Glucose Ingestion Matched With Total Carbohydrate Utilization Attenuates Hypoglycemia During Exercise in Adolescents With IDDM

Michael C. Riddell, Oded Bar-Or, Beatriz V. Ayub, Randolph E. Calvert, and George J.F. Heigenhauser

There are currently no guidelines regarding the carbohydrate (CHO) dosage required to prevent exercise-induced hypoglycemia in children with insulin-dependent diabetes mellitus (IDDM). To prevent hypoglycemia by matching glucose ingestion with total-CHO utilization, 20 adolescents with IDDM attended 2 trials: control (CT; drinking water) and glucose (GT; drinking 6–8% glucose). Participants performed 60 min of moderate-intensity cycling 100 min after insulin injection and breakfast. CT’s total-CHO utilization during exercise was determined using indirect calorimetry. In GT, participants ingested glucose in the amount equal to total CHO utilization in the CT. A total of 9 participants had BG <4.0 mmol/L in CT compared to 3 in GT (p < .05). In conclusion, glucose ingestion equal to total-CHO utilization attenuates the drop in blood glucose and reduces the likelihood of hypoglycemia during exercise in adolescents with IDDM.

Key Words: carbohydrates, IDDM, blood glucose, physical activity, children

Exercise can lower blood glucose concentration in individuals with insulin-dependent diabetes mellitus (IDDM) who have injected their insulin subcutaneously preexercise (2, 4, 5, 9, 11, 19). This fall in blood glucose may be due to the liver’s inability to increase glucose production in response to an increase in glucose utilization (16). Once exercise has commenced, exogenously injected insulin is released into the blood stream at an enhanced and sometimes unpredictable rate (8). This relative hyperinsulinemia leads to reduced hepatic glucose production (6, 8) and enhanced glucose clearance during exercise, which may result in hypoglycemia (2, 4, 5, 9, 11, 19).

Strategies to prevent hypoglycemia during exercise in patients with IDDM consist of altering calorie intake or decreasing the dosage of insulin injected preexercise. The latter does decrease the likelihood of hypoglycemia (7, 13, 19). However, this prescription may not be applicable for daily life, particularly among

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children and youth, whose activities may be spontaneous and of an unpredictable length and intensity. In contrast, consuming extra carbohydrate (CHO) may be a reasonable means for preventing hypoglycemia, particularly if ingested in divided doses throughout the period of activity.

Existing guidelines do not provide validated recommendations for the amount of CHO needed to prevent hypoglycemia during exercise in people with IDDM. Specifically, recommendations are lacking for people who vary in body mass (e.g., children vs. adolescents vs. adults), whose dietary and insulin requirements vary considerably. In addition, existing recommendations do not account for interindividual differences in actual CHO utilization during exercise, which is based on the type of activity, intensity, and duration. A quantitative assessment of individualized CHO requirements to maintain blood glucose levels during exercise may be beneficial.

Bar-Or (1) tried to prescribe an increased CHO intake before and during exercise to children and adolescents with IDDM according to the type of activity and individual body mass. “Exercise exchanges” are estimated for various activities for children with body mass of 20–60 kg. Each exercise exchange is equivalent to 420 J (100 kcal). Assuming that approximately 60% of the energy during children’s exercise is provided by CHO, one exercise exchange is equivalent to 15 g (60 kcal) CHO. From this estimation, CHO intake can be matched with utilization to prevent hypoglycemia. The above recommendations are based on the assumption that matching CHO ingestion with total (CHO_total) utilization maintains blood glucose concentrations during exercise in individuals with IDDM. However, this assumption has never been evaluated experimentally.

The main objective of this study, therefore, was to determine if glucose ingestion matched with total CHO utilization attenuates the drop in blood glucose during exercise and reduces the incidence of hypoglycemia in adolescents with IDDM.

**Method**

**Participants**

Participants were 20 adolescents with IDDM (17 boys, 3 girls) who volunteered through local public service announcements (n = 8) or were referred by their physicians for problems with exercise-induced hypoglycemia (n = 12). All were habitually active but not competitive athletes. Anthropometric and clinical data are shown in Table 1. Participants were all nonobese, had fair control of their diabetes during the study period (based on HbA1c levels) (21), and had no evidence of retinopathy, autonomic neuropathy, or nephropathy (as reported by their physicians). A total of 14 participants routinely injected a mixture of short- and intermediate-acting insulin before breakfast and dinner. The others injected this mixture at the same times, along with short-acting insulin prior to lunch. None of the participants injected fast-acting insulin analogs (e.g., Lispro) during the study period. The purpose, nature, and possible risks of the study were explained to participants and their parents. Participants age 14 or older signed informed consent. Younger individuals gave a verbal assent, and a parent then signed informed consent. The study was approved by the Research Ethics Board of the Faculty of Health Sciences at McMaster University.
Table 1  Participants’ Anthropometric and Clinical Data (n = 20)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI</th>
<th>HbA1c (%)</th>
<th>Insulin (U/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M SEM</td>
<td>M SEM</td>
<td>M SEM</td>
<td>M SEM</td>
<td>M SEM</td>
<td>M SEM</td>
</tr>
<tr>
<td>14  1.0</td>
<td>162  3.0</td>
<td>55  3.0</td>
<td>21  1.0</td>
<td>10.7  0.5</td>
<td>0.89  0.05</td>
</tr>
</tbody>
</table>

Note. BMI = Body mass index, HbA1c = Hemoglobin A1c.
*Normal range = 4.5–7.5%. Units of insulin injected per kg body mass per day.

Experimental Sessions

Two experimental trials were spaced 1–4 weeks apart. Participants were asked to maintain a similar diet, exercise, and insulin routine the day before each trial. They were instructed to inject their usual insulin dose into a site other than the legs and consume their usual breakfast on the morning of the trials. They were also instructed not to alter insulin dosage or dietary habits in anticipation of exercise. Compliance was confirmed when participants arrived at the laboratory on the morning of the two trials, which were identical except for differences in postbreakfast fluid/CHO consumption. Participants drank water only as fluid replenishment during an initial control trial (CT) and a 6–8% glucose, 18 mmol/L NaCl beverage solution during the second one (GT). After participants arrived at the lab, an indwelling catheter was inserted into an anticubital vein, from which blood was collected 10 min before and 10, 20, 30, 40, 50, and 60 min after the start of exercise to determine whole-blood glucose concentrations using an Accu-Check III glucose meter (Boehringer Mannheim, Laval, PQ, Canada). This meter allowed us to monitor blood glucose concentrations rapidly throughout the trials (as a safeguard against hypoglycemia) and has a high correlation to laboratory blood glucose assay measurements based on data from this experiment (r = .97, y [hexokinase assay] = ax + b, where a = 1.00, b = 0.39, and the standard error of the estimate = 1.53, n = 141 samples).

Participants started exercising approximately 100 min after their insulin injection. Exercise was performed on a cycle ergometer and consisted of either two 30-min bouts separated by a 5-min rest (volunteers) or six 10-min bouts with 5-min rests in between (referral patients). The exercise protocols differed somewhat for the two subgroups (volunteers vs. referral patients) since the former was also participating in a study on exogenous glucose oxidation rates during prolonged steady-state exercise. The 5-min rest period helped prevent boredom and allowed emptying of the bladder. The exercise protocol for the referral patients is typical and well tolerated by the range of pediatric conditions seen in our laboratory. An investigator adjusted resistance during the exercise bouts, which allowed participants to perform at an intensity that produced a heart rate of 145–160 bpm during the CT. This heart rate range was chosen to simulate physical activity at moderate intensity and corresponds to approximately 55–65% maximal aerobic capacity for this age group. The resulting intensities were recorded and reproduced by the participant during
the GT. The exercise task was terminated if a participant’s blood glucose concentration fell below 2.5 mmol/L or if an individual could not continue at the designated intensity.

Average oxygen consumption (\(\bar{VO}_2\)) and respiratory exchange ratio (RER) values were determined during 3-min sampling periods after 5, 15, 25, 35, 45, and 55 min of exercise in the CT. A metabolic cart (Quinton Q-plex I, Quinton Instruments, Seattle, WA) was used for volunteers, and the Vmax V6200, (Sensor Medics, Yorba Linda, CA) for referrals. Expired gas concentrations were validated periodically during both trials against \(CO_2\), \(O_2\), and \(N_2\) gas mass spectrometry (Perkin-Elmer Aero Space Systems, Pomona, CA). From these sampling periods, an average CHO\(_{\text{total}}\) utilization rate (g/min) was determined for the entire exercise period using a table of nonprotein respiratory quotients (14). Heart rate was measured continuously throughout exercise in both trials using a Polar Vantage XL heart rate monitor (Polar Electro Oy, Kempele, Finland). In both trials, beverages were consumed periodically in equal portions, starting 10 min before and each 10 min after the start of exercise, but not after the last bout. Total amount of glucose ingested in the GT was equivalent to the measured CHO\(_{\text{total}}\) utilization rate during exercise in the CT. The total amount of glucose was equally divided over the six drinking periods. As instructed, participants drank each dose of glucose beverage completely within 5 min.

Data Analysis

A two-way (Trial \(\times\) Exercise Duration) repeated measures analysis of variance (unbalanced data) was used to compare blood glucose concentrations during the two trials. If significance was found, a Tukey’s HSD post hoc test was used to identify differences between mean values. A McNemar’s chi-square analysis (two-tailed) for paired binomial samples was used to compare the proportion of individuals who had blood glucose concentrations <4.0 mmol/L in the two trials. Statistical analysis was performed using BMDP software (BMDP Statistical Software Inc., Los Angeles). Values are expressed as means \(\pm SEM\) unless otherwise stated.

Results

No significant differences in substrate utilization or blood glucose response to exercise existed between the referral patients and volunteers, or between males and females, so their data were pooled. The mean exercise duration was 52 \(\pm\) 3 and 58 \(\pm\) 1 min in the CT and GT, respectively (\(p < .05\)). A total of 13 participants completed 60 min of exercise in the CT vs. 16 in the GT (\(p = .48\), chi-square, two-tailed). The work rate during the trials was 80 \(\pm\) 7 W. \(\bar{VO}_2\) and RER averaged 1.41 \(\pm\) 0.09 and 0.92 \(\pm\) 0.02 L/min, respectively, during exercise in the CT. Heart rate during exercise was 150 \(\pm\) 2 bpm in the CT compared with 144 \(\pm\) 3 bpm in the GT (\(p < .01\)). CHO\(_{\text{total}}\) utilization averaged 1.46 \(\pm\) 0.08 g/min during exercise in the CT and was moderately correlated to both participant’s body mass (\(r = .53, p < .05\); see Figure 1) and power output (\(r = .56, p < .05\)). As stated above, individual CHO\(_{\text{total}}\) utilization rates were used to determine the amount of glucose to be ingested by participants during the GT. All participants successfully drank the provided beverages within the allotted time periods. Glucose ingestion was 87.3 \(\pm\) 5.1 g (46–127 g) during the entire GT, with an average of 207 \(\pm\) 8 ml of beverage consumed during each of the six drink periods.
Blood glucose concentrations for all 20 participants during the trials are shown in Figure 2. Significant main effects for Trial ($p < .001$) and Exercise Duration ($p < .001$) as well as a Trial by Time interaction ($p < .001$) on blood glucose concentration were seen. In the CT, average blood glucose levels decreased significantly from $13.3 \pm 1.2$ mmol/L at 10 min before the start of exercise to $6.6 \pm 0.9$ mmol/L after 60 min of exercise ($p < .001$). During the GT, blood glucose decreased from $13.6 \pm 1.4$ mmol/L at 10 min before the start of exercise to $11.3 \pm 1.2$ mmol/L after 60 min of exercise ($p < .001$). Blood glucose levels in the GT were significantly higher than in the CT at 30 ($p < .05$), 40, 50, and 60 min (all $p < .001$) exercise. A total of 9 participants had blood glucose levels drop below 4.0 mmol/L during exercise in CT compared with only 3 in the GT ($p < .05$). To analyze whether preexercise blood glucose levels may affect the exercise response, participants were subdivided into one of two classifications based on their value at −10 min in the CT: those $\geq 15$ mmol/L and those $< 15$ mmol/L (see Figure 3). In the 9 participants who were classified in the higher blood glucose category, concentrations decreased from $18.4 \pm 0.8$ mmol/L at −10 min to $8.3 \pm 1.3$ mmol/L ($p < .001$) by 60 min of exercise in the CT. In the GT, it decreased from $18.2 \pm 1.5$ mmol at −10 min to $14.7 \pm 1.3$ mmol/L ($p < .001$) by 60 min of exercise. Blood glucose values were significantly higher in the GT than in the CT at 50 ($p < .05$) and 60 ($p < .001$) min of exercise. For the 11 participants in the lower blood glucose category, concentrations decreased from $9.0 \pm 1.0$ mmol/L at −10 min to $3.9 \pm 0.5$ mmol in the CT ($p < .001$) and remained unchanged from $9.9 \pm 1.4$ mmol/L in the GT. Blood glucose values were higher in the GT than in the CT at 30 ($p < .05$), 40 ($p < .05$), 50 ($p < .001$), and 60 ($p < .001$) min of exercise.

The drop in blood glucose concentration during the entire exercise period (preexercise minus end of exercise) was significantly correlated to preexercise blood glucose concentration in the CT ($r = .85$, $p < .001$) and GT ($r = .70$, $p < .001$) (see Figure 4).
Figure 2 — Blood glucose concentrations before, during, and immediately after exercise in the control (CT) and glucose trials (GT). Exercise was either six 10-min bouts separated by 5-min rest periods, or two 30-min bouts separated by a 5-min rest. $n = 20$ unless otherwise stated.

*, ** GT is significantly higher than in CT at $p < .05$ and $< .001$, respectively; Values are means ± SEM.

Figure 3 — Blood glucose concentrations before, during, and immediately after exercise in the control (CT, closed symbols) and glucose trials (GT, open symbols). Participants were subdivided into one of two classifications based on their preexercise concentrations at -10 min: ≥15 mmol/L (circles) or <15 mmol/L (squares). A total of 8 of the 9 participants who began exercise with blood glucose levels ≥15 mmol/L completed 60 min of exercise in both trials; 5 of the 11 who began exercise with blood glucose <15 mmol/L completed 60 min of exercise in the CT compared to 8 in the GT.

* GT is significantly higher than in CT at $p < .05$. Values are means ± SEM.
Figure 4 — Relationship between the drop in blood glucose concentration (preexercise – end of exercise) and the preexercise blood glucose concentration in the control (CT) and glucose trials (GT). Individual values.

Discussion

The main finding of this study is that glucose ingestion matched with \( \text{CHO}_{\text{total}} \) utilization attenuates the drop in blood glucose concentration and reduces the likelihood of hypoglycemia during exercise in adolescents with IDDM (see Figures 2–3). The incidence of blood glucose concentrations approaching hypoglycemic levels (<4.0 mmol/L) was reduced from 45% with water ingestion to 15% with glucose ingestion matched to \( \text{CHO}_{\text{total}} \) utilization (\( p < .05 \)). The 3 individuals whose blood glucose levels dropped below 4.0 mmol/L during the GT experienced an increase in glycemic levels (to a value >4.0 mmol/L) by the end of the 60-min exercise. Thus, glucose ingestion matched with \( \text{CHO}_{\text{total}} \) utilization attenuates the drop in blood glucose even in patients who are susceptible to hypoglycemia during exercise. These findings support the exercise exchange hypothesis that matching glucose ingestion with \( \text{CHO}_{\text{total}} \) utilization is efficacious for children and adolescents with IDDM (1).

Few researchers have tested CHO intake regimens aimed at preventing exercise-induced hypoglycemia in individuals with IDDM (7, 12, 18, 20). Most of these experiments were performed with participants exercising in a fasted state, when insulin concentrations are low and the risk of hypoglycemia reduced. However, physical activity is often performed following insulin injection and a meal, when plasma insulin levels are much higher. This may be especially true for children and adolescents, who often perform spontaneous exercise throughout the day. Exercise during these times of higher insulin concentrations may require extra CHO to prevent hypoglycemia. However, no such intake recommendations exist for children and adolescents, who vary in body mass and whose energy demands may differ considerably from adults.
CHO ingestion before and during exercise is an alternative to reducing the amount of insulin injected before physical activity. A reduced insulin dosage does reduce the likelihood of hypoglycemia (7, 13, 19). However, preventing hypoglycemia by ingesting CHO is advantageous because it may allow the individual with IDDM to exercise for prolonged periods without having to anticipate the timing, duration, and intensity of the activity. Conceivably, individuals would consume CHO based on the activity in the next 15–30 min, thereby omitting the need to reduce the amount of insulin injected preexercise. In addition, intermittent consumption throughout an activity may reduce the likelihood of hyperglycemia associated with a large, single bolus of CHO.

In clinical practice, physical activity is not recommended for individuals with blood glucose concentrations of ≥15 mmol/L since glycemia may increase further and ketoacidosis may occur (21). A total of 9 participants started exercise with blood glucose levels ≥15 mmol/L in the CT. As shown in Figure 3, their glucose levels decreased continuously throughout the CT and leveled off in the GT. None experienced an increase in glycemia during exercise in the CT and only 1 encountered a minor increase (0.5 mmol/L) in the GT. Thus, there is apparently no risk of an increase in glycemia if the exercise is performed following insulin injection and a meal. In fact, we found that individuals with higher initial blood glucose concentrations experienced the greatest decreases during exercise (see Figures 3 and 4). One of these participants had a drop from 16.4 to 3.2 mmol/L by 50 min of exercise, at which point he could not continue. Thus, there appears to be no exaggerated risk of hyperglycemia in individuals with initially high blood glucose concentrations as long as the exercise is performed after insulin injection and a meal. If anything, such patients may have a risk of hypoglycemia if the exercise duration is prolonged.

One might argue that the drop in blood glucose levels during exercise with water ingestion (see Figure 2) does not present a clinical risk for hypoglycemia. However, we feel this may not be the case. During the 1 hr of exercise, 45% of the participants had blood glucose levels drop below 4.0 mmol/L. Moreover, the mean blood glucose concentration postexercise with water ingestion (6.6 mmol/L at 60 min in Figure 2) does not include values for the 7 individuals who had lower blood glucose concentrations at earlier stages of exercise and could not complete the entire exercise task. Moreover, had the exercise extended beyond 60 min, even more participants might have reached clinically hypoglycemic levels. For ethical and safety considerations, we stopped the experiment before this would happen.

Finally, blood glucose concentrations often continue to decrease postexercise, thereby increasing the risk for postexercise hypoglycemia. We therefore suggest that performing prolonged exercise tasks without CHO supplementation, as in this study, presents risk to patients with IDDM, even when initial blood glucose levels are high. We feel that it is much safer to maintain somewhat higher levels of blood glucose concentration, such as those shown in the glucose ingestion trials (see Figures 2 and 3).

A moderate correlation (r = .53, p < .05) was found between CHO utilization (and thus glucose ingestion that maintained glycemia) and a participant’s body mass (see Figure 1). This finding illustrates that individual body mass is not in itself an ideal predictor of CHO intake requirements to prevent exercise-induced hypoglycemia in adolescents.
The use of exercise exchanges to prevent exercise-induced hypoglycemia in IDDM, as initially described by Bar-Or (1), is based on providing CHO intake with estimated \( \text{CHO}_{\text{total}} \) utilization. Although this study is the first to aid in validating this concept for moderate-intensity exercise, certain limitations must be realized. While it may be ideal to prescribe exercise exchanges based on each patient’s actual \( \text{CHO}_{\text{total}} \) utilization rate, this may be somewhat impractical in most clinical environments. In such a setting, we recommend using tables that estimate exercise exchanges for a variety of specific activities at varying intensities (e.g., basketball, hockey, tennis) for children who vary in body mass (1). Because of the large intersubject variability in \( \text{CHO}_{\text{total}} \) utilization for a given body mass (see Figure 1), these tables should be used as a guideline only, and customized prescriptions, based on individualized energy expenditures, may be necessary. Since individual blood glucose responses to exercise are reproducible (11), individualized CHO intake strategies to prevent hypoglycemia during physical activity may be implemented into patient care regimes with some predictability.

Although our experiment was not designed to compare performance levels during the two trials, a greater percentage of the participants sustained exercise for longer periods with glucose ingestion compared to water (see Figure 2). In addition, they had lower heart rate levels during the GT, even though the exercise tasks were identical. These findings support the recent study by Ramires et al. (15), who showed that oral glucose intake postpones fatigue during exercise in adults with IDDM.

With glucose ingestion, it appears that only a small percentage (~12%) of the glucose beverage is oxidized during the first hour of exercise (17). It is not clear what happens to the portion of ingested glucose not oxidized during exercise. However, this remaining portion may be partially used to maintain the blood glucose and ultimately aid in replenishing glycogen stores postexercise. Campagne et al.’s (3) and MacDonald’s (10) findings indicate that hypoglycemia may occur up to 24–48 hr postexercise as glycogen stores are replenished. Further investigation is required to determine if glucose ingestion based on \( \text{CHO}_{\text{total}} \) utilization reduces the likelihood of postexercise late-onset hypoglycemia by providing excess glucose to replenish glycogen utilized during physical activity. In addition, one should determine whether ingesting other CHO sources (e.g., fructose and polysaccharides) matched with \( \text{CHO}_{\text{total}} \) utilization prevents exercise-induced and postexercise late-onset hypoglycemia in individuals with IDDM.

In conclusion, glucose ingestion matched with \( \text{CHO}_{\text{total}} \) utilization during exercise attenuates the decrease in blood glucose and helps prevent hypoglycemia in adolescents with IDDM. If determining the actual utilization is not possible, consider using the exercise exchange tables.

References


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