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Exercise management in type 1 diabetes: a consensus statement

Michael C Riddell, Ian W Gallen, Carmel E Smart, Craig E Taplin, Peter Adolfsson, Alistair N Lumb, Aaron Kowalski, Remi Rabasa-Lhoret, Rory McCrimmon, Carin Hume, Francesca Annan, Paul A Fournier, Claudia Graham, Bruce Bode, Pietro Galassetti, Timothy W Jones, Inigo San Millan, Tim Heise, Anne Peters, Andreas Petz, Lori M Laffel

Abstract

Type 1 diabetes is a challenging condition to manage for various physiological and behavioural reasons. Regular exercise is important, but management of different forms of physical activity is particularly difficult for both the individual with type 1 diabetes and the health-care provider. People with type 1 diabetes tend to be at least as inactive as the general population, with a large percentage of individuals not maintaining a healthy body mass nor achieving the minimum amount of moderate to vigorous aerobic activity per week. Regular exercise can improve health and wellbeing, and can help individuals to achieve their target lipid profile, body composition, and fitness and glycaemic goals. However, several additional barriers to exercise can exist for a person with diabetes, including fear of hypoglycaemia, loss of glycaemic control, and inadequate knowledge around exercise management. This Review provides an up to date consensus on exercise management for individuals with type 1 diabetes who exercise regularly, including glucose targets for safe and effective exercise, and nutritional and insulin dose adjustments to protect against exercise-related glucose excursions.

Introduction

Despite tremendous advances since the discovery of insulin almost 100 years ago, management of type 1 diabetes remains challenging.^{1,2} The majority of patients living with type 1 diabetes do not have a healthy body weight (about 60% are overweight or obese), about 40% have hypertension, about 60% have dyslipidaemia,³ and most do not engage in enough regular physical activity.⁴ Regular exercise can help patients achieve several goals: it improves the cardiovascular disease risk profile in paediatric patients⁵ and reduces HbA_{1c} by about 0.3% in this [A: paediatric? Children and young people?] population [A: edits OK?].⁶ Body composition, cardiorespiratory fitness, endothelial function, and blood lipid profile (ie, triglycerides and total cholesterol) all improve with regular physical activity in children and young people with type 1 diabetes. [A: ref 7 is a duplicate of ref 6; is this the correct ref, or did you want to cite a different ref here? References will be re-numbered as necessary] These cardiometabolic improvements are all important, given that cardiovascular disease is the leading cause of morbidity and mortality in people [A: reference title refers to 'youth'. Correct reference here?] with type 1 diabetes.⁸ In adults, both retinopathy and microalbuminuria are less common in those who are physically active than in those who are not.⁹ Active adults with type 1 diabetes tend to have better chance of achieving their HbA_{1c} and blood pressure targets, and a healthier BMI, than do inactive patients.³ Regular exercise also decreases total daily insulin needs.¹⁰ Having a high exercise capacity in adulthood is associated with a reduced risk of coronary artery disease, myocardial ischaemia, and stroke, regardless of whether a person has diabetes or not.¹¹ In a large cross-sectional study of 18 028 adults with type 1 diabetes,³ patients who were categorised as being most physically active (exercising two or more times per week) had better HbA_{1c} concentrations, a more favourable BMI,

less dyslipidaemia and hypertension, and fewer diabetes-related complications (retinopathy and microalbuminuria), than those who were less habitually active. In general [A: as you still refer to reference 3, would 'The study also showed that...' be more appropriate?], patients with type 1 diabetes who are more active tend to have less diabetic ketoacidosis and a reduced risk of developing severe hypoglycaemia with coma.³ However, older women who are physically active have higher rates of severe hypoglycaemia (with coma) than those who are inactive.³ Several barriers to exercise might exist, including a fear of hypoglycaemia, loss of glycaemic control, insufficient time, access to facilities, an absence [A:OK?] of motivation, issues around body image, and a general scarcity of knowledge around exercise management.¹²⁻¹⁴

For all adults living with diabetes, including those living with type 1 diabetes, 150 minutes of accumulated physical activity is recommended each week, with no more than two consecutive days of no physical activity [A: please give a reference for this sentence]. Resistance exercise is also recommended two to three times a week. Getting this much exercise is difficult for many patients; results from a large cross-sectional study showed that [A: insertion ok?] less than 20% of patients manage to do aerobic exercise more than two times per week, and about 60% of patients do no structured exercise at all.³ For children and young people, at least 60 minutes of physical activity should be done per day.¹⁵ Physical inactivity and prolonged sitting times increase gradually with age and are linked to high HbA_{1c} concentrations in young people with type 1 diabetes,¹⁶ and physical inactivity appears to be more common in women than in men.³

Regular exercise should be encouraged and supported by health-care professionals for many reasons, but primarily because the overall cardiometabolic benefits outweigh the immediate risks if certain precautions are

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[A: please check all affiliations carefully, provide highest degree for all authors, and indicate any full professors]

Muscle Health Research Centre, York University, Toronto, ON, Canada (M C Riddell PhD); Royal Berkshire NHS Foundation Trust Centre for Diabetes and Endocrinology, Royal Berkshire Hospital, Reading, UK

(I W Gallen); Hunter Medical Research Institute, School of Medicine and Public Health, University of Newcastle, Rankin Park, NSW, Australia (C E Smart); Department of Paediatric Diabetes and Endocrinology, John Hunter Children's Hospital, Newcastle, NSW, Australia (C E Smart); Division of Endocrinology and Diabetes, Department of Pediatrics, University of Washington, Seattle Children's Hospital, Seattle, WA, USA (C E Taplin); Department of Pediatrics, The Hospital of Halland, Kungälv, Sweden (P Adolfsson); Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (P Adolfsson); [PA: OK to split into two affiliations?]

Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK (A N Lumb); Juvenile Diabetes Research Foundation, New York, NY, USA (A Kowalski); Department of Nutrition and Institut de Recherches Cliniques de Montréal, Faculty of Medicine, University of Montreal, Montreal, QC, Canada (R Rabasa-Lhoret); Department of Cardiovascular and Diabetes Medicine, University of Dundee, Dundee, UK (R McCrimmon); London Medical, London, UK (C Hume);

[A: is there a departmental affiliation for CH?] Children and Young People's Diabetes Service, University College London Hospitals NHS Foundation Trust, London, UK

[A: is there a departmental affiliation for CH?] Children and Young People's Diabetes Service, University College London Hospitals NHS Foundation Trust, London, UK

(F Annan); School of Sport Science, Exercise, and Health (P A Fourmier), The University of Western Australia, Perth, WA, Australia

(Prof T W Jones FRACP); Department of Endocrinology and Diabetes, Princess Margaret Hospital for Children, Perth, WA, Australia

(Prof T W Jones); Telethon Kids Institute, Perth, WA, Australia (Prof T W Jones); [TW]: affiliations & title OK? Dexcom Inc, San Diego, CA, USA

(C Graham); Atlanta Diabetes Associates, Atlanta, GA, USA

(B Bode); Department of Pediatrics, University of California Irvine, Irvine, CA, USA

(P Galassetti); Department of Physical Medicine and Rehabilitation, University of Colorado, School of Medicine, Aurora, CO, USA (I San Millan);

Profil, Neuss, Germany (T Heise); Keck School of Medicine, University of Southern California, Los Angeles, CA, USA (A Peters);

StubbaekSkole, Aabenraa, Denmark (A Petz); Division of Endocrinology, Boston Children's Hospital, Boston, MA, USA (L M Laffel); and

Pediatric, Adolescent and Young Adult Section, Joslin Diabetes Center, Boston, MA, USA (L M Laffel) [LML: OK to split into two affiliations?]

Correspondence to: Dr Michael C Riddell, Muscle Health Research Centre, York University, Toronto, ON M3J 1P3, Canada
mriddell@yorku.ca

taken. In this Review, the basic categories of exercise are described from a physiological perspective, as are the starting points for nutritional and insulin dose adjustments to keep patients in a targeted glycaemic range. This Review summarises the authors' consensus on the available strategies that help incorporate exercise safely into the daily management plan for those adults with type 1 diabetes who are regularly engaging in exercise, sports, or competitive events. We hope these new guidelines for exercise management will improve glycaemic control [A:OK?] and encourage more individuals with type 1 diabetes to increase their physical activity.

Physiology of physical activity and exercise Modalities of exercise

An understanding of the metabolic and neuroendocrine responses to the various types of exercise done by people with type 1 diabetes is essential for determination of appropriate nutritional and insulin management strategies. Exercise is generally classified as aerobic or anaerobic, depending on the predominant energy systems used to support the activity, although most exercise activities include a combination of energy systems. Aerobic exercise (eg, walking, cycling, jogging, and swimming) involves repeated and continuous movement of large muscle groups that rely primarily on aerobic energy-producing systems. Resistance (strength) training is a type of exercise using free weights, weight machines, body weight, or elastic resistance bands that rely primarily on anaerobic energy-producing systems. High intensity interval training involves alternation between brief periods of vigorous exercise and recovery at low to moderate intensity (eg, from 20 s to 4 min intervals of exercise and rest, for up to ten cycles).¹⁷ Both aerobic and anaerobic [A:OK?] activities are recommended for most people living with diabetes,^{15,18} and guidelines now also incorporate high intensity interval training as a training modality with established benefits for individuals with prediabetes or type 2 diabetes.¹⁸ In some studies, high intensity interval training has been shown to be more effective than continuous aerobic training in improvement of cardiovascular fitness and various parameters related to glucose metabolism, including insulin sensitivity and glycaemic control in type 2 diabetes.¹⁹ At present, it is unclear what the most effective forms of exercise for improvement of cardiometabolic control in type 1 diabetes are.²⁰

Neuroendocrine and metabolic responses to exercise Individuals without diabetes

The metabolic responses to different forms of exercise are distinct. However, in almost all forms of exercise, regardless of the intensity or duration, blood glucose concentrations are normally held within a tight range (4–6 mmol/L). During aerobic exercise, insulin secretion decreases and glucagon secretion increases in the portal vein to facilitate release of glucose from the liver to match

the rate of glucose uptake into the working muscles.²¹ Exercise can increase glucose uptake into muscle by up to 50 times—a phenomenon that occurs independently of insulin signalling—²² so the decrease in circulating insulin does not restrict glucose provision to the working body. Although the main determinant of glucose production during aerobic exercise is an increase in glucagon concentrations, neural control of glucose release and other counter-regulatory hormones also have a supportive role.²³ An extended duration of exercise leads to reduced reliance on muscle glycogen as fuel and increased reliance on lipid oxidation and glucose derived from plasma.²⁴ If insulin concentrations do not fall during aerobic exercise [A: for example, during...?], the rise in counter-regulatory hormones is less effective than when they do fall [A:OK?] in the promotion of hepatic glucose production.²¹

When the intensity of exercise increases above 50–60% of maximal oxygen consumption (VO₂max), fat oxidation decreases, particularly in those who are untrained, and carbohydrates become the preferred fuel.²⁵ Prolonged high intensity exercise is supported by use of both muscle glycogen and blood glucose, with minimal contributions from lipid and protein.²⁶ During predominantly anaerobic activities²⁷ and during a high intensity interval training session,²⁸ circulating insulin concentrations do not decrease as markedly as in purely aerobic activities, in part because the duration of activity is typically shorter. High rates of external power output during high intensity interval training increase reliance on muscle phosphagens and glycogen, with lactate concentrations rising markedly in the circulation.²⁸ Insulin concentrations increase above baseline concentrations in early recovery from a high intensity interval training session to offset the rise in glucose caused by the elevations in counter-regulatory hormones and other metabolites.²⁷

Dysglycaemia during exercise in individuals with type 1 diabetes

In type 1 diabetes, the glycaemic responses to exercise are influenced by the location of insulin delivery, the amount of insulin in the circulation, the blood glucose concentration before exercise, the composition of the last meal or snack, as well as the intensity and duration of the activity²⁹ (figure 1).

During aerobic exercise, blood glucose concentrations fall [A: only drop? Or develop hypoglycaemia?] in most individuals with type 1 diabetes, unless they ingest carbohydrates, because insulin concentrations cannot be decreased rapidly enough at the start of the activity and might rise in the systemic circulation,³⁰ perhaps because of increased blood flow to subcutaneous adipose tissue during exercise.³¹ Even if basal insulin infusion rates are halved 60 min before the start of exercise in patients on continuous subcutaneous insulin infusion, circulating free insulin concentrations do not decrease upon commencement of exercise and concentrations tend to increase transiently during the activity.³² Increased

insulin concentrations in the circulation during exercise promote increased glucose disposal relative to hepatic glucose production, and might delay lipolysis—another feature that increases the reliance of muscles on glucose as a fuel. Hypoglycaemia develops in most patients [A: do references refer to children and adolescents only? If so, the term ‘patients’ may be too general] within about 45 min of starting aerobic exercise [A: OK as edited?].^{33,34} Trained individuals with type 1 diabetes have greater reductions in blood glucose concentrations during aerobic exercise than do individuals with reduced physical fitness,³⁵ possibly because the overall work rate is higher in those who are more aerobically conditioned than those who are not. As such, both trained and untrained individuals with type 1 diabetes typically require an increased carbohydrate intake [A: before commencing aerobic exercise?] or an insulin dose reduction, or both, [A: OK? Our style is to avoid the “and/or” contraction, and to replace with “and” or “or”] for prolonged aerobic exercise. High intensity interval sprint training promotes the increased oxidative capacity of skeletal muscle in type 1 diabetes and attenuates the rates of glycogen breakdown,³⁶ which might, in theory, protect against hypoglycaemia after exercise. Perhaps in line with this, individuals who are aerobically conditioned have lower glucose variability than do those who are unconditioned.³⁷ Low insulin concentrations due to aggressive reductions in insulin administration or a skipped insulin dose can cause hyperglycaemia before and during aerobic exercise,³⁸ and even mild activity could lead to development of ketosis.³⁹

Resistance exercise is associated with better glucose stability than continuous moderate intensity aerobic exercise,⁴⁰ although resistance exercise could cause a modest rise in glycaemia [A: addition OK?] in some individuals.⁴¹ Compared with aerobic exercise, a high intensity interval training session attenuates the decrease in glycaemia,⁴² as does resistance exercise done before aerobic exercise,⁴³ possibly because of increased concentrations of counter-regulatory hormones and various metabolites that restrict glucose disposal.⁴⁴ In situations of brief and intense anaerobic exercise (eg, sprinting, weight lifting, and some competitive sports),^{41,45} or during high intensity interval training,²⁸ glucose concentrations typically rise.

Dysglycaemia after exercise in individuals with type 1 diabetes
Glucose uptake into muscle decreases immediately after aerobic exercise, but overall glucose disposal remains elevated for several hours in recovery from exercise to help replenish glycogen stores.⁴⁶ The risk of hypoglycaemia is elevated for at least 24 h in recovery from exercise, with the greatest risk of nocturnal hypoglycaemia occurring after afternoon activity.⁴⁷ As mentioned above, weight lifting, sprinting, and intense aerobic exercise can promote increase in glycaemia that could last for hours in recovery. Although a conservative

Figure 1: Variability in blood glucose responses to different forms of exercise [A: in people with type 1 diabetes?]
High individual variability exists in the blood glucose responses to different form of exercise, as denoted by the arrows and grey shading. In general, aerobic exercise decreases glycaemia, anaerobic exercise increases glycaemia and mixed activities are associated with glucose stability. Individual responses are dependent on various additional factors, including the duration and intensity of the activity, initial blood glucose concentrations, individual fitness, concentrations of insulin, glucagon, and other counter-regulatory hormones in the circulation, and the nutritional status of the individual.

insulin correction after exercise might be prudent in some situations,⁴⁸ over-correction with insulin can cause severe nocturnal hypoglycaemia and lead to death.⁴⁹ High intensity interval training has been associated with a higher risk of nocturnal hypoglycaemia than continuous aerobic exercise in some⁵⁰—but not all—^{51,52} studies.

Exercise goals and glycaemic targets

Individuals with type 1 diabetes should engage in exercise for various health reasons. The evidence on whether regular exercise improves metabolic control in adults with type 1 diabetes is somewhat scarce,^{20,53} although exercise appears to be helpful in young people with type 1 diabetes.⁷ Exercise readiness questionnaires, such as Physical Activity Readiness Medical Examination (ePARmed-X+) and Physical Activity Readiness Questionnaire for Everyone (PAR-Q+), are available online for adults with diabetes who might be at increased risk of developing adverse events. Patient goals for exercise (eg, metabolic control, prevention of complications, fitness, weight loss, or competition and performance) should be considered before decisions on diabetes management are made. This is an important element of the diabetes management plan. For example, exercise for weight loss requires strategies that focus on reduction of insulin concentrations during and after exercise, as opposed to consumption of additional carbohydrates. By contrast, if maximisation of sports and exercise performance is the primary goal, then nutritional

For more on ePARmed-X+ and PAR-Q+ see <http://eparmedx.com>

Panel 1: Blood glucose concentrations before exercise commencement and recommended glucose management strategies

The carbohydrate intakes shown here aim to stabilise glycaemia at the start of exercise. Blood glucose at the start of exercise must also be viewed within a wider context. Factors to consider include directional trends in glucose and insulin concentrations, patient safety, and individual patient preferences based on experience. Carbohydrate intake will need to be higher if circulating insulin concentrations are high at the onset of exercise.

Starting glycaemia below target (<5 mmol/L)

- Ingest 10–20 g of glucose before starting exercise
- Delay exercise until blood glucose is more than 5 mmol/L (90 mg/dL) and monitor closely for hypoglycaemia

Starting glycaemia near target (5–6.9 mmol/L)

- Ingest 10 g of glucose before starting aerobic exercise
- Anaerobic exercise and high intensity interval training sessions can be started

Starting glycaemia at target levels (7–10 mmol/L)

- Aerobic exercise can be started
- Anaerobic exercise and high intensity interval training sessions can be started but glucose concentrations could increase

Starting glycaemia slightly above target (10.1–15.0 mmol/L)

- Aerobic exercise can be started
- Anaerobic exercise can be started but glucose concentrations could rise

Starting glycaemia above target (>15 mmol/L)

- If the hyperglycaemia is unexplained (not associated with a recent meal), check blood ketones. If ketones are modestly elevated (up to 1.4 mmol/L), exercise should be restricted to a light intensity for only a brief duration (<30 min) and a small corrective insulin dose might be needed before starting exercise. If blood ketones are elevated (≥ 1.5 mmol/L), exercise is contraindicated and glucose management should be initiated rapidly as per the advice of the health-care professional team.
- Mild to moderate aerobic exercise can be started if blood ketones are low (<0.6 mmol/L) or the urine ketone dipstick [A: correct?] is less than [A: what is this the equivalent of in mmol/L?] 2+. Blood glucose concentrations should be monitored during exercise to help detect whether glucose concentrations increase further. Intense exercise should be initiated only with caution as it could promote further hyperglycaemia

guidance specific to the sporting activity is needed and a modified insulin plan to match the increased nutritional requirements should be considered.⁵⁴ For all patients, blood glucose monitoring before, during, and after exercise is essential to inform strategies and maintain stable and safe glycaemia.

The appropriate blood glucose concentration at the start of exercise should be tailored to the individual. Based on consensus [A: whose consensus—the authors?], a reasonable starting range for most patients doing aerobic exercise lasting up to an hour is 7–10 mmol/L. This range balances performance considerations against the risk of hypoglycaemia. Concentrations higher than 7–10 mmol/L might be acceptable in some situations where added protection against hypoglycaemia is needed. Achieving and maintaining circulating glucose concentrations in this range is challenging. The glycaemic response to exercise is variable and based on several factors, including the

duration and intensity of exercise,^{44,55} the starting level of glycaemia,³⁴ the individual's aerobic fitness,³⁵ and the amount of insulin in circulation^{36,57} (figure 1). Anaerobic exercise and a high intensity interval training session can be initiated with a lower starting glucose concentration (5–7 mmol/L) because glucose concentrations tend to remain relatively stable and fall to a lesser extent than with continuous aerobic exercise, or rise slightly (figure 1). Strategies to cope with a range of glucose concentrations before the start of exercise are provided in panel 1, bearing in mind that for aerobic activities lasting longer than 30 min, additional carbohydrates are likely to be needed (table 1). If glucose concentrations are too high because of insulin omission, ketosis and further hyperglycaemia can occur,³⁹ and work effort [A: please clarify what is meant by “work effort”] probably increases. Although it is unclear if there is an optimal glycaemic range for exercise performance, clinical experience and data from a field study [A: in adolescents?]⁵⁸ suggest that maintenance of a concentration of about 6.0–8.0 mmol/L might be ideal.

Contraindications and cautions for exercise

Although few exercise restrictions should be placed on patients, some considerations are important, and are highlighted below.

Elevated ketones

Hyperglycaemia in conjunction with [A: addition ok?] elevated blood ketones (≥ 1.5 mmol/L) before a bout of exercise should be addressed before the start of the session via insulin administration or carbohydrate feeding, or both [A: edits OK, to avoid “and/or”?] (panel 1). The cause of elevated ketone concentrations should be identified (illness, diet manipulation, a recent bout of prolonged exercise, insulin omission, etc). Prolonged endurance type activities (eg, marathons and trekking) and diets very low in carbohydrate can elevate blood ketone concentrations in patients. The health-care professional should therefore define appropriate [A: are you referring to blood ketone levels here?] concentrations and provide tailored guidance for each individual. Blood ketone concentrations of 3.0 mmol/L or more should be managed immediately by a qualified health-care professional (eg, a hospital emergency department or physician).

Recent hypoglycaemia

Severe hypoglycaemia (defined here as blood glucose ≤ 2.8 mmol/L or a hypoglycaemic event requiring assistance from another individual) within the previous 24 h is a contraindication to exercise, because of the substantially increased risk of a more serious episode during exercise.⁵⁹ In situations where minor hypoglycaemia (blood glucose 2.9–3.9 mmol/L, with the ability to self-treat) has occurred, the increased risk of recurrence must be taken into account.⁶⁰ Vigilance

	Endurance exercise performance in athletes with and without diabetes	Hypoglycaemia prevention under low insulin conditions	Hypoglycaemia prevention under high insulin conditions
Meal (low fat, low glycaemic index) before exercise	A minimum of 1 g carbohydrate per kg body weight according to exercise intensity and type	A minimum of 1 g carbohydrate per kg body weight according to exercise intensity and type	A minimum of 1 g carbohydrate per kg body weight according to exercise intensity and type
Meal immediately [A: is this different from the low fat low GI meal timing?] before exercise (high glycaemic index)	No carbohydrate required for performance	If blood glucose concentration is less than 5 mmol/L, ingest 10–20 g carbohydrate	If blood glucose concentration is less than 5 mmol/L, ingest 20–30 g carbohydrate
Meal after exercise	1–1.2 g carbohydrate per kg body weight	Follow sports nutrition guidelines to maximise recovery with appropriate insulin adjustment for glycaemic management	Follow sports nutrition guidelines to maximise recovery with appropriate insulin adjustment for glycaemic management
Exercise (up to 30 min duration)	No carbohydrate required for performance	If blood glucose concentration is less than 5 mmol/L, ingest 10–20 g carbohydrate	Might require 15–30 g carbohydrate to prevent or treat hypoglycaemia
Exercise (30–60 min duration)	Small amounts of carbohydrate (10–15 g/h) could enhance performance	Low to moderate intensity exercise (aerobic): small amounts of carbohydrate (10–15 g/h) depending on exercise intensity and blood glucose concentration High intensity exercise (anaerobic): no carbohydrate required during exercise unless blood glucose concentration is less than 5 mmol/L; if so, ingest 10–20 g carbohydrate; replace carbohydrate needs after exercise	Might require up to 15–30 g carbohydrate every 30 min [A:OK?] to prevent hypoglycaemia
Exercise (60–150 min duration)	30–60 g carbohydrate per h	30–60 g carbohydrate per h to prevent hypoglycaemia and enhance performance	Up to 75 g carbohydrate per h to prevent hypoglycaemia and enhance performance*
Exercise (>150 min duration); mixture of carbohydrate sources	60–90 g carbohydrate per h spread across the activity (e.g. 20–30 g carbohydrate every 20 min) [A:OK?] Use carbohydrate sources that use different gut transporters (eg, glucose and fructose)	Follow sports nutrition guidelines (60–90 g/h) with appropriate insulin adjustment for glycaemic management	Follow sports nutrition guidelines (60–90 g/h) with appropriate insulin adjustment for glycaemic management

These guidelines are based on published studies,^{63,111,112} and on our own expert opinion. [A: OK — referring to your own (authors') opinions or to expert opinions of other authors? Pls clarify]

*Carbohydrate consumption at a high rate might cause gastric upset in some individuals and might contribute to hyperglycaemia during and after the activity. To increase the rate of carbohydrate absorption during exercise, and maintain hydration status, sports beverages containing glucose and fructose might be preferable. [A: what do the colours represent?]

Table 1: Carbohydrate requirements for endurance (aerobic) exercise performance and hypoglycaemia prevention

around monitoring should be stressed and exercise should be avoided if the setting is deemed particularly unsafe (eg, swimming or trekking alone).

Diabetes-related complications

Overall, the health benefits of being physically active outweigh the risks of being sedentary for people with diabetes. Those with complications can derive several health benefits from low intensity physical activities, with little risk of any adverse events.⁶¹ In individuals with long-standing disease or with HbA_{1c} concentrations well above the target, vigorous exercise, activities involving lifting of heavy weights, and competitive endurance events are contraindicated, particularly if the patient has unstable proliferative retinopathy, severe autonomic dysfunction, or renal failure.⁶¹

Inadequate preparation for exercise-associated hypoglycaemia

In preparation for exercise, individuals with type 1 diabetes should be aware of their starting glucose concentrations, and should also have blood glucose monitoring equipment and snacks to treat hypoglycaemia. They should also be advised to wear or carry some form of diabetes identification.

Nutritional management

Goals for nutritional management

³⁵ Nutritional management for people with type 1 diabetes should incorporate strategies that optimise glycaemic control while promoting long-term health.⁶² The main strategies around nutrition for exercise and sport discussed in this section primarily aim to maximise athletic performance and are based largely on studies done in highly trained healthy individuals without diabetes,⁶³ with few studies done in people with type 1 diabetes. Application of these strategies to people with type 1 diabetes must consider the individual's insulin management plan and include specific advice focused on nutrition for both athletic performance and glycaemic management. A registered dietitian with specialist diabetes and sports knowledge is the most qualified to help active people with type 1 diabetes.

⁵⁰ An individualised meal planning approach is central to improvement of performance and glycaemic outcomes. Daily carbohydrate intake should relate to the fuel cost of training in the athletic subpopulation and ensure prevention of hypoglycaemia for all active people. Balancing insulin dose to carbohydrate intake during exercise is essential. Various carbohydrate and insulin adjustment strategies can be used, such as reduction of

the pre-exercise bolus insulin dose by 30–50% up to 90 min before aerobic exercise,⁶⁴ consumption of carbohydrates with a high glycaemic index during sport (30–60 g/h), or replacement of carbohydrates after anaerobic exercise. Personal tolerance of ingested carbohydrate, particularly during exercise, is a key factor in tailoring of recommendations. The distribution of macronutrient intake over the day should take into account the timing of exercise so that liver and muscle glycogen stores are maximised before the activity and replenished in early recovery.⁶³ This strategy should include carbohydrate feeding well before exercise (~4 h) and early in recovery.^{63,65}

Daily energy and macronutrient balance

Athletes with type 1 diabetes need sufficient energy to meet the demands of their daily activities. These demands will vary with age, sex, body composition, and activity type.⁶⁶ Total energy requirements differ with individual aims. Predictive equations can be used to estimate resting energy expenditure;⁶⁷ however, they should serve only as a guide, as they could overestimate or underestimate actual requirements. An appropriate macronutrient balance and micronutrient intake,⁶³ coupled with a glycaemic control strategy, is required to maximise performance. The optimal macronutrient distribution will vary depending on the individualised assessment and exercise goals. A guide to the nutritional distribution of the total daily energy intake is as follows: 45–65% carbohydrate, 20–35% fat, and 10–35% protein,³⁰ with higher protein intakes indicated for individuals wanting to lose weight.⁶⁸

The major nutrients required to fuel performance are carbohydrates and lipids, while the addition of protein is needed to help foster recovery and maintain nitrogen balance.^{63,69} Protein requirements range from 1.2 to 1.6 g per kg body weight per day, and will vary with training type and intensity, and carbohydrate availability.^{63,70} Higher intakes might be needed for recovery from injury or for individuals on energy-restricted diets⁷¹ to maintain lean body mass.

Carbohydrate needs before, during, and after exercise

A distinction should be made between carbohydrate needs for performance and carbohydrate intake required for hypoglycaemia prevention (table 1). **[A: the first time a table, panel, or figure is mentioned in the text, any references in the table or figure that have not already been mentioned in the text should go into the reference list at that point, not at the end; refs 111 and 112 will therefore be moved here and cited after ref 71]** Carbohydrate requirements will alter insulin management strategies and vice versa. Most studies in type 1 diabetes have investigated the amount and distribution of carbohydrate required to prevent hypoglycaemia rather than to optimise performance, although the two might be at least partially related.^{34,64,72,73}

For example, although only 15–20 g/h of carbohydrate might be required to prevent hypoglycaemia in people who reduce their insulin concentrations in anticipation of exercise, this amount of carbohydrate could be insufficient for performance. Implementation of increased carbohydrate supplementation (up to 75 g/h) is possible for prolonged activity lasting longer than 2.5 hours (eg, marathons and other endurance type races) without having an adverse effect on glycaemia, as long as the insulin dose is titrated appropriately.⁵⁴ In general, carbohydrate requirements during shorter, intermittent, high-intensity, and anaerobic activities can be considerably decreased (table 1).

Nutritional needs for recovery

Nutrition requirements to maximise muscle recovery and muscle protein synthesis after exercise have been well studied in the athletic population without diabetes.⁷⁴ For replenishment of glycogen content after exercise, carbohydrate intake is essential.⁶³ For athletes with type 1 diabetes, rapid and adequate replenishment of muscle and liver glycogen stores is essential to help prevent late onset hypoglycaemia. Glycogen replacement strategies could also be important in prevention of euglycaemic ketosis in exercise recovery.⁷⁵ Ingestion of protein (~20–30 g) in addition to carbohydrate in the period after exercise is beneficial for muscle protein synthesis, but protein ingestion does not appear to facilitate glycogen replenishment in athletes who do not have diabetes.⁶³

Role of high and low glycaemic index foods for maintenance of euglycaemia

The glycaemic index of a carbohydrate-rich food can be used to assist with the selection of the carbohydrate type for exercise; sports drinks and energy gels with a high glycaemic index provide rapidly released carbohydrate to increase blood glucose concentrations during endurance events and **can [A: ok?]** treat hypoglycaemia. Consumption of foods with a low glycaemic index before exercise could sustain carbohydrate availability and maintain euglycaemia, whereas consumption of meals and snacks with a high glycaemic index after exercise could enhance recovery. Snacks with a low or moderate glycaemic index could also be preferred for long-distance activities such as trekking and long-distance cycling at low to moderate workloads. Consumption of a carbohydrate with a low glycaemic index (isomaltose) 2 hours before a high intensity run **in...** **[A: please describe study population]** showed better blood glucose responses during exercise than did consumption of a carbohydrate with a high glycaemic index (dextrose).⁷⁶ Consumption of a meal and **bedtime snack** with a low glycaemic index **[A: snack also low GI?]** after evening exercise **in...** **[A: please describe study population]** prevented postprandial hyperglycaemia **more effectively than [A: edit correct?]** a meal and **snack** with a high glycaemic index **[A: snack also high GI?]**, with both meal types being protective against hypoglycaemia for about 8 h.⁷⁷ The

protection provided by a snack was not sustained beyond 8 h, and the risk of hypoglycaemia remained high [A: for how long?].⁷⁷

Fluid replacement

Adequate fluid intake before, during, and after exercise is necessary for prevention of dehydration and optimisation of performance.⁶⁵ Water is the most effective drink for low-intensity and short-duration sports (ie, ≤ 45 min), as long as glucose concentrations are 7 mmol/L or higher. Sports beverages containing carbohydrate (6–8%) and electrolytes are useful for athletes with type 1 diabetes exercising for a longer duration; they are also useful as a hydration and fuel source for higher intensity exercise, and for prevention of hypoglycaemia.^{34,78} However, overconsumption of these beverages can result in hyperglycaemia. Milk-based drinks containing carbohydrate and protein can assist with recovery after exercise [A: correct?] and prevent delayed hypoglycaemia.⁷³

Low-carbohydrate high-fat diets and exercise

People with type 1 diabetes can choose a low carbohydrate high fat diet for various reasons. A review on low carbohydrate high fat diets and sports performance in individuals without type 1 diabetes concluded that, despite increasing the ability of muscles to utilise fat over time, no evidence was available to suggest performance benefits.⁷⁹ Long-term studies have yet to be done on the

health, glycaemia, or performance effects of low carbohydrate high fat diets in people with type 1 diabetes. A concern with these diets is that they could impair the capacity for high-intensity exercise.⁸⁰

Variation in carbohydrate intake (ie, periodisation throughout the training cycle according to fuel needs and performance) has been suggested by some researchers as a way to help promote adaptation of skeletal muscle to training.⁸¹ Additionally, various exercise-nutrient protocols are used to manipulate carbohydrate availability, such as training in a fasting state or withholding carbohydrate intake at a meal before or after exercise. These approaches have not been studied in individuals with type 1 diabetes, in whom manipulation of dietary carbohydrate as part of training presents unique challenges for insulin therapy and requires careful glucose monitoring.

Sports nutritional aids and type 1 diabetes

The use of ergogenic aids is a widespread performance enhancement strategy used by athletes, but little evidence is available on their use in athletes with type 1 diabetes.

Caffeine intake in athletes without diabetes has shown improvements in endurance capacity and power output.⁸² Caffeine intake (5–6 mg per kg body mass) before exercise attenuates decrease in glycaemia during exercise in individuals with type 1 diabetes, but it might increase the risk of late onset hypoglycaemia.⁸³

Figure 2: Decision tree for aerobic exercise and mixed aerobic and anaerobic activities lasting 30 min or longer in people with type 1 diabetes [A: correct?]

This decision tree can serve as a starting point for individuals with type 1 diabetes [A: correct?] planning to do aerobic exercise. *Mixed activities that include anaerobic bursts of exercise might require a lower carbohydrate intake or lower [A: OK?] insulin dose reductions than continuous moderate aerobic activities. †If both resistance and aerobic exercise are to be done, resistance exercise could be done first to help attenuate hypoglycaemia. ‡In some situations, such as... [A: please complete], increased carbohydrate feeding rather than insulin dose reduction might help improve endurance performance in prolonged activities. In other situations, both bolus and basal insulin dose reductions might be needed to help restrict or reduce carbohydrate intake. [A: OK as edited?] Continuous glucose monitoring could be considered where patient or parent preference dictates, or in individuals with a history of nocturnal or severe hypoglycaemia. CSII=continuous subcutaneous insulin infusion. [A: what does the red asterisk correspond to?]

Panel 2: Factors that to consider before adjustments are made for exercise in individuals with type 1 diabetes

Subcutaneous insulin injection and its adjustments

- Differences in the site and depth of insulin injection affect absorption characteristics^{113,114}
- Lipodystrophy can lead to... [A: please complete]
- Inadequate understanding [A:OK?] of insulin pharmacokinetics often leads to inappropriate insulin adjustments, including excessive insulin corrections (stacking), which could be particularly dangerous after exercise
- Rapid acting,³⁰ regular, and intermediate acting,^{115,116} but probably not long acting,¹¹⁷ insulin absorption rates are increased with exercise

Carbohydrate intake

- Variation in carbohydrate quantity (including inaccuracy in measurement of intake) and type will affect glycaemic excursions¹¹⁸

Self-monitoring of capillary blood glucose and continuous glucose monitoring

- Errors in self-monitored blood glucose sampling or measurement errors during self-monitoring or continuous glucose monitoring could result in inappropriate insulin dose estimations^{119,120}
- Although the accuracy of continuous glucose monitoring is improving, it can be compromised by poor accuracy in self-monitoring and calibrations methods¹²¹
- The lag time in continuous glucose monitoring could affect accuracy during exercise^{104,106}

Medications and alcohol

- Insulin sensitivity might be affected⁹⁹ as might glucose monitoring tools¹²⁰

Physiological cycles

- Diurnal endocrine variation, the menstrual cycle, and pregnancy affect insulin sensitivity and glycaemic patterns¹²²

Changes in work and sleep patterns

- Such changes require adjustments in timing of basal insulin dose administration
- The timing of exercise should be considered relative to insulin sensitivity and the risk of nocturnal hypoglycaemia⁴⁷

Intercurrent illness and stress

- Intercurrent illness or stress might necessitate changes in both basal and bolus insulin dose¹²³
- Vigorous exercise is contraindicated

Recommendations for management of glycaemia

Blood glucose responses to the various forms and intensities of exercise show high variability between and within individuals (figure 1). Glycaemic management is therefore based on frequent glucose monitoring, adjustments to both basal and bolus insulin dosing, and consumption of carbohydrates during and after exercise. These recommendations are intended to serve as a starting point for insulin adjustments and carbohydrate intake that can then be individualised (figure 2).

Clinical management strategies should be built around exercise types and individual aims, and implementation of these strategies should take into account the factors summarised in panel 2. Generally, sustained aerobic exercise requires more substantial reductions in insulin dose and [A: "and" OK?] a higher carbohydrate intake than a short-term high intensity interval training session.

By contrast, brief anaerobic exercise (eg, sprinting or weight lifting) could require increased insulin delivery, which is typically given in early recovery rather than before exercise for obvious safety reasons.⁴⁸ Strategies for insulin dose adjustments and [A: "and" OK?] carbohydrate intake during and after planned exercise are presented in table 2 and table 3. [A: citation to table 3 (previously table 5) added here so that first mention of table 3 is not within a non-text item. Refs 113–123 (in panel 2) and ref 124 (in table 2) will be cited after ref 83.]

Insulin adjustment for prolonged activities: bolus insulin approaches

Reductions in the bolus insulin dose accompanying [A: ok?] the meal before exercise and [A: "and" OK?] consumption of additional carbohydrate during exercise are typically needed to avoid hypoglycaemia during prolonged exercise (>30 min).^{34,55,64,84–86} Bolus dose reductions require planning in advance and are probably only appropriate for exercise with a predictable intensity performed within 2–3 h after a meal. As shown in table 3, the extent of a mealtime dose reduction is proportional to both the intensity and duration of the physical activity. This approach is safe and effective; even reducing the bolus insulin dose by as much as 75% does not appear to increase ketone production during exercise.⁸⁶

Another strategy is to combine a 75% reduction of the bolus insulin dose before exercise with ingestion of a snack or meal with a low glycaemic index.⁸⁷ This method also reduces the risk of hyperglycaemia before exercise. However, this approach will not protect against hypoglycaemia if the exercise is performed an hour or more after consumption of the snack.⁸⁷ As such, this combined approach might be preferable only for early [A: are you referring to time of day? Or exercise soon after a meal?] postprandial exercise.

Basal insulin approaches

Late postprandial hypoglycaemia (>4 h after a meal) following aerobic exercise is driven partly by circulating basal insulin concentrations. Elevated insulin sensitivity after exercise, and possibly a blunting of glucose counter-regulation, appear to place individuals at risk for at least 12 h. Reduction of circulating basal insulin concentrations can ameliorate this risk. For patients on multiple daily insulin injections, clinical observations and limited experimental data⁸⁸ show that reduction of long-acting basal (as well as prandial) insulin concentrations before exercise reduces the risk of hypoglycaemia during and after the activity, but might promote hyperglycaemia at other points during the day. Therefore, reduction in the basal insulin dose for patients on multiple daily insulin injections should not be routinely recommended but can be a therapeutic option for those engaging in considerably more planned activity than usual (eg, camps or tournaments). In general, basal insulins with a short half-life, such as NPH insulin or

	Prolonged endurance exercise (predominantly aerobic)	Brief intense exercise (aerobic and anaerobic)
Bolus insulin dose reduction at pre-exercise meal	Advised when exercise occurs within ~120 min of bolus dose; the magnitude of reduction varies according to timing, type, duration, and intensity of exercise	Bolus reduction not advised; might require additional conservative bolus dose correction if hyperglycaemia develops
Before exercise, basal insulin dose reduction (of ~20%) in patients on multiple daily injections	Useful especially if exercise is done less than every 3 days or if the frequency of exercise is high throughout the day; might also be useful if patients are on twice daily intermediate insulin	Basal insulin dose reduction not advised
Basal nocturnal insulin dose reduction (of ~20%) after exercise in patients on multiple daily injections and continuous subcutaneous insulin infusion to reduce the risk of nocturnal hypoglycaemia	Particularly important if the exercise was done in the afternoon or early evening	Useful for helping to prevent hypoglycaemia after a high intensity interval training exercise session
Temporary basal rate change (continuous subcutaneous insulin infusion)	Basal rate should be reduced to as low as total suspension of normal basal rate [A: please clarify] during exercise; to take into account rapid acting insulin pharmacokinetics, this basal rate reduction should ideally occur well before exercise is started (up to 90 min); normal basal rates can be resumed either at the end of exercise, or later in recovery depending on glucose trends	Increased basal rate might be needed to help prevent or treat hyperglycaemia either during or immediately after exercise
Carbohydrate intake before exercise	See table 1 for details	Not usually needed
Carbohydrate intake during exercise	Typically up to 60 g/h if no insulin dose adjustments have been made (see table 1 for additional information)	Not usually needed
Carbohydrate intake after exercise	Useful to reduce the risk of hypoglycaemia and improve recovery; might need a specified bolus insulin dose depending on the length and intensity of exercise (eg, a reduced insulin to carbohydrate ratio) [A:OK?]	Useful to reduce the risk of hypoglycaemia and enhance recovery but should be delayed if hyperglycaemia is initially observed; might need a specified bolus insulin strategy (eg, a reduced insulin to carbohydrate ratio)
Sprint before or after exercise	Might help reduce the risk of hypoglycaemia	Might increase the risk of hyperglycaemia; consider a prolonged aerobic cool down

Table 2: Therapeutic adjustment options (in insulin or food intake, or both) to minimise glycaemic excursions for prolonged aerobic exercise and brief high intensity aerobic and anaerobic exercise

insulin detemir, seem to lead to less hypoglycaemia in conjunction with exercise than do basal insulins with a longer half-life, such as insulin glargine,⁸⁹ although the mechanism through which this occurs is unclear. Although ultra-long-acting insulins (eg, insulin degludec, with a 25 h half-life) pose similar risks of hypoglycaemia with endurance exercise to those of insulin glargine,⁹⁰ dose reductions for exercise would have to be implemented at least 48 h before planned exercise. This is not recommended **[A: by the consensus authors?]**, as it would compromise overall **[A: glycaemic?]** control.

Continuous subcutaneous insulin infusion offers the flexibility to modify basal infusion delivery and obtain a quick effect (within ~1–2 h).⁹¹ Suspension of basal insulin infusion at the onset of 60 min exercise reduces the risk of hypoglycaemia during the activity, but it could increase the risk of hyperglycaemia after exercise.⁹² Moreover, glucose concentrations could still decrease by 2–3 mmol/L over 30–60 min even when basal insulin is dramatically reduced (or completely suspended),^{64,92,93} because of the lag time in the change in circulating insulin concentrations. Where practical, a basal rate reduction, rather than suspension, should be attempted 60–90 min before the start of exercise. An 80% basal reduction at the onset of exercise helps mitigate hyperglycaemia after exercise **more effectively [A: correct?]** than does basal insulin suspension, and appears to be associated with a reduced risk of hypoglycaemia both during and after the

	Exercise duration	
	30 min	60 min
Mild aerobic exercise (~25% VO ₂ max)	~25%*	~50%
Moderate aerobic exercise (~50% VO ₂ max)	~50%	~75%
Heavy aerobic exercise (70–75% VO ₂ max)	~75%	NA
Intense aerobic or anaerobic exercise (>80% VO ₂ max)	No reduction recommended	NA

Recommendations **[A: the authors?]** are based on published studies.^{31,55,72,124} NA=not assessed, since exercise intensity is typically too high to be sustained for 60 min for most individuals. *Estimated from the 60 min study. **[A: which ref does this correspond to?]**

Table 3: Suggested reduction in bolus insulin dose before exercise, based on intensity of exercise, for exercise started within 90 min of consumption of the meal

activity.⁶⁴ However, the optimal timing of basal rate reductions for aerobic and high intensity exercise activities and the maximal safe duration for insulin pump suspension have yet to be determined and remain open to debate. To limit the risk of compromised glycaemic control and ketosis, a time limit of less than 2 h is **proposed [A: by yourselves?]** on the basis of rapid-acting insulin pharmacokinetics.⁹¹

Hyperglycaemia commonly occurs in patients after intense exercise, particularly if insulin concentrations are reduced. Continuous subcutaneous insulin infusion seems to offer advantages over multiple daily insulin injections in the management of early onset⁹⁴ and late onset hypoglycaemia after exercise,⁹⁵ because of the

Search strategy and selection criteria

We searched PubMed and other relevant biomedical databases for articles containing the terms “type 1 diabetes” or “insulin-dependent diabetes” and “exercise” or “physical activity”, published between January, 1990 and July, 2016, [A: possible to give dates in the format “month, date, year”?] filtered for studies in human beings, and restricted to English language publications. Additional searches were done with the following terms for various subtopics within this Review: “nutrition”, “dietary carbohydrate”, “dietary protein”, “glycaemic index”, “hypoglycaemia”, “energy expenditure”, “glycaemic control”, “management”, “hypoglycaemia”, “hyperglycaemia”, or “prevention and control”.

increased flexibility around basal insulin adjustments. Overcorrection of hyperglycaemia after exercise via repeated insulin dose administration results in an increased risk of severe late onset hypoglycaemia, which could even be fatal.⁴⁹

Strategies to reduce the risk of late onset hypoglycaemia after exercise

Increased insulin sensitivity lasts up to 24–48 h following exercise.⁴⁶ Few studies have tested various nutrient or insulin dose adjustments to prevent hypoglycaemia after exercise. Nocturnal hypoglycaemia after exercise commonly occurs in individuals with type 1 diabetes,⁹⁶ with an increased risk after afternoon exercise.^{47,97} Immediate increases in insulin sensitivity after exercise can be addressed through a reduction of about 50% in the bolus insulin dose administered at meal after exercise, along with consumption of a snack with a low glycaemic index at bedtime.⁷⁷ In one study of 16 young people using an insulin pump, a temporary basal rate reduction of about 20% at bedtime for 6 h reduced the risk of nocturnal hypoglycaemia [A: OK as edited?].⁹⁵ Similarly, in another study of ten men on multiple daily insulin injections, a 20% basal rate reduction on the day of exercise along with provision of a free carbohydrate snack at bedtime (0.4 g carbohydrate per kg body mass) reduced the risk of nocturnal hypoglycaemia.⁸⁸ Individuals at high risk of severe nocturnal hypoglycaemia (eg, those with recurrent hypoglycaemia and those sleeping alone) should take additional preventive measures, including blood glucose checks at 0200 h or 0300 h, or the use of a real time continuous glucose monitoring system with alarms and automatic pump suspension.⁹⁸ Consumption of a snack alone, without changing basal insulin therapy, does not appear to entirely eliminate the risk of nocturnal hypoglycaemia,⁷⁷ and alcohol intake might increase the risk.⁹⁹

Emerging tools for exercise management

Several treatment regimens exist for people with type 1 diabetes. Continuous subcutaneous insulin infusion

offers better flexibility in basal insulin adjustments and management of exercise-associated hyperglycaemia than other methods of insulin delivery [A: comparator correct?].¹⁰⁰ Continuous subcutaneous insulin infusion is associated with reduced hyperglycaemia after exercise compared with multiple daily insulin injections,⁹⁴ but can create frustrating challenges for sports requiring disconnection of the insulin pump, for example... [A: please complete].¹⁰¹ Continuous subcutaneous insulin infusion could also contribute to a greater sense of being diseased and social stigma in some individuals by drawing undue attention to their condition [A: is there more stigma with CSII than MDI?].¹⁰¹ Prolonged disconnection of the pump (>60 min) should be managed by reconnecting, testing, and re-infusion of the pump if necessary, or by switching to basal insulin provision by needle. Continuous glucose monitoring provides comprehensive information on blood glucose concentrations, real-time trends, and rates of change, which can be used to prevent low concentrations during exercise,¹⁰² even in unique settings where self-monitoring of blood glucose is difficult.¹⁰³ Existing sensors are reasonably accurate for exercise,^{104,105} however, the lag time in glucose equilibrium with the interstitial space and the rapid turnover in glucose during exercise might affect accuracy (ie, overestimate blood glucose when concentrations are dropping and underestimate it when concentrations are rising).^{106,107}

Structured educational sessions can be implemented by downloading data on self-monitoring of blood glucose, continuous glucose monitoring, and continuous subcutaneous insulin infusion.¹⁰⁸ Continuous glucose monitoring systems now offer the option to add followers who can view glucose concentrations in real time and potentially alert the patient while they are playing sports. Threshold suspension of insulin delivery in continuous subcutaneous insulin infusion could offer additional protection against exercise-associated hypoglycaemia, according to some data.¹⁰⁹ The development of a fully artificial pancreas for exercise remains an elusive goal.¹¹⁰

Conclusion

Regular physical activity should be a routine objective for patients with type 1 diabetes, for various health and fitness reasons. Considerable challenges remain for people with type 1 diabetes, and their health-care team, in management of exercise and sports. Several small observational studies and a few clinical trials have been published to date that help to inform the consensus recommendations presented here. More studies are needed to determine how to best prevent exercise-associated hypoglycaemia with basal rate insulin dose adjustments and how to manage glycaemia in the recovery period after exercise. In general, aerobic exercise is associated with reductions in glycaemia, whereas anaerobic exercise might be associated with a transient increase in glucose concentrations. Both forms of exercise can cause delayed-onset hypoglycaemia in

recovery. A sound understanding of the physiology of different forms of exercise and the variables that can influence glycaemia during exercise and sport should underpin the implementation of safe and effective glycaemic management strategies. For aerobic exercise, reductions in insulin administration before the activity (ie, reductions in basal or bolus insulin, or both) can help ameliorate the risk of hypoglycaemia, as can increasing carbohydrate intake to 60 g per h or more. For anaerobic exercise, conservative insulin dose corrections might be required, although this too might increase the risk of nocturnal hypoglycaemia, particularly if the exercise is performed late in the day. In all instances, additional vigilance around glucose monitoring is needed before, during, and after the physical activity.

Contributors

The literature search was done by MCR, IWG, and CES. All authors (MCR, IWG, CES, CET, PA, ANL, AK, RRL, RM, CH, FA, PAF, CG, BB, PG, TWJ, ISM, TH, APete, APetz, and LML) contributed to the original draft of the manuscript. MCR, FA, and CES edited the revised manuscript. All authors approved the final submission. [A: statement OK?]

Declaration of interests

MCR has received personal fees from Medtronic Diabetes, Lilly, Ascensia Diabetes Care, and Insulet Corporation. CET has received personal fees from the Juvenile Diabetes Research Foundation (JDRF). PA has received personal fees from Abbott, Dexcom, Lilly, Medtronic, Nordic Infucare, Novo Nordisk, Roche, and Sanofi. He has also been a participant on advisory boards for Abbott, Lilly, and Roche during the course of this work. [A:OK?] ANL has received speaking fees from Novo Nordisk, Sanofi, Animas, Eli Lilly, and MSD, and is on the advisory board of Animas. [A:OK?] RR-L has received grants and personal fees from Astra Zeneca, consultancy fees from Boehringer Ingelheim, grants and personal fees from Eli Lilly, grants from Merck, Novo-Nordisk, and Sanofi-Aventis, and personal fees from Medtronic and Takeda. [A:OK?] RM has received personal fees from Novo Nordisk and Sanofi, and is on the advisory boards of both companies. [A:OK?] FA has received registration fees from Novo Nordisk and personal fees from JDRF Peak Program. CG is employed by Dexcom, Inc. BB has received grants and personal fees from Medtronic Diabetes, Novo Nordisk, Sanofi, Janssen, and Lilly, personal fees from Insulet Corporation and Astra Zeneca, and grants from Abbott and DexCom. TH has received grants from Adocia, AstraZeneca, Becton Dickinson, Biocon, Boehringer Ingelheim, Dance Pharmaceuticals, Grünenthal, Gulf Pharmaceuticals, Johnson & Johnson, Marvel, MedImmune, Medtronic, Novartis, Roche Diagnostics, Sanofi, Senseonics, and Zealand Pharma; grants, personal fees, and non-financial support from Eli Lilly and Novo Nordisk, and personal fees from Mylan. APete has received consulting and speaking fees from Abbott Diabetes Care, Becton Dickinson, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Lexicon, Medscape, Merck, Novo Nordisk, Omada Health, OptumRx, Roche, and Sanofi, research grants from Dexcom, and editorial fees from Medscape. [A:OK?] All other authors declare no competing interests. [A: please ensure this statement matches the information provided on your ICMJE forms. Awaiting disclosure statements from CES, CH, ISM, APetz, and LML.]

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