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Review

Glucose Control During Physical Activity and Exercise Using Closed Loop Technology in Adults and Adolescents with Type 1 Diabetes

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Key Messages

- Strategies and guidance provided for safe exercise and type 1 diabetes management while using automated insulin delivery.
- Aim of closed loop systems is to increase time in range, reduce hypoglycemia and reduce patient burden.

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ABSTRACT

Guidelines for safe exercise strategies exist for both pediatric and adult patients living with type 1 diabetes. The management of type 1 diabetes during exercise is complex, but making insulin dosing adjustments in advance of activity can yield positive outcomes and reduce the likelihood of hypoglycemia. Closed loop (also known as automated insulin delivery) systems are able to partially automate insulin delivery and can assist in exercise and overall management of type 1 diabetes. Current exercise guidelines, however, focus primarily on management strategies for patients using multiple daily injections or open loop insulin pump therapy. Closed loop systems require strategic approaches to type 1 diabetes management, including appropriate timing and duration of exercise targets and carbohydrates around exercise that have yet to be standardized. This review aims to showcase how closed loop technology has evolved over the last decade and summarizes a number of closed loop and exercise studies both in free-living conditions and clinical trials. This review also highlights strategies and approaches for exercise and type 1 diabetes management using closed loop systems. Some differences in closed loop strategies for exercise include the importance of pump suspension if disconnecting during exercise, fewer grams of uncovered carbohydrates before exercise and these should be taken close to exercise onset to avoid a rise in automated insulin delivery. A primary goal for future closed loop systems is to detect exercise without user input, so that patients are not required to preset exercise targets well in advance of activity, as are the current recommendations.

Mots clés:
administration automatisée d'insuline
boucle fermée
exercice
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RÉSUMÉ

Il existe des lignes directrices portant sur des stratégies pour la pratique sécuritaire de l'exercice qui sont destinées aux patients pédiatriques et adultes atteints du diabète de type 1. La prise en charge du diabète de type 1 durant l'exercice est complexe, mais la possibilité de faire les ajustements des doses d'insuline avant l'activité donne des résultats positifs et réduit le risque d'hypoglycémie. Les systèmes en boucle fermée (ou systèmes d'administration automatisée d'insuline) sont capables d'automatiser partiellement

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l'administration d'insuline et peuvent être utiles durant l'exercice et à la prise en charge globale du diabète de type 1. Toutefois, les lignes directrices actuelles sur l'exercice concernent principalement les stratégies de prise en charge des patients qui ont recours à de nombreuses injections quotidiennes ou à une insulinothérapie en boucle ouverte associée à une pompe à insuline. Les systèmes en boucle fermée nécessitent des approches stratégiques sur la prise en charge, notamment le moment et la durée appropriés pour fixer les objectifs d'exercice et les glucides liés à l'exercice encore non standardisés. La présente revue vise à montrer la façon dont la technologie en boucle fermée a évolué au cours de la dernière décennie et présente la synthèse d'un grand nombre d'études sur la boucle fermée et l'exercice dans des conditions de vie normales et d'essais cliniques. Cette revue présente également les stratégies et les approches sur l'exercice et la prise en charge du diabète de type 1 au moyen des systèmes en boucle fermée. Parmi les différences dans les stratégies en boucle fermée sur l'exercice, on note l'importance de l'interruption de la pompe si elle se débranche durant l'exercice, moins de grammes de glucides non couverts avant l'exercice, dont la prise devrait avoir lieu tout juste avant le début de l'exercice pour éviter une hausse de l'administration automatisée d'insuline. Le principal objectif des futurs systèmes en boucle fermée sera de détecter l'exercice sans les données de l'utilisateur, de telle sorte que les patients ne devront pas prérégler les objectifs de l'exercice bien avant l'activité comme le suggèrent les lignes directrices actuelles.

Introduction

Type 1 diabetes management requires exogenous insulin administration via multiple daily injections or continuous subcutaneous insulin infusion (CSII). The use of CSII, more commonly referred to as insulin pump therapy, has changed dramatically over the last decade. The first step toward reducing the burden and likelihood of hypoglycemia started with the low-glucose suspend feature in CSII, which suspends insulin delivery when continuous glucose monitoring (CGM) glucose drops below a certain threshold (e.g. 3.9 mmol/L) (1). Since then, advancements in technology have produced "closed loop" devices that automatically adjust insulin delivery in response to hypoglycemia and hyperglycemia. Closed loop algorithms adjust insulin needs based on a number of factors, some of which include the estimated amount of active insulin in the circulation, insulin sensitivity, CGM values and target glucose level. In most current systems, users still must bolus manually for meals. These systems are also called "hybrid closed loop," "automated insulin delivery" or "artificial pancreas" systems. CSII can be used in "open loop," whereby the patient uses the CGM glucose concentration and manually adjusts the insulin pump, or "closed loop," whereby CSII automatically adjusts insulin via an algorithm.

Closed loop systems are becoming more widely accepted and transitioning toward the standard of care for type 1 diabetes management. In recent years, there has been an increasing number of publications on the benefits and limitations of closed loop systems (2–6). Benefits of closed loop technology include improvements in glycemic control with increases in time-in-range (TIR) and reductions in percent time spent in hypo- and hyperglycemia (7,8), psychosocial benefits (i.e. peace of mind) (9) and improved sleep (9). Some challenges of closed loop systems include: current insulin pharmacokinetics (3); meal and exercise announcements (3); CGM accuracy, particularly how to use during exercise (10); cost (6); and, for some individuals, technical difficulties (9). Exercise has long been proposed as a major hurdle for closed loop systems because of the rapid rise in glucose turnover (11), and studies are now looking into how these systems are performing.

Regular physical activity is beneficial for individuals with type 1 diabetes and has been shown to not only improve insulin sensitivity, blood lipid profiles and psychological well-being, but also to lower cardiovascular disease risk and glycated hemoglobin levels (12,13). However, varying types, intensities and durations of activity can have different impacts on glycemia for individuals with type 1 diabetes. This added challenge and the heightened fear of hypoglycemia (14) are factors that contribute to the overall lower levels of activity seen with type 1 diabetes patients compared with their nontype 1 diabetes peers (15). Although consensus statements around safe exercise strategies for youth (16) and adults (13) with type 1 diabetes do exist, it is still difficult to provide precise recommendations that cover all aspects of physical activity and exercise. These guidelines cover topics including basal and bolus reduction strategies around exercise, blood glucose management strategies relative to starting glucose levels at exercise onset and carbohydrate requirements for exercise performance (13,16). Currently, there is limited information addressing safe exercise strategies with the use of closed loop technology and whether there are any differences compared with open loop insulin delivery systems. The purpose of this review is to summarize the development of closed loop technologies, review research studies that focus on exercise and type 1 diabetes and provide guidance on how to exercise safely while using closed loop features.

Technological Advancements for Type 1 Diabetes

Numerous health benefits are associated with regular physical activity, but this may come at the cost of increased likelihood of hypoglycemia (13). One technology that can help monitor glucose levels and hypoglycemia is CGM. There are a variety of manufacturers of real-time CGM (which display glucose data on a receiver, smart phone or pump) and intermittently scanned CGM systems (which require the user to swipe a reader across the sensor to obtain a reading). Studies have continued to demonstrate efficacy and benefits associated with CGM and intermittently scanned CGM for both CSII and multiple daily injection approaches (17,18). These studies established overall improvements in TIR, defined as a glucose level between 3.9 and 10.0 mmol/L, and reduced hypoglycemia (19,20). Compared with self-monitoring of blood glucose, one of the most valuable features of CGM and intermittently scanned CGM is the directional trend arrows that appear on the screen of the receiver or smartphone. Trend arrows provide anticipatory guidance on which direction glucose is changing, and allow patients to respond proactively (21). In addition, low-glucose alerts can be used to prevent hypoglycemia, and high-glucose alerts can prompt users to utilize more insulin.

When CGM is combined with CSII, the resulting sensor-augmented pump provides additional benefit toward avoiding hypoglycemia (22). Some sensor-augmented pump systems allow for some level of automation as the pump communicates with CGM and can suspend delivery of insulin if impending hypoglycemia is a concern. The terminology used for this algorithm detection of a

precipitating hypoglycemic event, and automated suspension of insulin delivery, is called the predictive low-glucose suspend feature. The predictive low-glucose suspend algorithm automatically stops insulin delivery when sensor glucose is predicted to reach or fall below a low-glucose preset value in 30 minutes. With some types of activity increasing the risk of hypoglycemia, this feature has become increasingly useful, especially for preventing nocturnal hypoglycemia in children, adolescents and adults (23,24).

Closed Loop Systems

Commercially approved systems

In North America, the most common manufacturers of CSII are currently Medtronic, Tandem and Insulet. More specifically, in Canada, at the time of this publication, the MiniMed 670G (Medtronic Canada) is the only approved automated closed loop insulin delivery system commercially available. In the United States, in addition to the MiniMed 670G system, the United States Food and Drug Administration (FDA) announced approval of the Tandem t:slim X2 pump with Control-IQ closed loop technology (Tandem Diabetes Care, San Diego, California, United States) in December 2019. Insulet (OmniPod tubeless pump) also has a closed loop system, called the Horizon system, which is currently undergoing clinical trials.

Do-it-yourself systems

Before any commercially approved devices came to market, "do-it-yourself" (DIY) artificial pancreas systems (APSs) were reaching the type 1 diabetes community (25,26). The estimated number of Canadians using DIY systems is likely small (~250 to 400), but growing. There are a number of different DIY systems, referred to as "Loop," "OpenAPS" or "AndroidAPS," all unregulated and not yet approved by Health Canada or the United States Food and Drug Administration. DIY systems are freely available open-source platforms that allow communication between a glucose-monitoring system and insulin pump either by using a Bluetooth-enabled pump or small hardware device, often referred to as a "rig." This became known as the #WeAreNotWaiting movement that has evolved into a large community sharing algorithms and DIY knowledge online (27).

To determine safety and efficacy of these devices, a number of these systems have been tested in initial studies as well as clinical trials. The general aims of these closed loop systems are to reduce mean glucose, increase glucose TIR, reduce the risk of hypoglycemia and reduce the burden of diabetes care.

Single- vs dual-hormone (bihormonal) systems

Single-hormone closed loop systems are specifically insulin-only systems, whereas dual-hormone or bihormonal systems are automated delivery systems that utilize both insulin and glucagon. The latter systems are only in the early proof-of-concept stage, for a variety of technical and practical reasons. The addition of glucagon to a closed loop system may be more protective against hypoglycemia compared with insulin-only systems (28). Relative to conventional sensor-augmented pump or insulin-alone closed loop therapy, bihormonal systems achieve slightly higher TIR (~73% vs 86%, respectively) with less time at <3.9 mmol/L (~10% vs 2%, respectively) (28,29). The dual-hormone approach may be particularly beneficial for exercise. Taleb et al (29) found that dual-hormone outperformed insulin-only closed loop during continuous- and interval-type exercise in adults with type 1 diabetes. Nonetheless, having 2 hormones in a closed loop system increases the system's complexity and expense, and may require that the user to wear 2 infusion sets. Studies have also introduced pramlintide injections to insulin-alone closed loop systems and found a reduction in postprandial glucose excursions (30,31). Recently, Haidar et al (32) introduced a novel closed loop system that delivers pramlintide and insulin in a basal-bolus manner and found better glucose control compared with an insulin-only system.

Exercise targets

Many closed loop systems allow for different automated insulin "targets" or "temporary presets" to be set in advance of exercise. This means that the algorithm will aim to keep glucose values at a higher level than during routine living, to reduce the risk of hypoglycemia. In addition, given the delayed offset in insulin action and the fact that we have to set an exercise target 1 or 2 hours beforehand, starting exercise at a higher glucose level gives a greater buffer with falling glucose levels. If exercise targets are set at the onset of activity, there is a significant risk of hypoglycemia, as it takes time to lower free insulin concentrations from the circulation (13). Depending on the closed loop system being used, these terms and criteria are defined in various ways (Table 1).

An exercise target is often set for a duration of time and automatically returns to the usual glucose target after the preset duration, but, depending on the system being used, may need to be turned off manually at the end of exercise. However, depending on the type, duration and intensity of exercise, glycemic responses to exercise may not always require less insulin delivery, and sometimes require more (12). These different responses to exercise make it challenging to know exactly when to set an exercise target and for what duration. Strategies for implementing different exercise targets are addressed in what follows.

Challenges to Open and Closed Loop Systems

Insulin action and absorption

A major challenge for both open and closed loop systems is insulin action time. With high rates of variability in subcutaneous absorption

Table 1
Exercise targets for various closed loop systems

Device system	Standard algorithm target	Activity terminology	Activity target	Notes
MiniMed 670G (Medtronic)	6.7 mmol/L	Temp target	8.3 mmol/L	Set for duration of time, will automatically deactivate at end
Control-IQ (Tandem)	6.2–8.9 mmol/L	Exercise activity	7.8–8.9 mmol/L	Tap to start, must tap to deactivate
DIY APS (OpenAPS, DIY, AndroidAPS, Loop)	Varies	Temporary target, profile switch, overrides or activity mode	Set target as desired	Set for duration of time or scheduled for specific time, will automatically deactivate at end

DIY, do it yourself.

of insulin among individuals with type 1 diabetes, there is also high glucose variability (33). Studies have shown that accelerated rates of insulin absorption occur with exercise (34), and this could be an added challenge to closed loop technology, particularly when the user does not program an exercise target, essentially leaving the activity unannounced. Setting exercise targets well in advance of aerobic exercise is one way to allow closed loop systems to be proactive in adjusting insulin. Future systems may have the ability to detect exercise, or allow the user to "announce" exercise, and, with exercise detection algorithms, a number of these systems have been shown to be successful and maintain high TIR (Table 2). The idea to link closed loop systems to calendar features and/or Global Positioning Satellite location may help to trigger earlier exercise settings (35).

CGM accuracy

Studies have shown that rapid changes in glycemia can also challenge the accuracy of glucose sensing (36–38). This is another challenge for open and closed loop systems, particularly during exercise and/or mealtime. In 2008, Kovatchev et al (39) reported that CGM accuracy was the primary limiting factor in the development of commercially viable closed loop systems. Significant lag time (CGM glucose values "lagging behind" the actual blood glucose value during periods of rapid change) remains, even with newer CGM technology during meals and exercise (38). To gain a better understanding of CGM accuracy and improvements in device accuracy, a greater emphasis is needed on various stressors that may challenge CGM accuracy during exercise (40) and, thus, closed loop efficacy (41). For now, individuals should consider increased vigilance using self-monitoring of blood glucose in times when the CGM is likely to lag further behind, such as with exercise or rapid glucose fluctuation.

Open Loop vs Closed Loop Exercise Strategies

Open loop adjustments

Common strategies for individuals using CSII in open loop include reducing basal and/or bolus insulin in preparation for exercise (Table 3) (13). Particularly for aerobic exercise, bolus insulin adjustments should be based on the timing relative to a meal. If exercise occurs ≥3 hours after the last meal, generally no bolus adjustments are recommended for the previous meal (42). However, if exercise onset is 1 to 3 hours after a meal, a 25% to 75% bolus insulin reduction is generally recommended (42). All of these recommendations are for aerobic activities that generally last >30 minutes. Bolus adjustments may also differ depending on the duration (<30 vs >30 minutes) and type of the activity (aerobic, resistance, intermittent high intensity or brief intense anaerobic) (42). It is unclear whether the same open loop strategies can be applied to closed loop insulin delivery or whether some modifications may be warranted. An important distinction between open and closed loop insulin delivery strategies is that the former is generally less flexible, because basal insulin rates are fixed (i.e. no option for insulin automation).

For individuals using CSII, basal insulin strategies for aerobic exercise should be performed well in advance of the planned activity. For example, reducing basal insulin 90 minutes before aerobic activity by 50% to 80% until the end of exercise may help reduce the likelihood of hypoglycemia (43). An additional concern is the risk of delayed nocturnal hypoglycemia after exercise (44). Although more research is required on the impact of various durations and intensities of activity after exercise, a general suggestion is that basal insulin can be reduced by 20% overnight for 6 hours to combat nocturnal hypoglycemia (43–45). These recommendations are good starting points to consider when managing exercise with CSII and will likely require some "fine-tuning" to determine what works best for each individual.

Closed loop adjustments

To date, fewer studies have been conducted on assessments of using closed loop systems for exercise. In this subsection, we describe a few strategies that can be used with open and closed loop systems (Table 3). We also provide a clinical summary to describe situations in which these strategies may lead to inconsistencies or challenges specifically to the closed loop system.

Exercise targets: Activities that are generally of low to moderate intensity for a longer duration tend to cause blood glucose levels to fall, often resulting in hypoglycemia (46). Setting a higher glucose target is a viable approach for specifically aerobic-based activities that last >30 minutes. The higher glucose target provides some protection by effectively lowering insulin delivery just before and throughout the activity. However, this may or may not translate to reduced insulin concentration in plasma because increased blood flow to subcutaneous adipose tissue during exercise may actually cause a rise in circulating insulin (47). For activities that tend to be anaerobic or of a very high intensity, glucose levels tend to be more stable, or even rise, and an increased target may not be desirable (48). However, few studies have focused on intense aerobic and anaerobic activities using closed loop technology.

Lee et al (49) recently assessed glucose homeostasis in adults with impaired awareness of hypoglycemia using the Medtronic MiniMed 670G closed loop system during 45 minutes of moderate- and high-intensity exercise in a controlled hospital environment. For both exercise conditions, the exercise target (from 6.7 to 8.3 mmol/L) was set 2 hours before exercise, lasting until 15 minutes after exercise. Overall median TIR was 100% (interquartile range, 75% to 100%) and 100% (interquartile range, 90% to 100%), respectively, during exercise. Similarly, Dovc et al (50) showed safety and efficacy of a closed loop system (GlucoSitter; DreaMed Diabetes, Petah Tikva, Israel) in young adults during and after unannounced exercise. The study included moderate-intensity and mixed-moderate and high-intensity sprints in both open and closed loop systems. They found that, irrespective of the exercise intensity, the closed loop system increased the TIR vs open loop (84% vs 69%), even when exercise was unannounced.

Clinical application for exercise targets: Exercise targets for closed loop systems have proven effective for activity, but generally still require advanced planning. Strategies include setting the exercise target from 30 minutes (51) up to 2 hours before exercise (49,52). If a patient is concerned about hypoglycemia during exercise, setting an earlier exercise target (e.g. 2 hours before exercise) should be beneficial. On the other hand, if before exercise hyperglycemia is of concern, exercise targets can be set closer to the start of activity (e.g. −30 minutes). Some closed loop systems in early development have built-in exercise detection algorithms that can automate and adjust insulin delivery with unannounced exercise (28,50,53–55). For these systems, preplanning is not necessarily required, but, if hypoglycemia continues to occur, a small snack at exercise onset may help counteract the drop in glycemia. To counteract delayed hypoglycemia after exercise, the exercise targets can be used for several hours after activity, similar to how a temporary basal rate may be used in CSII open loop. Closed loop users also have the option of turning off closed loop automation and using their systems in open loop mode. If the exercise targets are not able to prevent hypoglycemia during or after exercise, temporary basal rates can be used in open loop mode, as described previously.

For some exercise types (e.g. swimming, contact sports, etc), closed loop users may choose to remove their pump entirely (13).

Table 2
Research studies involving closed loop and physical activity

Author and year	Demographics	Type of system	Type of exercise	Duration of exercise	Outcomes (IQR)	Summary
Sherr et al (64), 2013	Adults (17±4 years), N=12	Open loop	Moderate intensity	60 min	%TIR = 72, %Hypo = 11, %Hyper = 17	• 48-h assessment, in-hospital • Medtronic Paradigm 715 insulin pump and external PID algorithm • Algorithm target glucose level set to 6.7 mmol/L during day and night • Data report only 10:00 PM to 6:00 AM after exercise
		Closed loop	Moderate intensity	60 min	%TIR = 91, %Hypo = 5, %Hyper = 4	
Breton et al (65), 2014	Adults (38±3 years), N=12	CTR closed loop system	Moderate intensity cycling	30 min	%TIR = 85±10, %Hypo = 3±2, %Hyper = 12	• 26-h admissions, in clinic • CTR closed loop feasibility • Algorithm predicts glycemic excursions 30–45 min ahead and computes predicted hypo- and hyperglycemic risks • CTR attenuates basal insulin delivery if hypoglycemia predicted • CTR+HR, exercise mode manually triggered when HR reached 125% of subjects resting HR • Data represent “during exercise”
		CTR + HR closed loop system	Moderate intensity cycling	30 min	%TIR = 91±7, %Hypo = 1±1, %Hyper = 8	
Jacobs et al (66), 2016	Adults (32±7 years), N=21	SAP	Moderate intensity	45 min	%TIR = 76±25, %Hypo = 2±4, %Hyper = 22±25	• 22-h sessions, in clinic • 3 arms: SAP, APX and APN • SAP subjects could adjust dosing before exercise • APX insulin decreased and glucagon increased at exercise onset • APN, no exercise dosing adjustment • Data represent “during exercise”
		Dual-hormone AP with adjustments (APX)	Moderate intensity	45 min	%TIR = 83±22, %Hypo = 0±0, %Hyper = 17±22	
		Dual-hormone AP with no adjustments (APN)	Moderate intensity	45 min	%TIR = 91±10, %Hypo = 0.1±0.3, %Hyper = 9±10	
Haidar et al (62), 2016	Adults (39±16 years), N=28	Conventional therapy	Moderate intensity	60 min	%TIR = 70 (58–81), %Hypo = 14 (4–28), %Hyper = 4 (0–20)	• Outpatient study in participant's home • 9:00 PM to 7:00 AM duration for each arm • Exercise prescribed, but not directly supervised • 6:00 PM exercise included 60 min of cycling or treadmill or 30 min of each (TIR = 4.0–10.0 mmol/L)
	Adolescents (15±2 years), N=7	Single-hormone AP	Moderate intensity	60 min	%TIR = 91 (76–97), %Hypo = 5 (0–13), %Hyper = 0 (0–5)	
		Dual-hormone AP	Moderate intensity	60 min	%TIR = 93 (81–99), %Hypo = 1 (0–8), %Hyper = 0 (0–2)	
Taleb et al (29), 2016	Adults (37±14 years), N=17	Single-hormone AP	Continuous cycling	60 min	%TIR = 68 (52–100), %Hypo = 23 (0–48), %Hyper = NA	• 4 interventions, in clinic • AP control from 3:30 PM until 7:30 PM • Exercise announced 20 min before exercise • Data represent “during exercise” (TIR = 4.0–10.0 mmol/L)
		Dual-hormone AP	Continuous cycling	60 min	%TIR = 100 (100), %Hypo = 0 (0), %Hyper = 0	
		Single-hormone AP	Interval cycling	60 min	%TIR = 73 (60–100), %Hypo = 0 (0–34), %Hyper = NA	
		Dual-hormone AP	Interval cycling	60 min	%TIR = 100 (100), %Hypo = 0 (0), %Hyper = 0	
Breton et al (63), 2017	Adolescents (13±2 years), N=32	RM-SAP	Skiing	5.5 h	%TIR = 63±31, %Hypo = 2±6, %Hyper = 35	• Participants wore systems for 6-day ski/snowboard camp • Randomized to RM-SAP vs UVA closed loop control • Data represents “during skiing”
		Closed loop control	Skiing	5.5 h	%TIR = 63±31, %Hypo = 1±2, %Hyper = 36	
Dovc et al (50), 2017	Adolescents (14±2 years), N=20	Open loop control	Moderate intensity cycling	40 min	%TIR = 68 (59–84), %Hypo = 0.2 (0–5), %Hyper = 25 (6–39)	• 4 visits, in-hospital • Open loop pump disconnected during exercise and basal insulin reduced by 20% for 4 h before exercise • Closed loop from 3:00 PM on day 1 to 1:00 PM • Exercise unannounced
		Closed loop control	Moderate intensity cycling	40 min	%TIR = 81 (64–92), %Hypo = 0 (0–0) %Hyper = 17 (7–33)	
		Open loop control	Interval cycling	40 min	%TIR = 68 (52–77), %Hypo = 0 (0–3), %Hyper = 30 (18–45)	
		Closed loop control	Interval cycling	40 min	%TIR = 75 (67–93), %Hypo = 1 (0–3), %Hyper = 21 (5–29)	

Huyett et al (67), 2017	Adolescents (15±2 years), N=10	SAP	Mild to moderate intensity	~30 min × 2–3 sessions per day	%TIR = 57±16, %Hypo = 4±3, %Hyper = 39±18	• Supervised, free-living conditions • ZPMC and HMS AP algorithms • Exercise unannounced
		Closed loop control	Mild to moderate intensity	~30 min × 2 or 3 sessions per day	%TIR = 71±10, %Hypo = 3±1, %Hyper = 26±11	
Jayawardene et al (52), 2017	Adults (40±13 years), N=12	Medtronic 670G	High intensity	~45 min	%TIR = 45±4, %Hypo = 0, %Hyper = 55	• Controlled, in-hospital visits • Closed loop temp target = 8.9 mmol/L for first 4 participants and 8.3 mmol/L for subsequent participants • Closed loop activated at ~8:00 AM • After 60 min in closed loop, 120 min before exercise, temp target activated until 15 min postexercise • Data represent during exercise (TIR = 4.0–10.0 mmol/L)
		Medtronic 670G	Moderate intensity	~45 min	%TIR = 52±4, %Hypo = 0, %Hyper = 48	
Castle et al (28), 2018	Adults (35±5 years), N=20	Single-hormone AP	Moderate intensity	45 min	%TIR = 83±17, %Hypo = 8±13, %Hyper = 9	• 4 study arms lasting 4 days each, in clinic • Exercise detection algorithm • After exercise detection, insulin turned off for 30 min and reduced by 50% of typical rate called for by algorithm for 60 min • Data represent start of exercise in clinic until next meal
		Dual-hormone AP	Moderate intensity	45 min	%TIR = 84±17, %Hypo = 3±5, %Hyper = 13	
		PLGS	Moderate intensity	45 min	%TIR = 78±19, %Hypo = 8±8, %Hyper = 14	
		Usual care (control)	Moderate intensity	45 min	%TIR = 78±26, %Hypo = 4±7, %Hyper = 18	
Petruzelkova et al (68), 2018	Children (12±2 years), N=22	Medtronic 640G with PLGS (n=12)	Camp: Skiing and disco dancing	~10 h/day (for 3 days)	%TIR = 82 (64–85), %Hypo = 5 (2–6), %Hyper = NA	• Winter sports camp study • Two groups separated into SmartGuard technology with PLGS and AndroidAPS • AndroidAPS target set to 6.0 mmol/L for 3 days • PLGS group basal rates, with preprandial and correction bolus reduced during activity by 30% to 50% according to age and TDD • Data represents all 3 days
		AndroidAPS (n=10)	Camp: Skiing and disco dancing	~10 h/day (for 3 days)	%TIR = 82 (77, 86), %Hypo = 3 (2–5), %Hyper = NA	
Pinsker et al (55), 2018	Adults (46±18 years), N=15	SAP	NA	NA	%TIR = 75±9, %Hypo = 8±6, %Hyper = 18±11	• 48-h closed loop admission, in clinic • Open loop run-in for 1 week (unsupervised, outpatient) • Closed loop system = eMPC algorithm • eMPC algorithm setpoint of 6.1 mmol/L • Data represent 24-h average of SAP vs closed loop • Exercise unannounced
		eMPC	Brisk walk outdoor	60 min	%TIR = 88±8, %Hypo = 2±2, %Hyper = 10±8	
Turksoy et al (69), 2018	Adults (25±5 years), N=10	MAAP system	Moderate intensity	~30 min	%TIR = 74±17, %Hypo = 3±5, %Hyper = 23±18	• 60-h closed loop experiments with 96 exercise, in-clinic sessions with 3 different protocols • Data represent 30 min before exercise to 2 h after exercise for all exercises combined • Exercise unannounced
		MAAP system	Resistance exercise	3 sets × 10 reps × 4 exercises	%TIR = 68±18, %Hypo = 3±6, %Hyper = 29±19	
		MAAP system	High intensity	~36 min	%TIR = 69±20, %Hypo = 2±4, %Hyper = 29±19	
Ekhlaspour et al (70), 2019	Adolescents (12±3 years), N=48	RM-SAP	Skiing	~5 h	%TIR = 56±31, %Hypo = 0 (0–0.4), %Hyper = 42±30	• 48-h ski camp • RM-SAP group had all PLGS and threshold low-glucose suspend deactivated during study • Both groups had 10% to 20% reduction in insulin dose upon arrival to camp • SAP group pump settings reduced by 20% for exercise in younger children • Data represents “skiing period”
		Tandem Control-IQ	Skiing	~5 h	%TIR = 58±27, %Hypo = 0 (0–0.8), %Hyper = 41±28	

(*continued on next page*)

Table 2 (*continued*)

Author and year	Demographics	Type of system	Type of exercise	Duration of exercise	Outcomes (IQR)	Summary
Forlenza et al (71), 2019	Adults (37±14 years), N=12	Omnipod MPC algorithm: Raised set point	Moderate intensity	~30 min	%TIR = 89±18, %Hypo = 10±18, %Hyper = 1±3	• 54-h closed loop period, in supervised hotel setting • First exercise session, glucose setpoint increased from 7.2 to 8.3 mmol/L, and second exercise, temporary basal rate of 50% (both started 90 min before exercise) • Data represents 12-h period from start of exercise
		Omnipod MPC algorithm: Reduced basal	Moderate intensity	~30 min	%TIR = 89±11, %Hypo = 9±12, %Hyper = 2±3	
Paldus et al (72), 2019	Adults (51±15 years), N=11	Medtronic s-HCL	Moderate intensity	40 min	%TIR = 69±11, %Hypo = 2±2, %Hyper = 29±11	• Data captured 1-week supervised setting with multiple glycemic challenges • Data represent 1 week on each system
		Medtronic e-HCL	Moderate intensity	40 min	%TIR = 74±10, %Hypo = 1±1, %Hyper = 24±9	
Hanaire et al (51), 2020	Adults (49±12 years), N=13	Open loop control	Sustained and repeated bouts of exercise • 45 min afternoon at high intensity • 30 min afternoon at moderate intensity • 30 min morning at moderate intensity • 45 min morning at high intensity		%TIR = 64±16, %Hypo = 3±4, %Hyper = 32±18	• 72-h testing period, in hospital • Open loop continued usual care for activity • Closed loop adjustments consisted of reduction in insulin dose and higher set-point (8.3–10 mmol/L) • Exercise announced 30 min before exercise • Data represents whole day
		Diabeloop closed loop control			%TIR = 80±9, %Hypo = 3±2, %Hyper = 17±8	
Lee et al (49), 2020	Adults (53 [42–57] years)	Medtronic 670G	Moderate intensity	45 min	%TIR = 100 (90−100), %Hypo = 0, %Hyper = 0	• 24-h testing period, in hospital for 120 min around exercise and sent home • 2-h before exercise, target increased from 6.7 to 8.3 mmol/L until 15 min after exercise • Data represent 45 min during exercise
		Medtronic 670G	High intensity	45 min	%TIR = 100 (75−100), %Hypo = 0, %Hyper = 0	
Dovc et al (73), 2020	Adults (21±2 years), N=20	DreaMed standard closed loop	Moderate vigorous	40 min	%TIR = 83 (52−100), %Hypo = 0 (0), %Hyper = NA	• 27-h study period, inpatient • Data represents start of exercise until 2 h after exercise • Exercise unannounced
		DreaMed faster closed loop	Moderate vigorous	40 min	%TIR = 79 (63−100), %Hypo = 0 (0), %Hyper = NA	
Schoelwer et al (74), 2020	Adolescents (15±2 years), N=18	Control (Control-IQ), N=9	Skiing	~5 h	%TIR = 78±13, %Hypo = 1.4 (0–2.4), %Hyper = 20±13	• 72-h study period • Encouraged to use “activity mode” during ski camp and at home • Data represents end of 3-day ski camp
		Control-IQ with MyTDI, N=9			%TIR = 77±8, %Hypo = 3.8 (0.5–4.7), %Hyper = 20±7	

AP, artificial pancreas; *APN*, artificial pancreas with no exercise dosing adjustments; *APX*, artificial pancreas with exercise dosing adjustments; *e-HCL*, enhanced hybrid closed loop; *eMPC*, enhanced model predictive control; *h*, hours; *HCL*, hybrid closed loop; *HMS*, health monitoring system; *HR*, heart rate; *%Hyper*, percent of time in hyperglycemia; *%Hypo*, percent of time in hypoglycemia; *IQR*, interquartile range; *MAAP*, multimodal multivariable adaptive artificial pancreas; *min*, minutes; *MPC*, model predictive control; *NA*, not available; *OpenAPS*, open artificial pancreas system; *PID*, proportional-integral-derivative controller; *PLGS*, predictive low-glucose suspend; *RM-SAP*, remote monitored sensor-augmented pump; *s-HCL*, standard hybrid closed loop; *SAP*, sensor-augmented pump; *%TIR*, percent of time in range; *TDD*, total daily dose (MyTDI parameters); *UVA*, University of Virginia; *ZMPC*, zone model predictive control.

Notes: CGM metrics defined as: TIR glucose between 3.9 and 10.0 mmol/L; %Hypo glucose <3.9 mmol/L; %Hyper glucose >10.0 mmol/L (unless otherwise noted in parentheses in the Summary column).

Table 3
Open vs closed loop diabetes management strategies for exercise

	Open loop	Closed loop
Contraindications	• Recent severe hypoglycemia (i.e. loss of consciousness, seizure or inability to self-treat) • Significant hyperglycemia (>15.0 mmol/L) • Ketones (≥1.5 mmol/L)	
Before exercise meal bolus	• Meal bolus >3 h before exercise: Usual bolus with or without correction • Meal bolus <1–3 h before exercise: Reduce bolus by: 25% for light exercise 50% for moderate aerobic exercise 75% for heavy aerobic exercise	
Before exercise basal adjustment	50% to 80% reduction 90 min before exercise and/or Pump suspension at exercise start	Exercise target 1–2 h earlier and/or If pump disconnected, should be suspended
Before exercise CHO (if glucose <7.0 mmol/L)	• <5.0 mmol/L: 10–30 g CHO • 5.0–6.9 mmol/L: 10 g CHO (aerobic)	• As per open loop * • Give <10 min before exercise
Before exercise CHO (if glucose 7.0–10.0 mmol/L)	0 g CHO	
Before exercise CHO (if glucose >10.0 mmol/L)	0 g CHO • 10.1–15.0 mmol/L: Start exercise (aerobic) Ketones <0.6 mmol/L (mild to moderate exercise) Ketones 0.6–1.4 mmol/L (light/short-duration exercise)	
Before exercise meal bolus	0% to 50% bolus reduction	Usual bolus/slight reduction (<25%)
Before exercise basal adjustment	20% basal reduction for 6 h at bedtime	Exercise target off †

CHO, carbohydrate; *h*, hours; *min*, minutes.
Note: Modified from Riddell et al (13).
* Denotes less CHO may be required with closed loop (~10 to 20 g).
† Denotes that, if patients are at high risk of hypoglycemia after exercise (e.g. prolonged aerobic or mixed activity), consider continuing exercise target for several hours after activity or overnight.

It is important in this case to have the user suspend insulin delivery if the system will be off for >15 minutes (vs simply letting the pump drip insulin during the disconnection) (56). This is more important for closed loop, because, if the system stays activated, it would still automate basal insulin while disconnected. This may cause underdelivery of insulin when the system is placed back on the body, as the system will have an inaccurate record of how much insulin is active (57).

Uncovered carbohydrates: Consumption of uncovered carbohydrates (i.e. meals/snacks containing carbohydrates that are taken without bolus insulin) are additional areas in which closed loop systems may be challenged. Unfortunately, there has been no research focused on this topic specifically, but is important to discuss whether patients continue to experience hypoglycemia during exercise. Some people choose to eat a snack ~30 minutes or more before exercise to reduce the likelihood of hypoglycemia during activity (58). However, with closed loop technology, the rise in sensor glucose level associated with the uncovered snack leads to a subsequent rise in automated insulin delivery (59). Further research is required regarding the timing and composition of snacks for exercise when using closed loop systems.

Clinical application for uncovered meals: Because the topic of uncovered carbohydrates for exercise has not been studied in detail with closed loop technology, there is limited clinical advice that can be provided. It is important to discuss with patients who experience recurring hypoglycemia during exercise what strategies they are using and to provide possible solutions. As previously discussed, to reduce the likelihood of hypoglycemia during exercise, setting exercise targets (higher glucose targets) well in advance of the activity is recommended. This will help patients exercise with lower levels of active insulin or "insulin-on-board" at exercise onset, which is beneficial (60). It is also important to note that consuming carbohydrates far in advance of exercise onset may result in relative hyperinsulinemia during exercise, as closed loop systems may deliver extra insulin to compensate for the rising glucose level. It may, therefore, be wise to delay carbohydrate intake or consume a small snack (~10 to 20 g) in these circumstances just before exercise onset to avoid the possibility of extra automated insulin delivery (61).

Discussion

The overarching goal for developing closed loop technology around exercise is for these systems to adopt to a range of exercise settings with little to no user input. In the interim, for single-hormone closed loop systems, exercise settings may be initiated 1 or 2 hours before aerobic exercise (49,52) to allow the system time to adjust insulin-dosing to reduce circulating insulin levels. Dual-hormone closed loop systems may not require exercise targets to be set as early, because a rise in glucagon can reduce the likelihood of hypoglycemia (28,62), but these systems are not yet commercially available. Another theoretical challenge with dual-hormone systems includes situations after high-intensity exercise where patients may experience elevated ketone levels and falling glucose levels in recovery. In these instances, the closed loop algorithm only responds to glucose changes, but not ketone levels, and may subsequently increase glucagon to address the fall in glucose concentrations, which may exacerbate ketosis. A more appropriate response in this theoretical situation would be eating a carbohydrate snack, yet additional research is needed.

Some limitations in this review include the various study designs and protocol implementations (summarized in Table 2), and, although we have reported TIR and CGM metrics, the TIR duration differs between studies. For clarification, we have added notes with the study design differences in the Summary column of Table 2. Also, for Table 2, although an extensive literature search was performed, we did not use the Cochrane risk of bias tool in order to establish validity and acknowledge this as another limitation. In addition to a thorough meta-analysis and quality assessment, a greater emphasis is also needed on exercise and closed loop research to establish a sound body of evidence.

Future closed loop systems will aim to reduce patient burden by eliminating meal announcements, carbohydrate counting and user-initiated exercise settings, although each of these advancements will require considerable development (3). Until then, it is important that clinicians, diabetes educators, researchers and diabetes care team members understand how strategies may differ between open and closed loop control (Table 3) and know how to optimize care for active individuals with type 1 diabetes.

In conclusion, in recent years, closed loop insulin delivery systems have shown reduced frequency and overall percent time spent in hypoglycemia during exercise and generally increased percent TIR (28,51,63). Closed loop systems have also effectively shown reductions in risk of nocturnal hypoglycemia after prolonged afternoon physical activity (64). These important findings all help to reduce the fear of hypoglycemia as one of the primary barriers to regular exercise and physical activity. However, a few important points should be made regarding closed loop technology and exercise including the timing and amount of carbohydrates before exercise and the exercise targets set in advance of activity (Table 3). Individuals with type 1 diabetes using closed loop systems should be cautious about the timing of consuming uncovered carbohydrates before exercise, because, if taken too far in advance of activity (i.e. >10 minutes), there may be a rise in sensor glucose and a subsequent rise in automated insulin delivery. In addition, exercise targets are generally turned off after exercise, but for patients at higher risk of hypoglycemia after exercise (e.g. prolonged aerobic or mixed activity), it is important to consider continuing the exercise target for several hours after activity or potentially overnight. Overall, further research is required regarding different exercise settings and the impact of various intensities, durations and types of exercise with closed loop technology.

Author Disclosures

D.P.Z. has received speaking honoraria from Medtronic Diabetes, Ascensia Diabetes and Insulet. L.H.M. has received speaking/consulting honoraria from Tandem Diabetes and Dexcom, and has also done consulting for Clinical Sensors and Capillary Biomedical. B.P. has received speaking honoraria from Medtronic. D.N.O. has been on advisory boards and has received support for research and honoraria from Medtronic, Novo, Sanofi and Abbott. D.M.M. has received research support from the National Institutes of Health, the Juvenile Diabetes Research Foundation, the National Science Foundation and the Helmsley Charitable Trust, and his institution has received research support from Medtronic Diabetes, Dexcom, Insulet, Bigfoot Biomedical, Tandem and Roche. D.M.M. has also served as consultant for Abbott, the Helmsley Charitable Trust, Sanofi, Novo Nordisk, Eli Lilly, Medtronic and Insulet. M.C.R. has received lecture fees from Medtronic Diabetes, Novo Nordisk and Insulet, and consulting/advisory board fees from Xeris and Zucara, research grants from Sanofi and Novo Nordisk and material funding from Dexcom.

Author Contributions

D.P.Z. wrote the first draft of the manuscript. The literature search was conducted by D.P.Z. and reviewed by all authors. D.P.Z., L.H.M., B.P., D.N.O., D.M.M., and M.C.R. contributed to manuscript revisions and all authors approved the submitted manuscript.

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