7):1175–1179. https://doi.org/10.2337/dc15-2716
26. Huyett LM, Ly TT, Forlenza GP et al (2017) Outpatient closed-loop control with unannounced moderate exercise in adolescents using zone model predictive control. Diabetes Technol Ther 19(6):331–339. https://doi.org/10.1089/dia.2016.0399
27. Pinsker JE, Laguna Sanz AJ, Lee JB et al (2018) Evaluation of an artificial pancreas with enhanced model predictive control and a glucose prediction trust index with unannounced exercise. Diabetes Technol Ther 20(7):455–464. https://doi.org/10.1089/dia.2018.0031
28. Dovc K, Macedoni M, Bratina N et al (2017) Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial. Diabetologia 60(11):2157–2167. https://doi.org/10.1007/s00125-017-4395-z
29. Tagougui S, Taleb N, Molvau J, Nguyen É, Raffray M, Rabasa-Lhoret R (2019) Artificial pancreas systems and physical activity in patients with type 1 diabetes: challenges, adopted approaches, and future perspectives. J Diabetes Sci Technol 13(6):1077–1090. https://doi.org/10.1177/1932296819869310
30. Gingras V, Taleb N, Roy-Fleming A, Legault L, Rabasa-Lhoret R (2018) The challenges of achieving postprandial glucose control using closed-loop systems in patients with type 1 diabetes. Diabetes Obes Metab 20(2):245–256. https://doi.org/10.1111/dom.13052
31. Franc S, Daoudi A, Pochat A et al (2015) Insulin-based strategies to prevent hypoglycaemia during and after exercise in adult patients with type 1 diabetes on pump therapy: the DIABRASPORT randomized study. Diabetes Obes Metab 17(12):1150–1157. https://doi.org/10.1111/dom.12552
32. McAuley SA, Horsburgh JC, Ward GM et al (2016) Insulin pump basal adjustment for exercise in type 1 diabetes: a randomised crossover study. Diabetologia 59(8):1636–1644. https://doi.org/10.1007/s00125-016-3981-9
33. Moser O, Mader JK, Tschakert G et al (2016) Accuracy of continuous glucose monitoring (CGM) during continuous and high-intensity interval exercise in patients with type 1 diabetes mellitus. Nutrients 8(8):489. https://doi.org/10.3390/nu8080489
34. Larose S, Rabasa-Lhoret R, Roy-Fleming A et al (2019) Changes in accuracy of continuous glucose monitoring using Dexcom G4 Platinum over the course of moderate intensity aerobic exercise in type 1 diabetes. Diabetes Technol Ther 21(6):364–369. https://doi.org/10.1089/dia.2018.0400
35. Cappon G, Vettoretti M, Sparacino G, Facchinetti A (2019) Continuous glucose monitoring sensors for diabetes management: a review of technologies and applications. Diabetes Metab J 43(4):383–397. https://doi.org/10.4093/dmj.2019.0121
36. Haidar A, Tsoukas MA, Bernier-Twardy S et al (2020) A novel dual-hormone insulin-and-pramlintide artificial pancreas for type 1 diabetes: a randomized controlled crossover trial. Diabetes Care 43(3):597–606. https://doi.org/10.2337/dc19-1922
37. Sherr JL, Patel NS, Michaud CI et al (2016) Mitigating meal-related glycemic excursions in an insulin-sparing manner during closed-loop insulin delivery: the beneficial effects of adjunctive pramlintide and liraglutide. Diabetes Care 39(7):1127–1134. https://doi.org/10.2337/dc16-0089
38. Diabetes Canada Clinical Practice Guidelines Expert Committee, Houlden RL (2018) Introduction. Can J Diabetes 42(Suppl 1):S1–S5. https://doi.org/10.1016/j.jcjd.2017.10.001