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TITLE: The effect of midday moderate-intensity exercise on post-exercise hypoglycemia risk in individuals with type 1 diabetes

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Exercise increases the risk of hypoglycemia in type 1 diabetes.

Objective Recently, we reported a biphasic increase in glucose requirements to maintain euglycemia following late afternoon exercise, suggesting a unique pattern of delayed risk for nocturnal hypoglycemia. This study examined whether this pattern of glucose requirements occurs if exercise is performed earlier in the day.

Design, Participants and Intervention Ten adolescents with type 1 diabetes underwent a hyperinsulinemic euglycemic glucose clamp on two different occasions during which they either rested or performed 45 minutes of moderate-intensity exercise at midday. Glucose was infused to maintain euglycemia for 17 hours post-exercise.

Main Outcome Measures Glucose infusion rate (GIR) to maintain euglycemia, glucose rates of appearance (Ra) and disappearance (Rd), and levels of counterregulatory hormones were compared between conditions.

Results GIRs to maintain euglycemia were not significantly different between groups at baseline (9.8 ± 1.4 and 9.5 ± 1.6 g/hr before the exercise and rest conditions, respectively) and did not change in the rest condition throughout the study. In contrast, GIR increased more than 3-fold during exercise (from 9.8 ± 1.4 to 30.6 ± 4.7 g/hr), fell within the first hour of recovery, but remained elevated until 11 hours post-exercise before returning to baseline levels.

Conclusions The pattern of glucose requirements to maintain euglycemia in response to moderate-intensity exercise performed at midday suggests that the risk of exercise-mediated hypoglycemia increases during and for several hours after moderate-intensity exercise, with no evidence of a biphasic pattern of post-exercise risk of hypoglycemia.
Participation in regular physical activity is recommended for individuals with type 1 diabetes mellitus (T1DM) because of its many health benefits (1-3). Unfortunately, exercise increases the risk of hypoglycemia and associated adverse outcomes including seizures, coma and irreversible brain dysfunction and damage (4,5). A further complication of exercise-mediated hypoglycemia is that this risk occurs not only during exercise, but also for up to 31 hours post-exercise (6,7). This late onset post-exercise hypoglycemia (LOPEH) is particularly concerning during nighttime as there is a significantly higher incidence of overnight hypoglycemia following 75 minutes of afternoon exercise (26%) compared to afternoon rest (6%; p<0.05; 8). Furthermore, the use of continuous glucose monitoring technology reveals that this high risk for nocturnal hypoglycemia following exercise may be related to the intensity of exercise (9).

The mechanisms underlying LOPEH are multifactorial and include impaired counterregulation following exercise (6,10) that may be further compromised during sleep (11), as well as an increase in glucose uptake by skeletal muscle to replenish glycogen stores and a rise in insulin sensitivity (6,12). These latter two factors contribute to increasing the risk of LOPEH by increasing the amount of exogenous glucose required to maintain euglycemia.

Previously, we have shown that the exogenous glucose requirements to maintain euglycemia in individuals with T1DM increase during and shortly following afternoon exercise, and again early during night time (7-11 hours post-exercise), but with no increase in glucose requirements during the 2-7 hour recovery period (7). This biphasic response in glucose requirements suggests a unique pattern of delayed risk for nocturnal hypoglycemia. It is not clear, however, whether the increase in glucose requirements at night is related to sleep and whether this would occur if exercise was performed earlier in the day. This information is important for the design of guidelines aimed at helping people with T1DM to enjoy the benefits of regular physical activity without the concern of hypoglycemia. For this reason, the aim of this study was to determine the effect of midday moderate-intensity exercise on the pattern of post-exercise exogenous glucose requirements in individuals with T1DM.
Methods

Participants
Ten adolescents (9 males, 1 female) aged 15.9 ± 1.1 years (mean ± SD), with a duration of clinically diagnosed T1DM of 6.3 ± 3.5 years, glycated haemoglobin of 8.4 ± 2.1%, BMI of 22.2 ± 3.2 kg/m², and \( \dot{V}\text{O}_{2}\text{peak} \) of 43.3 ± 7.3 ml kg\(^{-1}\) min\(^{-1}\) were recruited to this study. All participants were free from diabetes complications, had undetectable levels of c-peptide and were hypoglycemia aware. The participants were not taking any medications other than insulin and their insulin regimens were stable prior to the study. The study was approved by the Princess Margaret Hospital Ethics Committee, and informed consent was obtained from the participants prior to their involvement.

Experimental procedures
Following a familiarization session where anthropometric measures, \( \dot{V}\text{O}_{2}\text{peak} \) and lactate threshold were determined as described previously (7), the participants attended the laboratory on two further occasions during which they performed either 45 minutes of moderate-intensity exercise or rest. All participants completed both conditions following a randomised, counterbalanced study design, with the female participant studied in the follicular phase of her menstrual cycle. Testing was rescheduled if the participants experienced an episode of hypoglycemia 48 hours prior to each study, and they were required to abstain from any physical activity other than light walking 24 hours before each study, since both antecedent hypoglycemia (13) and antecedent exercise (10) reduce key glucoregulatory responses to subsequent moderate-intensity exercise. To ensure that the diet was matched between studies, the participants were required to keep a food diary for 24 hours prior to their first study and then match their food intake the day before their second study.

On the morning of testing, each participant arrived in the laboratory at 0700 h where a cannula was inserted into a vein in the dorsum of one hand for sampling blood. This hand was placed in a HotBox
(Omega CN370) at ~60°C to arterialise venous blood prior to sampling. Another cannula was inserted into a vein in the contralateral antecubital fossa for infusion of glucose and insulin. Insulin was infused at a constant rate and at a dose based on 50% of the participants usual daily dose to match the conditions adopted by McMahon and colleagues (7). Blood glucose level was maintained at 5-6 mmol/L for the duration of the studies by varying the infusion rate of a 20% (wt/vol) dextrose solution. The adjustments to the infusion rate of dextrose were guided by blood glucose measurements obtained every 15 minutes. At 8:00 am, each participant was provided with a standardised breakfast and given a bolus of intravenous insulin based on the amount of carbohydrate consumed. The participants fasted for the remainder of the study. At approximately 9:00 am, a blood sample was drawn for the determination of background enrichment of [6,6-$^2$H]glucose. Thereafter, the infusion of [6,6-$^2$H]glucose commenced with a priming bolus of 3mg/kg and a constant infusion of 2.4 mg/kg/hr that continued for the duration of the experiment to measure glucose rate of appearance (Ra) and disappearance (Rd). In addition, the variable infusion of dextrose was “spiked” with [6,6-$^2$H]glucose (2.48 mg/ml) to minimise the changes in the isotopic enrichment of plasma glucose in response to adjustments in dextrose infusion rate to maintain euglycemia (14). The infusion of [6,6-$^2$H]glucose continued for at least 150 minutes prior to the commencement of exercise. Following this, blood samples were collected for baseline measurements of glucoregulatory hormones, metabolites, and [6,6-$^2$H]glucose enrichment.

At ~1200 h, the participants either exercised for 45 minutes on a cycle ergometer (Repco) at 95% of their lactate threshold (corresponding to 63.6 ± 10.6% $\dot{V}O_2$peak) to match the conditions adopted by McMahon and colleagues (7) or sat on the ergometer without pedalling. During exercise, the constant rate of [6,6-$^2$H]glucose infusion was doubled to prevent large changes in isotopic enrichment (15,16). Throughout recovery, the participants rested in a seated position. The rate of O$_2$ consumption and CO$_2$ production were determined from expired air samples collected at various stages of testing using a mask during exercise and a canopy after exercise connected to an indirect calorimetry system (VMax Spectra, SensorMedics Corporation, USA). Carbohydrate oxidation rates were calculated using the
non-protein respiratory quotient according to the equation
\[ 4.585 \, \text{V CO}_2 - 3.226 \, \text{V O}_2 \] (17). To calculate the additional glucose requirements to maintain euglycemia during exercise, the difference in glucose infusion rates between the exercise and rest conditions were determined and the area under the curve was analysed. Blood samples for the measurement of hormones, metabolites and \(^{6,6-}\text{H}\)glucose enrichment were obtained at 15-minute intervals during exercise (or rest) and every 2 hours during recovery until 0600 h the following morning.

Measurement of glucoregulatory hormones and \(^{6,6-}\text{H}\)glucose enrichment

Arterialised venous blood samples were analysed for glucose using a YSI analyser (Yellow Springs Instrument, Yellow Springs, Ohio), and free insulin, glucagon, free fatty acids, cortisol and growth hormone were measured as previously described (18). Epinephrine and norepinephrine levels were determined in heparinised plasma samples treated with sodium metabisulphite using a BI-CAT ELISA kit (DLD Diagnostika, Germany). Isotopic enrichment was determined by gas chromatography-mass spectrometry (GC-MS; Bioanalytical Mass Spectrometry Facility, Sydney, Australia). The readings obtained were corrected for background enrichment of naturally occurring \(^{6,6-}\text{H}\)glucose and the rates of glucose appearance (Ra) and disappearance (Rd) were estimated using the single compartment fixed-volume model proposed by Steele (19) and modified by Finegood and colleagues (14) to account for the infusion of exogenous glucose. Only glucose Ra and Rd measured during recovery are shown here because glucose enrichment was not stable prior to exercise.

Statistical analyses

Data were analysed using a two-way repeated-measures ANOVA and Fisher’s least significant difference test for \textit{a posteriori} analysis using SPSS 17.0 software. Statistical significance was accepted at \(p < 0.05\). Unless otherwise stated, all results are expressed as mean ± S.E.M.

Results
There were no differences in blood glucose or plasma insulin levels between the exercise and rest conditions at any time point (Fig. 1A,B). Before exercise and rest, blood glucose levels were 5.54 ± 0.20 and 5.50 ± 0.18 mmol/L \( (p=0.39) \), respectively, and did not change during either condition. Similarly, plasma insulin levels were 125.9 ± 32.5 and 129.8 ± 20.6 pmol/L \( (p=0.89) \) before the exercise and rest conditions, respectively, and did not change during or following exercise or rest.

In response to exercise, glucagon, epinephrine, norepinephrine, growth hormone and cortisol increased above baseline levels, and returned to pre-exercise levels during early recovery (Fig. 1D-H). Later during recovery, cortisol levels increased to above baseline levels. Free fatty acid levels steadily increased post-exercise reaching a peak after 3 hours of recovery from exercise (Fig. 1C). However, there were no differences in the levels of any of counterregulatory hormones measured here or free fatty acids between exercise and rest conditions from the first hour of recovery until 17 hours of recovery (Fig. 1C-H).

The glucose infusion rate (GIR) to maintain stable blood glucose levels was not different between groups at baseline \( (9.8 ± 1.4 \text{ and } 9.5 ± 1.6 \text{ g/hr before the exercise and rest conditions, respectively} ; p=0.46) \) and did not change in the rest condition for the duration of the study. In contrast, GIR increased more than 3-fold during exercise (from 9.8 ± 1.4 to 30.6 ± 4.7 g/hr; \( p=0.00 \)), fell within the first hour of recovery to a level above baseline \( (14.9 ± 1.3 \text{ g/hr}; p=0.00) \), and remained elevated until 11 hours post-exercise before returning to baseline levels (Fig. 2A; Table 1). Over this period, an additional 56.6 g of glucose was infused to maintain euglycemia in the exercise compared to the rest condition.

From 1 hour of recovery until 17 hours of recovery, there was no difference in glucose Ra between exercise and rest conditions (Fig. 2B; Table 2). Similarly, there was no difference in glucose Rd over this period between exercise and rest conditions (Fig. 2C, Table 2).
Before exercise, the rates of carbohydrate oxidation were similar between the exercise and rest conditions ($13.9 \pm 0.75$ and $11.4 \pm 0.74$ g/hr, respectively; $p=0.00$). During exercise, the absolute rate of carbohydrate oxidation increased compared to rest ($127.4 \pm 7.7$ versus $13.4 \pm 1.7$ g/hr, respectively; $p=0.00$) equating to 95.5 g and 10.1 g of carbohydrate oxidized during exercise and rest treatments, respectively.

**Discussion**

This study shows that in response to moderate-intensity exercise performed close to midday, the exogenous glucose requirements to maintain euglycemia increase during exercise and remain elevated for 11 hours post-exercise in adolescents with T1DM. This finding thus suggests that the risk of exercise-mediated hypoglycemia increases during and for several hours after moderate-intensity exercise, with no evidence of a biphasic pattern of post-exercise risk of hypoglycemia when exercise is performed at midday.

Previously, we have shown that the glucose requirements to maintain euglycemia increase during and shortly following late afternoon exercise, and again from 7-11 hours post-exercise (7), with no extra glucose required during the 2-7 hour recovery period. Such a biphasic response was not observed here since our results show that, following midday exercise, the glucose requirements to maintain euglycemia remain significantly elevated above resting levels for up to 11 hours after exercise. This was the case despite the fact that plasma insulin levels and exercise conditions were matched between studies. Our findings thus suggest not only that the risk of LOPEH is elevated for the first 11 hours following midday moderate-intensity exercise, as mentioned earlier, but also that midday exercise does not increase the risk of hypoglycemia during the night. What remains to be determined, however, are the mechanisms underlying the different patterns of glucose requirements to maintain euglycemia between this study and that of McMahon and colleagues (7). This task is a particularly challenging one given that the biphasic response reported by McMahon and colleagues (7) remains to be explained.
The sustained increase in glucose requirements during the first 11 hours of recovery is likely to be explained by the trend for higher glucose Rd during recovery from exercise compared to the rest condition. Indeed, although glucose Rd did not differ statistically between experimental groups, there was a trend ($p<0.13$-$0.19$) for glucose Rd to be higher for up to 11 hours during recovery from exercise compared to rest. In contrast, there were no differences in glucose Ra following the exercise and rest conditions. These findings suggest that an increase in peripheral glucose utilisation contributes to the increase in glucose requirements post-exercise and associated risk of post-exercise hypoglycemia.

It is likely that the sustained increase in GIR above baseline post-exercise serves to replenish muscle and hepatic glycogen stores. In support of this view, others have reported that increases in insulin sensitivity and the rate of muscle glucose uptake are favourable to the replenishment of muscle glycogen stores following prolonged moderate-intensity exercise (12,20). This is likely to be the case here as suggested by the following calculations. Assuming that all of the glucose infused during exercise was oxidised, one can estimate based on our indirect calorimetry data that 74.3g of muscle/hepatic glycogen was oxidized during that time. During the first 11 hours of recovery, the difference between whole body carbohydrate oxidation (112.9g/11 hours) and total amount of glucose infused to maintain euglycemia (158.6g/11 hours) provides an estimate of the amount of glycogen deposited during that time, which here corresponds to 45.7g of glycogen. These findings thus indicate that approximately 30% of the glucose required to maintain euglycemia during the first 11 hours of recovery is used to replenish muscle glycogen stores. However, the amount of glycogen thus replenished is insufficient to replace all the glycogen used during exercise since it accounts for approximately 60% of the glycogen oxidized during that time.

The observation that there were no differences in glucose Ra during recovery from exercise and rest is consistent with the absence of significant differences in the levels of the glucoregulatory hormones between conditions. Since, insulin, glucagon, epinephrine, norepinephrine, growth hormone and
cortisol have acute and chronic stimulatory effects on hepatic glucose production (21), the absence of differences in the levels of these hormones between exercise and rest conditions would be expected to result in similar glucose Ra between conditions. Our findings also suggest that the sensitivity of glucose Ra to insulin is not affected by exercise as shown by others (22,23). It is important to note that although changes from baseline levels of growth hormone and cortisol were observed, these responses were consistent with normal diurnal variations in the levels of these hormones (24,25).

Importantly, there are limitations with our findings that limit their translation to clinical practice. Firstly, since the amount of glucose required to prevent hypoglycemia depends on insulin concentrations (26), and the participants in this study performed exercise at insulin levels moderately above their basal insulin requirements, it follows that our results cannot be used to estimate the extra glucose required to prevent hypoglycemia in individuals exposed to different insulin levels. This is an important limitation given that many people may exercise when they are relatively hyperinsulinemic (27). Furthermore, it remains to be determined if the amount of exogenous glucose required to prevent exercise-mediated hypoglycemia differs depending on whether glucose is ingested rather than infused, since factors related to gastrointestinal absorption rate and food composition may become important confounding variables. Another limitation relates to the duration of the period of increased hypoglycemia risk post-exercise determined here as it only applies to circumstances where no carbohydrate-rich meal is consumed after exercise. Since most individuals are likely to consume a meal within the first 11 hours of recovery from exercise, it follows that the duration of the post-exercise increased risk of hypoglycemia would be expected to be less than reported here. Also, since our findings relate only to a fixed period of aerobic exercise, they do not exclude the possibility that factors such as the intensity and duration of exercise (28,29) may contribute to differences in post-exercise glucose requirements to maintain euglycemia and associated risk of post-exercise hypoglycemia. Finally, since the participants in this study were mostly male, it is possible that these results may have been affected by a sex bias.
Although measuring the amount of extra glucose required to maintain euglycemia during and after exercise provides a valuable approach to indirectly determine the risk of exercise-mediated hypoglycemia, it is important to note that this approach only represents a partial evaluation of this risk. This is because the absence of a difference in GIR between experimental conditions does not exclude the possibility that the counterregulatory response to hypoglycemia is differentially affected by these conditions. Indeed, moderate-intensity exercise has been shown to reduce the counterregulatory responses to a subsequent episode of hypoglycemia (30-32), thus increasing the risk of hypoglycemia when blood glucose levels are falling following exercise.

In conclusion, the pattern of glucose requirements to maintain euglycemia in response to moderate-intensity exercise performed at midday suggests that the risk of exercise-mediated hypoglycemia increases during and for several hours after moderate-intensity exercise, with no evidence of a biphasic pattern of post-exercise risk of hypoglycemia as opposed to what has been reported when exercise is performed late in the afternoon. Whether these differences relate to the diurnal pattern of change in counterregulatory hormones such as cortisol and growth hormone or other factors remains to be determined. On clinical grounds, our results also suggest that the time of day when exercise is performed may be an important factor affecting the risk of post-exercise hypoglycemia during sleep, with mid-day and late afternoon exercise increasing the risk of hypoglycemia in the evening and after mid-night, respectively. Strategies to reduce this risk, such as increasing carbohydrate intake or reducing insulin doses following moderate-intensity exercise, may be indicated, but it is important to note that the extent of these adjustments remains unclear. The effect of exercise intensity (e.g. anaerobic exercise) and duration on post-exercise glucose requirements and the risk of post-exercise hypoglycemia in T1DM are also important avenues for future research.

Acknowledgements

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Fig. 1. Responses of plasma free insulin (A), blood glucose (B), plasma free fatty acids (C), plasma glucagon (D), epinephrine (E), norepinephrine (F), serum growth hormone (G), and serum cortisol levels to exercise (closed circles) and rest (open circles). Shaded box, exercise period. a, significant difference between exercise and rest conditions; b, significant difference compared to baseline (exercise); c, significant difference compared to baseline (rest), p<0.05.
Fig. 2. Responses of glucose infusion rate (A), rate of endogenous glucose appearance (B), and rate of glucose disappearance (C) to exercise (closed circles) and rest (open circles). Shaded box, exercise period. a, significant difference between exercise and rest conditions; b, significant difference compared to baseline levels (exercise), p<0.05.
Table 1. Glucose infusion rates necessary to maintain euglycemia before, during and after exercise and rest.

<table>
<thead>
<tr>
<th>Time</th>
<th>GIR (g/h) Exercise condition</th>
<th>GIR (g/h) Rest condition</th>
<th>Difference in GIR between conditions</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-exercise</td>
<td>9.8 ± 1.4</td>
<td>9.5 ± 1.6</td>
<td>0.2 ± 2.3</td>
<td>0.46</td>
</tr>
<tr>
<td>End of exercise</td>
<td>30.6 ± 4.7</td>
<td>10.9 ± 3.7</td>
<td>20.7 ± 7.2</td>
<td>0.02</td>
</tr>
<tr>
<td>1h post-exercise</td>
<td>14.9 ± 1.3</td>
<td>10.9 ± 0.9</td>
<td>5.1 ± 1.8</td>
<td>0.02</td>
</tr>
<tr>
<td>3h post-exercise</td>
<td>14.6 ± 2.2</td>
<td>10.5 ± 1.3</td>
<td>4.1 ± 2.1</td>
<td>0.04</td>
</tr>
<tr>
<td>5h post-exercise</td>
<td>12.8 ± 1.6</td>
<td>9.4 ± 1.5</td>
<td>3.4 ± 1.7</td>
<td>0.03</td>
</tr>
<tr>
<td>7h post-exercise</td>
<td>13.5 ± 1.6</td>
<td>10.5 ± 1.0</td>
<td>2.9 ± 1.8</td>
<td>0.06</td>
</tr>
<tr>
<td>9h post-exercise</td>
<td>13.4 ± 1.8</td>
<td>10.4 ± 1.3</td>
<td>3.1 ± 1.8</td>
<td>0.05</td>
</tr>
<tr>
<td>11h post-exercise</td>
<td>12.4 ± 1.7</td>
<td>9.7 ± 1.5</td>
<td>2.7 ± 1.5</td>
<td>0.05</td>
</tr>
<tr>
<td>13h post-exercise</td>
<td>10.8 ± 1.5</td>
<td>9.8 ± 0.8</td>
<td>1.1 ± 1.3</td>
<td>0.21</td>
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<tr>
<td>15h post-exercise</td>
<td>10.2 ± 1.6</td>
<td>8.4 ± 0.9</td>
<td>1.8 ± 1.3</td>
<td>0.09</td>
</tr>
<tr>
<td>17h post-exercise</td>
<td>9.0 ± 1.0</td>
<td>8.9 ± 0.7</td>
<td>0 ± 1.5</td>
<td>0.31</td>
</tr>
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</table>
Table 2. Glucose rates of appearance and disappearance following exercise and rest.

<table>
<thead>
<tr>
<th>Time</th>
<th>Exercise condition</th>
<th>Rest condition</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ra (g/h)</td>
<td>Rd (g/h)</td>
<td>Ra (g/h)</td>
</tr>
<tr>
<td>1h post-exercise</td>
<td>7.8 ± 0.7</td>
<td>21.6 ± 1.3</td>
<td>8.8 ± 2.1</td>
</tr>
<tr>
<td>3h post-exercise</td>
<td>7.0 ± 0.8</td>
<td>20.4 ± 2.4</td>
<td>6.9 ± 1.5</td>
</tr>
<tr>
<td>5h post-exercise</td>
<td>5.6 ± 0.7</td>
<td>17.5 ± 1.7</td>
<td>5.8 ± 1.3</td>
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<tr>
<td>7h post-exercise</td>
<td>4.6 ± 0.5</td>
<td>17.0 ± 2.0</td>
<td>4.9 ± 1.0</td>
</tr>
<tr>
<td>9h post-exercise</td>
<td>4.2 ± 0.4</td>
<td>16.8 ± 2.1</td>
<td>4.7 ± 1.1</td>
</tr>
<tr>
<td>11h post-exercise</td>
<td>4.7 ± 0.4</td>
<td>15.7 ± 1.8</td>
<td>4.3 ± 1.0</td>
</tr>
<tr>
<td>13h post-exercise</td>
<td>3.7 ± 0.4</td>
<td>14.5 ± 1.8</td>
<td>4.2 ± 1.0</td>
</tr>
<tr>
<td>15h post-exercise</td>
<td>3.8 ± 0.5</td>
<td>13.3 ± 1.9</td>
<td>4.3 ± 1.0</td>
</tr>
<tr>
<td>17h post-exercise</td>
<td>4.7 ± 0.7</td>
<td>12.4 ± 0.8</td>
<td>4.5 ± 0.8</td>
</tr>
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</table>