

Strategies to optimize glucose control during exercise in subjects with type 1 diabetes

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Keywords: Type 1 diabetes, T1D, Exercise, Physical activity, Carbohydrates, Insulin therapy, MDI, CSII.

ABSTRACT

Regular physical activity is highly recommended in subjects with type 1 diabetes (T1D) because of its beneficial impact on body composition, cardiovascular disease risk profile, glucose control and psychological wellbeing. However, exercise is challenging for many individuals with T1D, particularly due to the fear of hypoglycaemia, loss of glycaemic control and lack of motivation. The aim of this commentary is to briefly summarize the patterns of dysregulation of glucose homeostasis during and after exercise in subjects with T1D. In addition, we focus on carbohydrate intake and adjustment of insulin dosing as the main strategies used in clinical settings to optimize glucose control and prevent hypoglycaemia before, during and after exercise.

INTRODUCTION

Regular physical activity is highly recommended in subjects with type 1 diabetes (T1D) due to its beneficial impact on body composition, cardiovascular risk profile, glucose control and psychological wellbeing¹⁻⁵. Children and adolescents with T1D should do at least 60 minutes/day of aerobic exercise, along with muscle and bone strengthening activities at least three days per week^{1,2}. On the other hand, adults with T1D should do at least 150 minutes/week of accumulated physical activity, avoiding physical inactivity for more than two consecutive days^{2,6}. Nevertheless, several barriers to exercise still exist for the majority of diabetic patients, particularly fear of hypoglycaemia, loss

of glycaemic control and lack of motivation^{6,7}. Moreover, effects of exercise on glucose control are complex and extremely variable between and within T1D individuals, depending on initial blood glucose concentrations, individual fitness and type, duration and intensity of physical activity⁶. Therefore, exercise remains challenging for most individuals with T1D.

Exercise is generally classified into three different categories: I) aerobic exercise (e.g., walking, jogging, cycling, swimming), which involves repeated and continuous movement of large muscle groups whose function physiologically depends on aerobic energy-producing systems; II) resistance (strength) training, which includes exercises using free weights, elastic resistance bands, weight machines or body weight, and primarily involves anaerobic energy-producing systems; III) high intensity interval training (HIIT, also referred to as high-intensity intermittent exercise), which consists of the alternation of short periods of intense and vigorous anaerobic exercise and recovery periods at low to moderate intensity⁶.

A meta-analysis of physical activity intervention studies in youth with T1D showed that regular physical activity (both aerobic and resistance exercise) may be beneficial in terms of improvement in glucose control⁸. However, there is still scarce evidence on the most effective type, intensity, timing and duration of exercise aimed to achieve an optimal glucose control in patients with T1D. Indeed, blood glucose responses to exercise in T1D are highly variable and depend on several factors, including: type and duration of physical activity, pre-exercise blood glucose concentrations, pre-exercise carbohydrate ingestion, composition of the last snack or meal, amount of “insulin on board” from previous insulin boluses, circulating levels of

glucagon and other counter-regulatory hormones, and individual fitness and nutritional status⁶. Remarkably, T1D is a highly heterogeneous disease in terms of clinical and immunopathological features⁹, resulting in a heterogeneous degree of residual beta-cell function, impairment in alpha-cell function and glucagon response to exercise and hypoglycaemia across individuals^{10,11}.

DYSREGULATION OF GLUCOSE HOMEOSTASIS DURING AND AFTER EXERCISE IN SUBJECTS WITH T1D

In T1D, glucose responses to exercise are highly variable and depend on several factors, which we have previously mentioned^{6,12}. Aerobic exercise usually leads to reduced blood glucose levels and increased risk for exercise-induced hypoglycaemia (especially during prolonged activity)¹³⁻¹⁵, because circulating insulin levels often increase as a likely result of the augmented blood flow to subcutaneous adipose tissue occurring during physical activity^{6,16}. Furthermore, higher circulating insulin levels and skeletal muscle contraction during exercise exert additive effects on glucose transporter 4 (GLUT-4) translocation, resulting in increased glucose uptake in peripheral tissues¹⁷. Also, exercise-induced increase in muscle perfusion further contributes to the increased glucose disposal¹⁸. Finally, higher circulating insulin levels suppress lipolysis in adipose tissue and reduce fat oxidation in skeletal muscles, thus preventing the use of lipids as alternative fuels^{7,19}. Altogether, these pathophysiological mechanisms predispose T1D individuals to exercise-induced hypoglycaemia⁶. Importantly, augmented GLUT-4 translocation and increased skeletal muscle microvascular perfusion can persist after exercise^{7,20,21}. Indeed, increased glucose disposal typically remains elevated for several hours during recovery from aerobic exercise, in order to adequately replenish liver and muscle glycogen stores^{6,22}. Thus, the increased risk for hypoglycaemia can persist for 24 hours or more during recovery from exercise. In particular, afternoon exercise is associated with an increased risk of developing late-onset, nocturnal hypoglycaemia^{6,23}. In addition, subjects with T1D also show a blunted rise in glucagon levels during exercise, which potentially leads to a reduced ability to promote hepatic gluconeogenesis²⁴. Subjects with T1D who perform exercise in the early morning hours and in a fasting state exhibit a lower risk of late-onset hypoglycaemia compared to those who perform exercise

in the afternoon²³. This could also be explained by the circadian rhythm of the counterregulatory hormone cortisol: lower cortisol concentrations in the afternoon (especially at midnight) may promote hypoglycaemia by reducing the hepatic response to glucagon and gluconeogenesis^{25,26}.

For these reasons, CHO intake at bedtime may be advisable particularly after exercise performed in the evening hours, in order to avoid nocturnal hypoglycaemia and replenish glycogen stores in early recovery^{23,27}.

Resistance training can provide better glucose stability compared to continuous moderate aerobic exercise, although it can also lead to a rise in blood glucose in some patients, particularly upon brief and intense anaerobic exercise²⁸⁻³¹. Resistance training and HIIT can mitigate the reductions in blood glucose levels^{28,32}, potentially by decreasing glucose uptake and leading to a shift towards consumption of alternative substrates^{33,34}. Therefore, mixed activities may help to achieve better glucose stability during exercise².

In general, blood glucose levels tend to rise during anaerobic exercise due to the increase in counter-regulatory hormones (e.g. epinephrine, norepinephrine, and growth hormone)³⁴. This often leads subjects with T1D to use insulin correction boluses after exercise. However, insulin correction boluses should always be used with caution, in order to avoid overcorrection and subsequent risk of (severe) hypoglycaemia, which can occur even several hours after exercise (late-onset, nocturnal hypoglycaemia)⁶.

Exercise-induced hypoglycaemia can be categorized in two different categories according to the time of onset in relation to exercise. Early hypoglycaemia occurs during or shortly after exercise (early recovery period), particularly in trained subjects (possibly because of the higher overall work rate)³⁵. As we already mentioned, late-onset hypoglycaemia occurs in the late recovery period after exercise due to the increased insulin sensitivity. Of note, the increased risk of late-onset hypoglycaemia (e.g. nocturnal hypoglycaemia) depends on the intensity and duration of the exercise bout and can last for more than 30 hours^{7,36}. Since the risk of nocturnal hypoglycaemia is increased especially after afternoon or evening exercise, caution should be paid in presence of blood glucose levels at bedtime of <7.0 mmol/L (<126 mg/dL). It is important to outline that the occurrence of severe hypoglycaemia

(defined as blood glucose levels ≤ 2.78 mmol/L (50 mg/dL) or a hypoglycaemic event requiring assistance from another individual) within the previous 24 hours represents a contraindication to exercise, due to the increased risk of more serious hypoglycaemic episodes during exercise^{6,37}.

Despite the remarkable advances in technology used to treat patients with T1D (e.g. hybrid closed-loop insulin delivery systems and continuous glucose monitoring devices)³⁸, attainment of good glucose control during and after exercise still remains challenging for most patients with T1D³⁹. In this context, blood glucose monitoring before, during and after exercise plays a pivotal role in glucose management among patients with T1D. In particular, real-time continuous glucose monitoring (CGM) provides more detailed information about daily patterns of hyperglycaemia and hypoglycaemia, thus allowing for a more efficient patient decision-making in terms of insulin dosing (especially during and after exercise). Also, the most advanced CGM sensors allow other people (e.g. parents, friends, coaches) to remotely monitor patient glucose data and trends through specific mobile apps, thus rendering T1D subjects (particularly children) more confident in glucose control during exercise⁴⁰. In this commentary, we aim to briefly summarize the main carbohydrate and insulin adjustment strategies to optimize glucose control and reduce the risk of hypoglycaemia during and after exercise in patients with T1D.

MANAGEMENT OF CARBOHYDRATE INTAKE AND INSULIN THERAPY DURING PHYSICAL ACTIVITY IN PATIENTS WITH T1D

Carbohydrate intake and proper adjustments of insulin dosing represent two key aspects that subjects with T1D need to carefully take into account before, during and after physical activity in order to achieve a good glucose control and to avoid clinically significant hyperglycaemic and hypoglycaemic events.

CARBOHYDRATE INTAKE

The main strategies pertinent to carbohydrate intake aimed to maintain performance and avoid exercise-induced hypoglycaemia include three fundamental aspects: I) the amount of carbohydrates ingested, II) the timing of the intake, and III) the quality of the carbohydrates⁷. Importantly, mixed meals containing protein, fat and/or fibers can also influence the glycae-

mic response by affecting gastric emptying and the absorption rate of carbohydrates.

Carbohydrates can be classified into three main categories: i) monosaccharides, which represent the basic units of carbohydrates (e.g., glucose, fructose and galactose), ii) disaccharides, which are composed of two monosaccharide molecules (e.g., lactose, maltose, sucrose, isomaltulose), and iii) polysaccharides, which are long chains of carbohydrate molecules composed of several monosaccharide units (e.g., glycogen, cellulose, amylose, and amylopectin).

Approximately 15-20 g/h of carbohydrate may be required to prevent exercise-induced hypoglycaemia in T1D subjects who reduce their insulin infusion rate before starting exercise. However, carbohydrate requirements are highly variable depending on pre-exercise blood glucose levels and the type and duration of physical activity. For example, carbohydrate requirements are usually lower during short, high intensity and anaerobic activities. Also, the amount of carbohydrates required to prevent hypoglycaemia may be not sufficient to guarantee the performance, adding more complexity to the choice of the most proper amount of carbohydrate to be ingested before exercise⁶.

With regard to the quality of carbohydrates, it is worth noting that different carbohydrates increase the levels of blood glucose according to the degree of intestinal absorption (slow vs. fast absorption) and to the value of their glycaemic index. Glycaemic index (GI) indicates the blood glucose response measured as area under the curve (AUC) in response to a test food consumed by a subject under standard conditions, expressed as a percentage of the AUC following the consumption of a reference food (usually 50 g of glucose) consumed by the same subject on a different day. Foods are categorized as having a low (<55), medium (55–69) or high GI (≥ 70)⁴¹. In general, consumption of snacks or drinks with high GI is effective in increasing blood glucose levels during endurance exercise, treating or preventing hypoglycaemia, and enhancing recovery after exercise; on the other hand, ingestion of foods with a low GI before exercise can promote carbohydrate availability and contribute to maintain euglycaemia⁶.

Glucose is assigned the maximal GI of 100, thus explaining why it represents the most proper carbohydrate to treat hypoglycaemia. For example, isomaltulose is a low-GI carbohydrate (GI 32),

which has been shown to increase blood glucose levels of half as much as compared to dextrose (GI 92) during the rest period and to maintain blood glucose levels 21% lower compared to dextrose for three hours of recovery after exercise in subjects with T1D⁴². Isomaltulose consumption also leads to lower carbohydrate and higher lipid oxidation rate during the later stages of exercise, resulting in improved blood glucose response during and after exercise compared to dextrose⁴². In addition, some studies suggest fructose as a valid alternative to glucose to mitigate the drop in glucose levels after exercise^{43,44}. This likely occurs because fructose displays a different metabolic pathway compared to glucose. Fructose is mainly absorbed across the apical membrane of the enterocytes by the glucose transporter 5 (GLUT5), whereas glucose is absorbed by sodium-glucose cotransporter 1 (SGLT1). After ingestion and intestinal absorption, fructose is first metabolized in the liver and reach the systemic circulation at lower concentrations, while glucose reach directly the systemic circulation⁴⁵. These differences in metabolic pathways account for the low GI of fructose (GI 18). Therefore, pre-exercise fructose ingestion may offer metabolic benefits to subjects with T1D, due to its reduced glycaemic impact and the partial conversion into lactate and lipids which can be used as alternative energy substrates by skeletal muscles⁷. However, ingestion of large amounts of fructose and chronic high fructose consumption is not devoid of possible side effects and risks, including gastrointestinal distress⁴⁶, impairment in hepatic insulin sensitivity and dyslipidemia⁴⁷.

Another important aspect to be considered is the timing of carbohydrate ingestion. Ingestion of 10 g of carbohydrates before starting aerobic exercise is advisable in presence of pre-exercise glucose levels ranging between 5.0 and 6.9 mmol/l (90 and 124 mg/dL)⁶. In addition, T1D subjects performing exercise in the post-absorptive state should take into account the so-called “insulin on board”, which is the insulin still active from previous mealtime bolus doses (discussed later). In this scenario, consumption of proper amounts of carbohydrates may be useful to account for the insulin on board⁴⁸. On the other hand, ingestion of a bedtime snack (particularly slowly absorbed snacks) may be a valid tool to reduce the risk of post-exercise nocturnal hypoglycaemia⁴⁸⁻⁵⁰.

ADJUSTMENT OF INSULIN DOSING BEFORE, DURING AND AFTER EXERCISE

Apart from frequent glucose monitoring and carbohydrate consumption, a careful adjustment of insulin dosing (both basal and bolus insulin dosing) is paramount to maintain an optimal glucose control and avoid hypoglycaemia during and after exercise. In general, continuous aerobic exercise requires more pronounced reduction in insulin dose (along with a higher carbohydrate intake), whereas short anaerobic exercise often requires an increase in insulin dose during early recovery after exercise.

When performed within up to 3 hours after a meal, prolonged (>30 min) aerobic physical activity often requires reductions in the bolus insulin dose administered at the meal prior to the exercise, which can also be accompanied by the additional consumption of carbohydrates (typically snack or foods with a low GI) to prevent hypoglycaemia^{6,50,51}. The degree of insulin dose reduction is highly variable based on the type, intensity and duration of exercise. However, it has been shown that even marked reductions (up to 75%) in the bolus insulin dose before exercise do not increase the risks in terms of ketogenesis⁵². Notably, West et al⁴⁸ showed that consumption of a low GI carbohydrate (75 g isomaltulose) and 75% reduction in rapid-acting insulin dose administered 30 minutes prior to running improved pre- and post-exercise blood glucose responses in subjects with T1D on multiple daily injection (MDI) insulin therapy.

On the other hand, proper reductions in the basal insulin dose can prevent late postprandial hypoglycaemia (occurring >4 hours after a meal) and late-onset nocturnal hypoglycaemia following aerobic exercise⁶. However, in this context it is worth distinguishing patients on MDI therapy from those on continuous subcutaneous insulin infusion (CSII). Indeed, reductions in the basal insulin dose is not routinely recommended for T1D subjects on MDI, unless they are involved in frequently planned physical activity (e.g., diabetes camps)⁶. Conversely, T1D subjects on CSII can modify basal rates of insulin infusion in a more flexible manner. Suspension of basal insulin infusion at the onset of exercise is a potential tool to reduce the risk of hypoglycaemia during exercise. However, circulating insulin is still detectable for a certain period after the suspension of basal insulin infusion, and insulin delivery suspension can increase the risk of

hyperglycaemia during the recovery period. Moreover, according to the current guidelines and to the pharmacokinetics of rapid-acting insulin analogs, a time limit of less than 2 hours is recommended for pump suspension, in order to avoid the risk of deterioration in glucose control and ketone production⁶. In light of these remarks, a reduction in basal rates of insulin infusion may be preferred over the complete delivery suspension and should be attempted approximately 60-90 minutes before the initiation of physical activity^{6,53}. The latter approach may be more effective in preventing hypoglycaemia during and after exercise, and in reducing the risk of post-exercise hyperglycaemia^{6,54}. As we previously mentioned, overcorrection of hyperglycaemia after exercise through excessive insulin correction boluses should be avoided in order to reduce the risk of severe, late-onset hypoglycaemic episodes⁶. CSII has been shown to limit post-exercise hyperglycaemia compared to MDI therapy in T1D subjects performing regular moderate-to-heavy intensity aerobic exercise⁵⁵.

When adjusting insulin therapy, it is also worth considering the importance of taking into account the so-called “insulin on board” (also known as “active insulin”), which is defined as the insulin still active after 3-4 hours from previous meal-time bolus doses. Without considering “insulin on board”, titration and adjustment of insulin dosing can lead to an increased risk of hypoglycaemia. Another important aspect is that T1D patients who use continuous glucose monitoring (CGM) sensors are used to monitor their glycaemia more frequently, with less fear of hypoglycaemia and a better management of glucose control before, during and after exercise^{7,8,17}.

CONCLUSIONS

Regular physical exercise is highly recommended in subjects with T1D since it has a beneficial impact on body composition, cardiovascular risk profile, glucose control and psychological wellbeing. However, exercise is challenging for many individuals with T1D, particularly due to the fear of hypoglycaemia. Moreover, subjects with T1D display different patterns of dysregulation of glucose homeostasis on the basis of type, intensity and duration of exercise. Planning physical activity, frequent glucose monitoring, careful adjustments of insulin dosing, intake of carbohydrates in the form of snacks, and adequate fluid replacement all re-

main key strategies to maintain an optimal glucose control, optimize performance and avoid hypoglycaemia before, during and after exercise.

FUNDING:

No funding is declared for this article.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interests regarding the publication of this manuscript.

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