

The Decline in Blood Glucose Levels Is Less With Intermittent High-Intensity Compared With Moderate Exercise in Individuals With Type 1 Diabetes

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OBJECTIVE — To compare the response of blood glucose levels to intermittent high-intensity exercise (IHE) and moderate-intensity exercise (MOD) in individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Seven healthy individuals with type 1 diabetes were tested on two separate occasions, during which either a 30-min MOD or IHE protocol was performed. MOD consisted of continuous exercise at 40% VO_{2peak} , while the IHE protocol involved a combination of continuous exercise at 40% VO_{2peak} interspersed with 4-s sprints performed every 2 min to simulate the activity patterns of team sports.

RESULTS — Both exercise protocols resulted in a decline in blood glucose levels. However, the decline was greater with MOD (-4.4 ± 1.2 mmol/l) compared with IHE (-2.9 ± 0.8 mmol/l; $P < 0.05$), despite the performance of a greater amount of total work with IHE ($P < 0.05$). During 60 min of recovery from exercise, glucose levels remained higher in IHE compared with MOD ($P < 0.05$). Furthermore, glucose levels remained stable during recovery from IHE, while they continued to decrease after MOD ($P < 0.05$). The stabilization of blood glucose levels with IHE was associated with elevated levels of lactate, catecholamines, and growth hormone during early recovery from exercise ($P < 0.05$). There were no differences in free insulin, glucagon, cortisol, or free fatty acids between MOD and IHE.

CONCLUSIONS — The decline in blood glucose levels is less with IHE compared with MOD during both exercise and recovery in individuals with type 1 diabetes.

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Exercise is generally recommended for individuals with type 1 diabetes for the same reasons as the rest of the population. That is, regular physical activity has physiological benefits, including improved physical work capacity, body composition, blood pressure, and

blood lipid profile (1–3) and is associated with less risk of diabetes complications and mortality in individuals with type 1 diabetes (4). In addition, exercise has psychological benefits, including increased sense of well-being, quality of life, and ability to cope with stress (3). Particularly

in children, participation in sports is an important recreational and social activity that benefits both social interaction and peer group assimilation (5).

Unfortunately, participation in exercise can also increase the risk of experiencing hypoglycemia in individuals with type 1 diabetes, both during exercise (6,7) and for up to 31 h of recovery (8). Consequently, many individuals with type 1 diabetes feel negatively toward physical activity (9) and are discouraged from participating in sports and games by their parents, school staff, or physicians (10).

Existing guidelines to minimize the risk of hypoglycemia associated with exercise are often general (11) and fail to take into account that different precautions are required for exercise of varying type, duration, and intensity. Specifically, there are no evidence-based guidelines for individuals wanting to participate in intermittent high-intensity exercise (IHE), a type of activity involving short repeated bouts of intense activity interrupting longer periods of low- to moderate-intensity exercise (MOD) or rest. This is unfortunate given that this type of activity is typical of most team and field sports (12–14) and also of spontaneous play in children (15). Furthermore, it has been suggested that managing blood glucose levels during this type of activity is more difficult compared with continuous or prolonged efforts (16).

The lack of adequate guidelines for managing blood glucose levels during IHE can be attributed to little research on this type of exercise in individuals with type 1 diabetes. Recently, we examined for the first time the response of blood glucose levels to IHE that simulates the activity patterns of team sports in individuals with type 1 diabetes (17). However, the recovery between the high-intensity exercise bouts in this study was passive, while in the field intense bursts of high-intensity activity are often interspersed by periods of lower-intensity activity (12–

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Abbreviations: FFA, free fatty acid; IHE, intermittent high-intensity exercise; MOD, moderate-intensity exercise.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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14). For these reasons, it was the purpose of the current study to investigate the response of blood glucose and glucoregulatory hormones to IHE with active recovery (MOD) between high-intensity bouts. In addition, our goal was to compare the glucoregulatory response to IHE with that of MOD alone. This should assist in the development of improved guidelines to allow individuals with type 1 diabetes to safely enjoy the benefits of regular physical activity.

RESEARCH DESIGN AND METHODS

Seven healthy physically active male ($n = 4$) and female ($n = 3$) volunteers with type 1 diabetes (aged 21.6 ± 4.0 years, BMI 24.7 ± 3.5 kg/m², peak oxygen uptake (VO_{2peak}) 39.3 ± 7.4 ml · kg⁻¹ · min⁻¹, type 1 diabetes duration 8.6 ± 5.0 years [means \pm SD]) were informed of the purpose of the study and the possible risks associated with exercise and blood sampling. These individuals gave informed consent in accordance with both the University of Western Australia and Princess Margaret Hospital Human Ethics Committees, which approved the study. Six of the participants were on a multiple injection regime consisting of short-acting insulin given before each meal and intermediate-acting insulin at bedtime. The other participant was on a twice-daily regime with short- and intermediate-acting insulin administered before breakfast and dinner. All participants were in moderate glycemic control (HbA_{1c} $7.4 \pm 1.5\%$), free of complications, and not taking any prescribed medication other than insulin, and female participants were regularly menstruating.

The participants visited the exercise physiology laboratory at the University of Western Australia on three occasions, each separated by at least 1 week. First, they attended a familiarization session, during which anthropometric measurements, determination of VO_{2peak} , and familiarization with the IHE and MOD protocols were performed. This visit was followed by either an MOD or IHE trial administered in a randomized counter-balanced order. Participants were instructed to consume a similar diet and avoid caffeine, alcohol, and physical activity in the 24 h before all testing sessions. In addition, testing was rescheduled if a participant experienced an episode of hypoglycemia in the 48 h before testing. All female participants

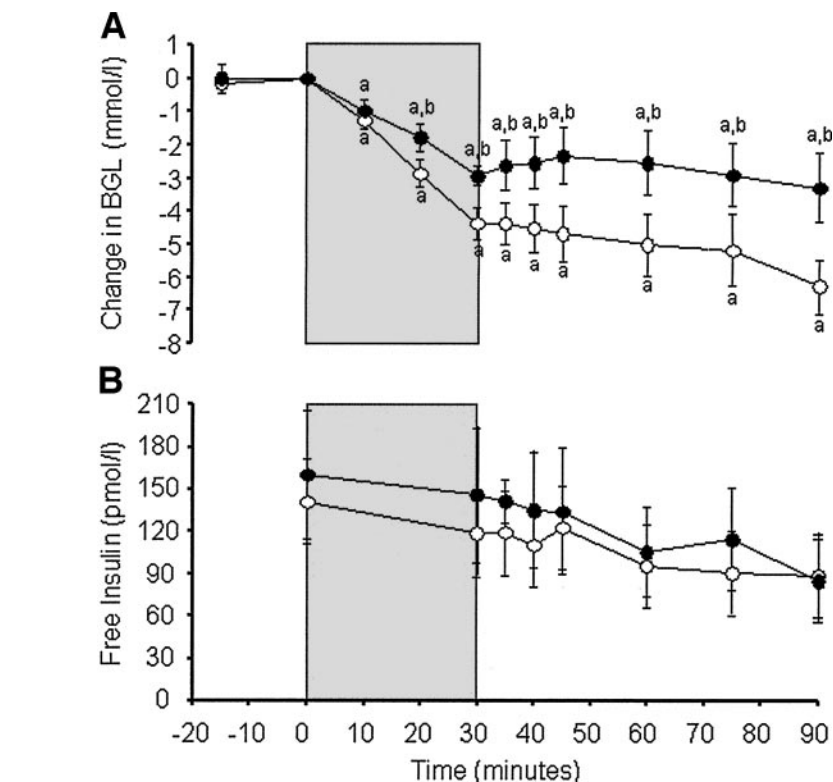


Figure 1—Effect of 30 min (represented by box) of IHE (■) or MOD (□) on normalized blood glucose levels (A) and free insulin levels (B). Results are expressed as means \pm SE. ^aStatistically significant difference ($P < 0.05$) from resting. ^bStatistically significant difference ($P < 0.05$) between IHE and MOD.

were tested during the follicular phase of the menstrual cycle (days 4–12), with \sim 1 month between trials.

At 8:00 A.M. on MOD and IHE trial days, the participants self-injected their usual morning short- or rapid-acting insulin into the abdomen (mean dose 14.8 ± 7.5 units), with the one patient on a twice-daily regime self-administering both rapid- and intermediate-acting insulin as per normal. Thus, insulin dosage was the same for both trials. Following this, all participants consumed their typical breakfast, which was standardized to be identical on both visits. No adjustments in insulin dose or food intake from the participant's usual morning routine were made in anticipation of exercise or to adjust for preprandial glucose levels. A 21-gauge cannula (BD Insyte) was then inserted into an antecubital vein and kept patent with regular infusion of 0.9% saline. At the same time, fentanyl cream (Boehringer Ingelheim) was placed on one earlobe for \sim 5 min before being wiped off to induce hyperemia, after which capillary blood (35μ l) was sampled every 15 min for the determination

of blood glucose levels. Collection of each sample involved sterilizing the earlobe with an alcohol swab before perforating the skin using an Accu-Chek Softclix lancet device (Roche Diagnostics, Castle Hill, Australia).

The MOD or IHE protocols were commenced \sim 3.5 h (215 ± 30 vs. 208 ± 18 min; MOD vs. IHE; $P = 0.305$) after insulin injection and at a blood glucose level of \sim 11 mmol/l. This value was selected to represent a typical “real-life” pre-exercise glucose level. However, six of the participants were administered additional carbohydrate supplementation in the form of oral polycose (Abbott Laboratories) to achieve this desired blood glucose level at the appropriate time. There was no difference in polycose administration between trials (1.5 ± 1.6 vs. 1.5 ± 2.1 portions of carbohydrate; MOD vs. IHE; $P = 1.000$).

Before exercise, 15 ml of venous blood was sampled for baseline measurements, and either the MOD or IHE protocol was commenced. The MOD protocol consisted of 30 min of continuous exercise at 40% VO_{2peak} performed on a Front

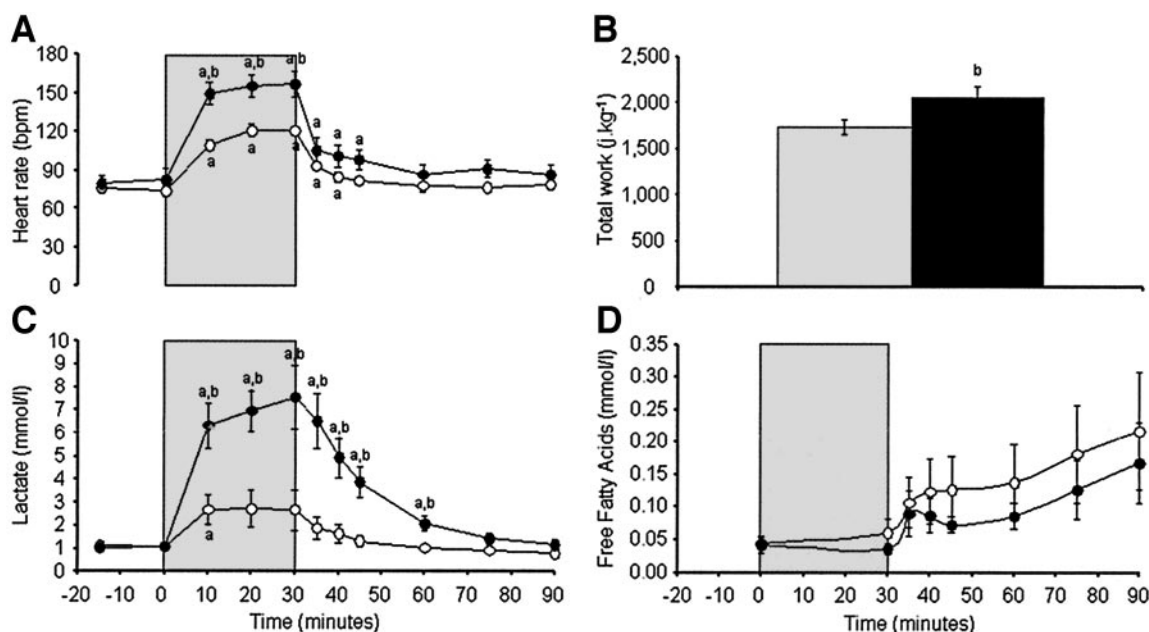


Figure 2—Effect of 30 min (represented by box) of IHE (■) or MOD (□) on heart rate (A), total work (B), lactate (C), and FFA (D) levels. Results are expressed as means \pm SE. ^aStatistically significant difference ($P < 0.05$) from resting. ^bStatistically significant difference ($P < 0.05$) between IHE and MOD.

Access Cycle Ergometer (RepcO, Melbourne, Australia) to simulate the intensity of a light jog. The IHE protocol also involved a continuous cycling exercise at 40% $\dot{V}O_{2peak}$, but this was interspersed with additional 4-s maximal sprint efforts performed every 2 min to simulate the activity patterns of team sports (16 sprints in total). The duration of the high-intensity bouts and recovery was based on time-motion analyses of various field sports (12–14) and of spontaneous play in children (15). During both 30-min exercise protocols, capillary blood (35 μ l) was sampled at 10-min intervals for determination of blood glucose and lactate. On completion of the MOD or IHE protocol, both venous (15 ml) and capillary blood (35 μ l) were sampled at 0, 5, 10, 15, 30, 45, and 60 min of recovery or until blood glucose declined to 4 mmol/l, in which case the experiment was ended, and the participants were fed to prevent the occurrence of hypoglycemia.

Measurement of metabolites

Capillary blood was used to measure blood glucose and lactate using an ABL 625 Blood Gas System (Radiometer, Copenhagen, Denmark), while venous blood was used to determine free insulin, free fatty acids (FFAs), glucagon, growth hormone, cortisol, and catecholamines. Heparinized plasma treated with polyeth-

ylene glycol was assayed for free insulin (Coat-a-Count Insulin Kit; Diagnostic Products), while FFAs were measured in EDTA-treated plasma (Roche Half Micro Test Free Fatty Acids Assay Kit; Roche Diagnostics, Mannheim, Germany). Glucagon was assayed from EDTA-treated plasma collected with trasylol (Bayer Pharmaceuticals) (Linco Glucagon RIA Kit; Linco Research), while growth hormone and cortisol were determined from venous serum (Immulate Growth Hormone and Cortisol Assay Kits; Diagnostic Products). Catecholamine levels were determined via reverse-phase high-performance liquid chromatography using a Waters Novapak C18 reverse-phase column and a model 5200A Coulochem detector (ESA Biosciences) on heparinized plasma treated with sodium metabisulphite.

Statistical analyses

Data were analyzed using two-way (time \times trial) repeated-measures ANOVA and paired-samples *t* tests to determine where the differences lay using SPSS 11.0 for Windows computer software package. Statistical significance was accepted at the $P < 0.05$ level. Data are expressed as means \pm SD when referred to in the text and as means \pm SE in all figures.

RESULTS

Response of blood glucose to MOD and IHE

Mean blood glucose level immediately before exercise was 11.0 ± 2.3 and 11.5 ± 3.9 mmol/l in MOD and IHE trials, respectively ($P = 0.636$), and blood glucose results were normalized relative to these starting levels (Fig. 1A). Both exercise protocols resulted in a decline in blood glucose levels; however, the decline was greater with MOD (-4.4 ± 1.2 mmol/l) compared with IHE (-2.9 ± 0.8 mmol/l; $P = 0.006$). During the subsequent 60 min of recovery, blood glucose levels remained stable following IHE ($P = 0.378$), while they continued to decrease following MOD ($P = 0.009$). After the completion of both trials, blood glucose had declined a total of 6.3 ± 1.8 and 3.3 ± 2.6 mmol/l for the MOD and IHE, respectively ($P = 0.021$). On three occasions (during one IHE and two MOD trials), in two separate individuals, blood glucose levels declined to <4 mmol/l. There was no difference in free insulin levels between trials at any time point (Fig. 1B; $P = 0.677$).

Heart rate and total work response to MOD and IHE

Heart rate increased in response to both exercise protocols; however, the increase

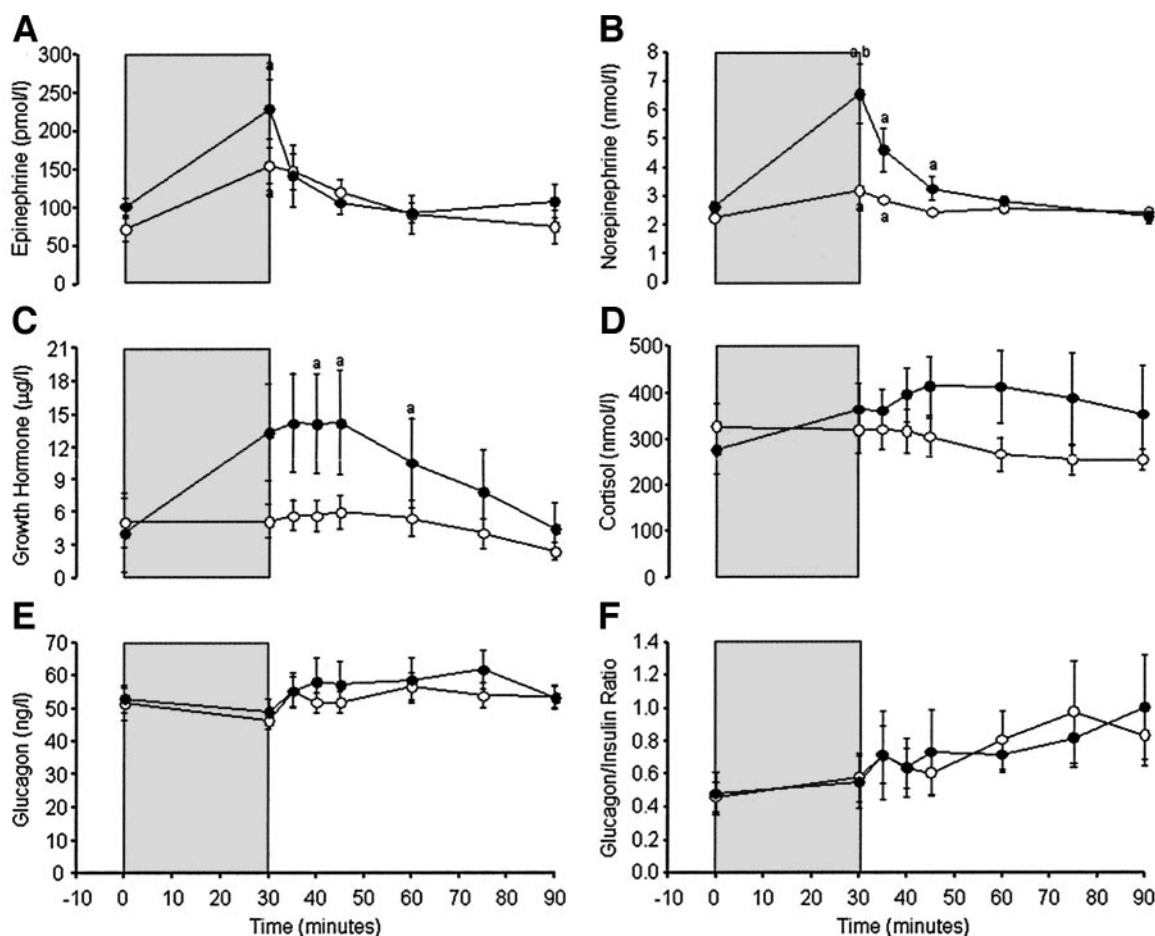


Figure 3—Effect of 30 min (represented by box) of IHE (■) or MOD (□) on epinephrine (A), norepinephrine (B), growth hormone (C), cortisol (D), glucagon (E), and the glucagon-to-insulin ratio (F). Results are expressed as means \pm SE. ^aStatistically significant difference ($P < 0.05$) from resting. ^bStatistically significant difference ($P < 0.05$) between IHE and MOD.

was greater with IHE compared with MOD ($P = 0.002$; Fig. 2A). The higher heart rate with IHE was associated with greater total work performed during the IHE protocol compared with MOD ($P = 0.011$; Fig. 2B).

Blood lactate and FFA response to MOD and IHE

Blood lactate increased from resting levels in response to both exercise protocols. However, the increase was greater with IHE compared with MOD ($P = 0.011$; Fig. 2C). In contrast, the levels of circulating FFAs were not different between MOD and IHE (Fig. 2D).

Glucoregulatory response to MOD and IHE

Both epinephrine (Fig. 3A) and norepinephrine (Fig. 3B) levels were increased in response to exercise, with the increase in norepinephrine being greater with IHE

than MOD ($P = 0.001$). Similarly, growth hormone levels increased in response to IHE ($P = 0.022$; Fig. 3C). In contrast, cortisol (Fig. 3D), glucagon (Fig. 3E), and the ratio of glucagon to insulin (Fig. 3F) were not altered in response to MOD or IHE, and there was no difference between trials.

CONCLUSIONS— This study compared the response of blood glucose and glucoregulatory hormones to MOD and IHE that simulates the high-intensity work-to-recovery ratios observed in intermittent sports in individuals with type 1 diabetes. The experiment was designed to reproduce a “real-life” situation in which insulin is injected and food is consumed as per normal before exercise. This study shows for the first time that under these conditions, the decline in blood glucose levels is less with IHE compared with MOD during both exercise and early recovery. The lesser decline in blood glu-

cose levels occurred despite a higher heart rate and greater total work performed during the IHE trial. This observation has implications for safe participation in exercise by individuals with type 1 diabetes, with a greater decline in blood glucose levels, suggesting that the risk of hypoglycemia may be increased with MOD compared with IHE. This is an important observation, since many individuals with type 1 diabetes are discouraged from engaging in vigorous exercise because of a fear of exercise-induced hypoglycemia (10).

There are relatively few guidelines to assist individuals with type 1 diabetes in managing the risk of exercise-induced hypoglycemia. Existing guidelines are often general and emphasize an individualized trial-and-error approach to adjusting insulin dosage and carbohydrate intake based on the patient’s own blood glucose response to exercise (11). However, the American Diabetes Association position

statement on physical activity/exercise and diabetes (11) also states that avoiding exercise-induced hypoglycemia requires an understanding of the metabolic and hormonal responses to exercise. But until recently, the blood glucose response to IHE that simulates the high-intensity work-to-recovery ratios observed in team and field sports was not known (17). Before this, research on intermittent exercise (18,19) was limited by the use of exercise protocols that do not accurately reflect the intermittent nature of most sports activities and spontaneous play in children, in which the high-intensity intervals are of much shorter duration (2–4 s) (12–15). Consequently, there are no evidence-based guidelines for safe participation in IHE that accounts for much of the physical activity played by children and adolescents with type 1 diabetes (9,20). In addition, current general guidelines often do not distinguish between continuous and intermittent exercise and may recommend similar strategies to manage blood glucose levels for these distinct types of activities. For instance, Birrer and Sedaghat (21) recommend a similar reduction in insulin and increase in carbohydrate supplementation for intermittent activities such as soccer and basketball as they recommend for more continuous activities like jogging and cycling. Similarly, Peirce (22) suggests that the appropriate reduction of insulin before vigorous team sports like football and hockey should be more pronounced than for moderate exercise and may be similar to that required for intense prolonged exercise including marathons or triathlons. These non-evidence-based recommendations for minimizing the risk of exercise-induced hypoglycemia are not supported by our present findings.

The smaller decline in blood glucose levels with IHE compared with MOD during both exercise and early recovery is most likely attributed to the repeated bouts of high-intensity exercise, which stimulate a metabolic and hormonal response that would be expected to be antagonistic to declining blood glucose levels (17). First, the elevated lactate levels compared with MOD may contribute to attenuating the decline in blood glucose levels during IHE and early recovery by inhibiting the action of insulin on peripheral glucose uptake in skeletal muscle (23) and supporting the production of glucose via hepatic gluconeogenesis (24).

In addition, the increase in catecholamine levels in response to IHE would likely stimulate increased hepatic glucose production (25) and at the same time inhibit insulin-mediated glucose uptake (26). Elevated levels of growth hormone would further support the inhibition of insulin-mediated glucose uptake following IHE (27). In contrast, FFAs and other glucoregulatory hormones such as glucagon and cortisol are unlikely to contribute to the lesser decline in blood glucose with IHE compared with MOD, since there was no difference in their response to the two exercise protocols.

In summary, we have found that participation in 30 min of IHE compared with MOD is associated with a smaller decline in blood glucose levels both during exercise and for the 1st h of recovery, despite being more total work. The attenuated decline in blood glucose levels with IHE is most likely attributed to the repeated bouts of high-intensity exercise, which stimulate an increase in catecholamine and growth hormone levels. Consequently, an additional practical implication of our results is that the decline in blood glucose levels associated with MOD, such as a light jogging or cycling, may be reduced if this type of exercise is interspersed with several short high-intensity bouts of activity. Caution should be taken, however, against the generalization of these findings to all types of IHE, since typical team games may last for up to 90 min, and the risk of late-onset postexercise hypoglycemia has not yet been investigated. In addition, varied work-to-recovery ratios may elicit a different blood glucose response. Clearly, further research of the kind described here is required for the development of more detailed evidence-based guidelines to allow individuals with type 1 diabetes to safely enjoy the benefits of regular physical activity.

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