Glucose ingestion and substrate utilization during exercise in boys with IDDM

M. C. Riddell, O. Bar-Or, M. Hollidge-Horvat, H. P. Schwarcz, and G. J. F. Heigenhauser. Glucose ingestion and substrate utilization during exercise in boys with IDDM. J Appl Physiol 88: 1239–1246, 2000.—This study was intended to compare exogenous $[13C]$glucose (Gluexo) oxidation in boys with insulin-dependent diabetes mellitus (IDDM) and healthy boys of similar age, weight, and maximal $O_2$ uptake. In a control trial with water intake (CT) and in a $13C$-enriched glucose trial (GT), subjects cycled for 60 min (58.8 ± 0.9% maximal $O_2$ uptake) while the utilization of total glucose, total fat, and Gluexo was assessed. In CT, total glucose was $84.7\pm 9.2$ vs. $91.3\pm 6.6$ g/60 min (not significantly different) and total fat was $13.3\pm 2.2$ vs. $11.1\pm 1.7$ g/60 min (not significantly different) in IDDM vs. healthy boys, respectively. In GT, Gluexo was $10.4\pm 1.7$ vs. $14.8\pm 1.1$ g/60 min, corresponding to $9.0\pm 1.0$ vs. $12.4\pm 0.5$% of the total energy supply in IDDM and healthy boys, respectively ($P<0.05$). Endogenous glucose was spared in both groups by $12.6\pm 3.5$% ($P<0.05$). Blood glucose and plasma insulin concentrations were two- to threefold higher in IDDM vs. healthy boys in both trials. In conclusion, Gluexo is impaired in exercising boys with IDDM, even when plasma insulin levels are elevated.

EXOGENOUS GLUCOSE (Gluexo) postpones fatigue during prolonged, moderate-intensity exercise both in healthy adults (12) and in adults with insulin-dependent diabetes mellitus (IDDM) (31). Gluexo ingestion is thought to limit fatigue by elevating blood glucose concentrations ([glucose]) and by maintaining high rates of glucose oxidation late in exercise (10). Gluexo oxidation during exercise in healthy male subjects has been investigated intensively by using stable $^{13}$C-glucose tracers (for review see Ref. 27); however, only one study (21) has examined Gluexo oxidation in individuals with IDDM. In that experiment, Krzentowski et al. (21) showed that Gluexo oxidation in intravenously insulin-infused, euglycemic men with IDDM was similar to that in controls but was reduced by 50% when the insulin was withheld. Hawley and colleagues (19) and, more recently, Weltan et al. (37) have shown that, at least in healthy nondiabetic individuals, experimentally induced hyperinsulinemia and hyperglycemia increase glucose oxidation during exercise. Despite the above evidence indicating that Gluexo oxidation may be increased by high plasma insulin concentrations ([insulin]), no studies exist that examine Gluexo oxidation during exercise performed after subcutaneous insulin injection in individuals with IDDM. Indeed, individuals with IDDM often perform spontaneous physical activities 1–2 h after insulin injection, causing elevations in circulating plasma [insulin] compared with nondiabetic individuals (41). To combat hypoglycemia, caused by relative hyperinsulinemia, these individuals are often advised to consume additional carbohydrates either before or during exercise (1). It is possible, therefore, that Gluexo oxidation may be elevated in individuals with IDDM who exercise after subcutaneous insulin injection, compared with their nondiabetic peers. No studies exist to test this hypothesis, however. We therefore compared Gluexo oxidation during prolonged, moderate-intensity exercise performed after insulin injection in boys with IDDM and in healthy nondiabetic boys of similar age, weight, and maximal $O_2$ uptake ($V_\text{O2max}$).

METHODS

Subjects. Eight 13- to 19-yr-old boys with IDDM and six healthy nondiabetic boys of similar age, weight, and $V_\text{O2max}$ volunteered in response to local public service announcements. Their physical and functional characteristics are shown in Table 1. Volunteers with IDDM were eligible for the study if they had no residual $\beta$-cell function, as indicated by a postmeal plasma C-peptide level of $<0.03$ nmol/l. All IDDM subjects took two insulin injections per day and were nonobese, actively active, but not competitive athletes. They were considered to be in fair to poor control of their diabetes during the study period (40) (on the basis of glycosylated hemoglobin ranging from 9 to 15%, normal range from 4 to 7%) and had no evidence of retinopathy, autonomic neuropathy, or nephropathy, as assessed by their physician. The purpose, nature, and possible risks of the experiment were explained to the subjects and their parents. Subjects 14 yr or older and their parents signed informed consent. Those under 14 yr of age gave a verbal assent, and a parent then signed an informed consent. The study was approved by the Research Ethics Board of the Faculty of Health Sciences, McMaster University.

Preliminary session. At least 1 wk before the first experimental trial, height, weight, and percent body fat (1990B Bio-resistance Body Composition Analyzer, Valhalla Scientific) were measured, and 3-day dietary intake forms were

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Table 1. Physical and functional characteristics for the two subject groups

<table>
<thead>
<tr>
<th></th>
<th>IDDM (n = 8)</th>
<th>Healthy (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>15.1 ± 0.7</td>
<td>14.9 ± 0.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.8 ± 2.8</td>
<td>60.4 ± 2.8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166.4 ± 3.3</td>
<td>169.5 ± 3.8</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>16.1 ± 2.3</td>
<td>15.4 ± 2.1</td>
</tr>
<tr>
<td>Maximal heart rate, beats/min</td>
<td>194 ± 1.2</td>
<td>197 ± 1.0</td>
</tr>
<tr>
<td>Maximal work rate, W</td>
<td>224 ± 12</td>
<td>228 ± 11</td>
</tr>
<tr>
<td>VO2max, ml·kg⁻¹·min⁻¹</td>
<td>42 ± 1.4</td>
<td>43 ± 1.6</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. IDDM, insulin-dependent diabetes mellitus; VO2max, maximal O2 uptake. No significant group differences exist in any of these variables.

provided for dietary assessment. VO2max was determined during progressive cycle ergometry, each stage lasting 2 min (3). Measurements of (VO2) and CO2 production (VCO2) were made continuously by using a Quinton metabolic cart (Quinton Q-plex 1, Quinton Instrument, Seattle, WA) and averaged over the final 30 s of each stage. Heart rate was measured throughout the test by using a Sports Tester PE 3000 system (Polar Electro, Kempele, Finland).

Experimental trials. Two experimental trials [control trial (CT) followed by a glucose trial (GT)] were spaced 1–4 wk apart. Subjects were asked to maintain a similar diet, exercise, and insulin routine (IDDM group) the day before each experimental session. The two trials were identical except for carbohydrate intake before and during exercise. After the subjects arrived at the laboratory on the mornings of the trials (0800), capillary blood was sampled from a finger at 100 min before the start of exercise (time = −100 min) and analyzed for fasting capillary blood glucose by using an Accu-Check III mg+ monitor (Boehringer Mannheim, Laval, PQ). This meter was shown to have a high correlation to blood glucose assay measurements on the basis of data pairs from blood drawn in our laboratory (r = 0.97, y = ax + b, where y is hexokinase assay, a = 1.00, b = 0.39, and SE of estimate = 1.53; n = 141). Subjects with IDDM then injected their usual morning insulin dose into their left arm (7 IU long-acting insulin). No adjustment in insulin dose was made in anticipation of exercise. An individualized breakfast was provided by the investigators that matched for percent carbohydrate, protein, and fat composition on the basis of the 3-day dietary intake forms filled out by the subjects. The meal provided 2,201 ± 854 (SD) kJ of total energy (~65% carbohydrate, ~15% protein, and ~20% fat). Foods naturally enriched in 13C-carbohydrate (i.e., corn and food items derived from corn) were avoided to limit baseline shifts in expired 13CO2. After breakfast, an indwelling catheter was inserted into a forearm vein from which blood was collected into heparinized syringes intermittently throughout the trials. One portion of the sample was deproteinized in 2 vol of 6% perchloric acid, stored at −20°C, and subsequently analyzed for blood [glucose], lactate concentration ([lactate]), and glycerol concentration ([glycerol]) by using standard fluorometric techniques (6). A second portion was centrifuged at 15,900 g for 2 min, and the plasma supernatant was stored at −20°C and subsequently analyzed for free fatty acid concentration ([FFA]; enzymatic colorimetric technique, Wako NEFA C kit, Wako Chemicals, Dallas, TX) and [insulin] (Coat-A-Count radioimmunoassay, DPC Diagnostics). In addition, the Accu-Check glucose meter was used to measure all venous samples for [glucose] as a safety measure in case of hypoglycemia, especially in the subjects with IDDM. Exercise on a cycle ergometer began 80–90 min after the start of breakfast and consisted of two 30-min bouts, separated by a 5-min rest. The rest period was provided to limit boredom and to allow the subjects to empty their bladder. During both trials, subjects exercised at an intensity corresponding to 58.8 ± 0.9% of their predetermined VO2max. During the CT, they were given water intermittently as fluid replenishment in quantities individualized to maintain euhydration (ranging from 625 to 1,000 ml/h exercise). In the GT, subjects consumed five equal amounts of Gluexo beverage at −20, −5, 15, 30, and 50 min (time = 0 min denotes the start of the first exercise bout). The amount of Gluexo consumed in the entire GT was equal to the total glucose (Gluexo) oxidized in the CT. This Gluexo feeding pattern was chosen because it attenuates the drop in [glucose] and reduces the likelihood of hypoglycemia in adolescents with IDDM (33). The Gluexo was provided in an 18 mmol/L NaCl, grape-flavored solution (8% d-glucose). The d-glucose in the beverage was derived from corn (BDH-Chemical, Toronto, ON) and artificially enriched with uniformly labeled [13C]glucose (99 atom % excess, Isotec, Miamisburg, OH) to an isotopic composition of +16.3 change per 1,000 difference vs. the 12C/13C ratio from the international standard 13C Pee Dee Belemnitella-1 (PDB-1; +16.3‰ 13C/PDB-1). This high level of enrichment, compared with that of normal expired gas (−22.4‰ 13C/PDB-1 in this study), provides a strong measurement signal and reduces the error associated with the small shift in the isotopic composition of CO2 arising from the oxidation of endogenous substrates during exercise (23).

Respiratory gas and substrate oxidation. Resting VO2 and VCO2 were determined with subjects sitting quietly in a chair during a 5-min collection period at ~25 min. In addition, VO2 and VCO2 were determined during exercise from 3-min sampling periods at 10, 25, 40, and 60 min. Expired gas concentrations were validated periodically during each trial against CO2, O2, and N2 gas mass spectrometry (Perkin-Elmer AeroSpace Systems, Pomona, CA). Gluexo and total fat (Fatox) oxidation rates were calculated at each time point from respiratory exchange ratio (RER) and VO2 averaged over the collection period by using a table of nonprotein respiratory quotients (28). During gas sampling in the GT, duplicate 20-ml expired gas samples were drawn from Douglas bags connected to the exhaust port of the metabolic cart and stored in vacutainer tubes for subsequent determination of 13C in expired CO2 and Gluexo oxidation. In these tubes, water vapor and CO2 were separated from other gases by a liquid nitrogen trap (−196°C). CO2 was then separated from water vapor by using an acetone-dry ice slush trap (−80°C). The isotopic composition of the CO2 was then determined by using a dual-inlet mass spectrometer (VG-Sira 10, series II, Manchester, UK) and expressed in %Δ13C/PDB-1. Gluexo oxidation was calculated for the sampling periods by using the formula of Mosora et al. (26).

\[
\text{Gluexo} = \text{VCO2} \times (\text{Rexp} - \text{Rref}) / (\text{Rexo} - \text{Rref}) \\
(1 / k)
\]

Where VCO2 is in liters per minute STPD, Rexp is the isotopic composition of expired CO2 during exercise, Rref is the isotopic composition of expired CO2 at rest before Gluexo ingestion, Rexo is the isotopic composition of the Gluexo and k (0.7426 l/g) is the volume of CO2 provided by the complete oxidation of glucose (28). This method of determining Gluexo oxidation assumes that 13CO2 recovery in expired gas during exercise is complete or almost complete (22). Endogenous glucose (Gluendo) oxidation was calculated by subtracting Gluexo from total carbohydrate oxidation.
Statistical analyses. Data are presented as means ± SE. For measurements taken repeatedly during both trials and in both groups, a three-way mixed-design ANOVA was used. Tukey’s honest significant difference post hoc test for unequal cell size was used to determine significance among mean values. Intergroup differences in physical and functional characteristics were compared by using a nonpaired t-test.

RESULTS

All subjects successfully completed the two 30-min exercise bouts and consumed the provided beverages in the allotted time periods. The average volume of Gluexo beverage consumed at each of the five drink periods in the GT was 213 ± 23 and 228 ± 17 ml (corresponding to 17.0 ± 1.8 and 18.2 ± 1.3 g glucose) for IDDM and healthy groups, respectively.

RER, heart rate, \( V_\text{O}_2 \), and substrates. RER at rest before beverage intake was similar between trials but was lower in the IDDM group (0.83 ± 0.01) vs. healthy group (0.89 ± 0.01; \( P < 0.05 \)). During exercise, mean heart rate, \( V_\text{O}_2 \), and RER were similar for groups, trials, and time points (Table 2). The work rate was also similar among the groups, trials, and time points, averaging 90 ± 8 W.

Gluexo oxidation during the entire 60-min exercise in the CT was 85 ± 9.2 vs. 92 ± 6.6 g in the IDDM and healthy groups, respectively (not significantly different). In the GT, Gluexo oxidation was similar to that in CT in the IDDM group (85 ± 9.9 g) but tended to increase (97 ± 7.6 g; \( P = 0.09 \)) in the healthy group. Fattot oxidation during the entire 60-min exercise in the CT was 13 ± 2.2 vs. 11 ± 1.7 g in the IDDM and healthy groups, respectively (not significantly different). In the GT, Fattot oxidation was similar to that in CT in both groups averaging 11 ± 1.9 vs. 9 ± 1.4 g in IDDM and healthy groups, respectively.

Gluexo oxidation in the GT increased linearly in both groups to a maximal rate of 0.40 ± 0.066 and 0.48 ± 0.031 g/min at 65 min in the IDDM and healthy groups, respectively (Fig. 1, Table 3). The total amount of Gluexo oxidized during the 60-min exercise period (area under the curves in Fig. 1, omitting the 5-min rest period at 30 min) was 10.4 ± 1.7 and 14.8 ± 1.3 g in the IDDM and healthy boys, respectively (\( P = 0.06 \)). To correct for differences in the amount of Gluexo ingested among subjects (ranging from 52 to 127 g/h), Gluexo oxidation was also expressed as a percentage of that ingested.

Table 2. Heart rate, \( V_\text{O}_2 \), and RER during exercise in the CT and GT for the two subject groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Heat Rate, beats/min</th>
<th>( V_\text{O}_2 ), l/min</th>
<th>RER</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDDM (n = 8)</td>
<td>CT 147 ± 5.6</td>
<td>1.49 ± 0.06</td>
<td>0.91 ± 0.006</td>
</tr>
<tr>
<td></td>
<td>GT 141 ± 5.2</td>
<td>1.41 ± 0.07</td>
<td>0.92 ± 0.006</td>
</tr>
<tr>
<td>Healthy (n = 6)</td>
<td>CT 152 ± 6.6</td>
<td>1.51 ± 0.04</td>
<td>0.92 ± 0.005</td>
</tr>
<tr>
<td></td>
<td>GT 152 ± 5.8</td>
<td>1.51 ± 0.05</td>
<td>0.94 ± 0.006</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n \), no. of subjects. \( V_\text{O}_2 \), \( O_2 \) uptake; RER, respiratory exchange ratio; CT, control trial; GT, glucose trial. No significant differences either between trials or between groups exist.

This value was 12.1 ± 1.3 vs. 16.2 ± 0.8% in the IDDM and healthy boys, respectively (\( P = 0.02 \)).

Substrate oxidation rates during the second exercise bout are shown in Table 3. There were no significant differences among groups, trials, or time points for Gluexo oxidation or Fattot oxidation. There was a tendency, however, for Fattot oxidation to be lower in the GT than in the CT in both IDDM and healthy subjects (\( P = 0.051 \)). Gluendo was lower in GT than in CT for both IDDM and healthy groups (\( P < 0.001 \)) and was also significantly lower during the 25- to 30-min collection period than during the 5- to 10-min period in the GT (\( P < 0.05 \)). Gluexo oxidation was not significantly different between the groups during the second exercise bout.

Figure 2 shows the percentages of energy contribution from Gluendo, Gluexo, and Fattot oxidation during both trials in both groups. In the CT, percent energy contribution from Gluendo was similar between groups and decreased steadily from 78 ± 2 at 10 min to 72 ± 3% at 60 min (\( P < 0.001 \)). In the GT it was also similar between groups and decreased steadily from 80 ± 3 at 10 min to 54 ± 2% at 60 min (\( P < 0.001 \)). Percent energy contribution from Gluendo was significantly lower in the GT than in the CT at 30 (\( P < 0.01 \)), 45 (\( P < 0.001 \)), and 65 min (\( P < 0.001 \)). Energy contribution from Fattot oxidation was similar between groups and trials, averaging 20 ± 1 at 10 min and increasing to 26 ± 2% by 65 min (\( P < 0.001 \)). Energy contribution from Gluexo increased from 0.7 ± 0.77 and 3.1 ± 0.54% at 10 min to 21.0 ± 6.4 and 24.2 ± 2.2% by 65 min in IDDM and controls, respectively. The average percent energy contribution from Gluexo in the entire 60-min exercise was significantly lower in IDDM vs. healthy boys (9.1 ± 1.02 vs. 12.4 ± 0.50%, respectively; \( P = 0.02 \)).

Blood variables. Blood [glucose] in the healthy boys was similar in both trials at fasting (−100 min) and before beverage intake (−20 min), averaging 5.0 ± 0.1
mmol/l (Fig. 3). In the CT, [glucose] remained relatively stable in the healthy group but was somewhat elevated (+1–2 mmol/l; P < 0.05) after beverage intake in the GT. In the IDDM group, [glucose] was, on average, higher than in the healthy group (P < 0.01). Levels were similar in both trials before beverage intake, increasing from 8.0 ± 1.2 at fasting to 14.9 ± 1.3 mmol/l (P < 0.001) by ~20 min. In the CT, [glucose] decreased throughout exercise from 15.0 ± 2.0 at ~5 min to 6.9 ± 1.5 mmol/l at 65 min (P < 0.001), with four subjects experiencing levels below 4.0 mmol/l by the end of exercise. During the GT, [glucose] was significantly higher than in the CT at all time points during exercise but also decreased from 16.3 ± 2.1 at ~5 min to 11.7 ± 1.6 mmol/l by 65 min (P < 0.01) with no subjects experiencing levels below 4.0 mmol/l.

Plasma [insulin] in the healthy group during the CT decreased gradually from 55.5 ± 15.9 at ~5 min to 11.2 ± 2.8 µIU/ml at 65 min (P < 0.05; Fig. 4). In the GT, [insulin] decreased from 60.7 ± 12.3 at ~5 min to 27.0 ± 8.2 µIU/ml (P < 0.01) but was significantly higher than in the CT at 30 (P < 0.05) and 65 min (P < 0.05). In the IDDM group, [insulin] was approximately twofold higher than in the healthy group (P < 0.05) but was similar in both trials and at all time points, averaging 112.5 ± 13.4 µIU/ml.

Blood [lactate] was not significantly different between groups or trials, although there was a tendency for higher values during exercise in the IDDM group (P = 0.10; Fig. 4). At rest, [lactate] averaged 0.55 ± 0.1 mmol/l in both groups and in both trials. During exercise, [lactate] increased to 1.46 ± 0.24 and 1.10 ± 0.09 mmol/l at 30 min (both P < 0.05) and then decreased to 1.11 ± 0.17 and 0.80 ± 0.06 mmol/l at 65 min (both P < 0.05) in the IDDM and healthy group, respectively.

In the healthy group, plasma [FFA] was similar between trials at rest before beverage intake, averaging 0.30 ± 0.05 mmol/l (Fig. 5). [FFA] increased gradually from 0.33 ± 0.05 at ~5 min to 0.50 ± 0.09 mmol/l

### Table 3. Substrate oxidation during the second exercise bout in IDDM and healthy boys

<table>
<thead>
<tr>
<th>Group</th>
<th>Glu&lt;sub&gt;tot&lt;/sub&gt;</th>
<th>Glu&lt;sub&gt;exo&lt;/sub&gt;</th>
<th>Glu&lt;sub&gt;endo&lt;/sub&gt;</th>
<th>Fat&lt;sub&gt;tot&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>GT</td>
<td>CT</td>
<td>GT</td>
</tr>
<tr>
<td>IDDM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–10 min</td>
<td>1.36 ± 0.17</td>
<td>1.37 ± 0.20</td>
<td>0.25 ± 0.05</td>
<td>1.36 ± 0.17</td>
</tr>
<tr>
<td>25–30 min</td>
<td>1.39 ± 0.15</td>
<td>1.45 ± 1.18</td>
<td>0.40 ± 0.07</td>
<td>1.39 ± 0.15</td>
</tr>
<tr>
<td>Healthy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–10 min</td>
<td>1.47 ± 0.14</td>
<td>1.58 ± 0.13</td>
<td>0.34 ± 0.03</td>
<td>1.47 ± 0.14</td>
</tr>
<tr>
<td>25–30 min</td>
<td>1.47 ± 0.13</td>
<td>1.54 ± 0.12</td>
<td>0.48 ± 0.03</td>
<td>1.47 ± 0.13</td>
</tr>
</tbody>
</table>

Values are means ± SE given in g/min. Glu<sub>tot</sub>, total glucose; Glu<sub>exo</sub>, exogenous glucose; Glu<sub>endo</sub>, endogenous glucose; Fat<sub>tot</sub>, total fat. Main effects of trial (P < 0.001) and time (P < 0.05) as well as a trial by time interaction (P < 0.001) on Glu<sub>endo</sub> oxidation were found. Main effects for trial on Fat<sub>tot</sub> oxidation (P < 0.05) time on Glu<sub>exo</sub> oxidation (P < 0.001) were also found.

Fig. 2. Percent energy contribution from endogenous (Glu<sub>endo</sub>) Glu<sub>exo</sub> and total fat (Fat<sub>tot</sub>) oxidation in IDDM and healthy boys during control trial and glucose trial. Values for 10–60 min of exercise (omitting rest period at 30 min) are shown. A: IDDM boys in control trial. B: IDDM boys in glucose trial. C: healthy boys in control trial. D: healthy boys in glucose trial. See results for statistical differences. Note: because of the delay in measuring 13CO<sub>2</sub> production at the mouth, Glu<sub>exo</sub> oxidation may be underestimated and Glu<sub>endo</sub> may be overestimated during first exercise bout.

Fig. 3. Blood glucose concentrations before and throughout exercise in control trial (Δ, ○) and glucose trial (Δ, ●) in IDDM (○, ●) and healthy (○, ●) boys. Hatched bars indicate timing of exercise. Values are means ± SE. P < 0.05 vs. †control trial and ‡–20 min. Main effect of group, P < 0.05.
by 65 min (P < 0.05) in the CT but remained relatively stable in the GT. In the IDDM group, [FFA] at rest before beverage intake was also similar between trials but was significantly higher than in the healthy group (P < 0.05), averaging 0.48 ± 0.05 mmol/l (Fig. 5). During exercise, [FFA] decreased in both trials in the IDDM group from 0.47 ± 0.04 at −5 min to 0.28 ± 0.02 mmol/l by 65 min (P < 0.05).

Blood [glycerol] at rest before beverage intake was similar in both groups and in both trials, averaging 0.024 ± 0.001 mmol/l (Fig. 5). In the healthy boys, levels increased steadily from 0.020 ± 0.001 at −5 min to 0.08 ± 0.010 mmol/l at 65 min (P < 0.05) in the CT but remained unchanged significantly in the GT. In the IDDM group, [glycerol] was similar in both trials and unchanged during exercise, averaging 0.034 ± 0.001 mmol/l.

**DISCUSSION**

The main finding of this study is that, despite higher circulating [insulin] (Fig. 4), Gluexo oxidation during 60 min of moderate-intensity exercise in adolescent boys with IDDM is lower than in healthy age- and weight-matched controls (Figs. 1 and 2). This finding is similar to the results of Krzentowski et al. (21), who found that Gluexo oxidation was somewhat impaired during prolonged exercise in adult men with IDDM compared with healthy controls. The IDDM subjects in that study, however, were treated with a low basal rate of intravenous insulin infusion and were fasted during the exercise. In our study, subjects injected insulin subcutaneously and ingested a preexercise meal before exercise. Our protocol was designed to examine Gluexo oxidation during exercise in adolescents with IDDM during their usual insulin and diet therapy when [glucose] and [insulin] are elevated in comparison to their nondiabetic peers. Because hyperinsulinemia and hyperglycemia increase glucose oxidation in healthy nondiabetic subjects (19, 37), we hypothesized that Gluexo oxidation would be higher in the subjects with IDDM compared with healthy controls. However, although our subjects with IDDM were exercising with high [glucose] (Fig. 3) and [insulin] (Fig. 4), Gluexo oxidation was lower at all time points than in healthy controls (Fig. 1).

Because the $^{13}$CO$_2$ production at the mouth may lag behind the actual Gluexo oxidation rate as a result of the presence of the large bicarbonate pool (9), we have also reported substrate utilization during the second exercise bout separately (Table 3). No differences in substrate utilization were found during the second exercise bout between groups, although there was a tendency for Gluexo oxidation to be lower in the IDDM group (P = 0.20). The failure to show a quantitative difference in substrate utilization during the second bout between the IDDM and healthy groups may have resulted from our relatively small sample size (n = 8 vs. n = 6, respectively). Nevertheless, although an exact quantitative assessment of Gluexo oxidation may not have been reached during the initial 30-min exercise in our study, we assume that the $^{13}$C/$^{12}$C equilibrium kinetics are similar in IDDM and healthy adolescents and that any small error in determining Gluexo oxidation should be equal for both groups. We believe, therefore, that from...
the qualitative assessment of Gluexo oxidation (Figs. 1 and 2), it appears that Gluexo oxidation in IDDM is impaired. This finding not only causes us to reject our initial hypothesis that hyperinsulinemia would enhance Gluexo oxidation in IDDM but also further indicates that Gluexo oxidation is impaired even during exercise performed after subcutaneous insulin injection.

Previous studies have shown that glucose uptake and utilization are clearly impaired in animal models of IDDM when insulin is absent or reduced (5, 38). In addition, in insulin-deprived IDDM human subjects, Gluexo oxidation is impaired by ~50% compared with controls (21). There are contrasting data, however, regarding the influence of normalizing insulin levels on glucose utilization during exercise in patients with IDDM. Plasma glucose utilization has been reported to be both similar (35) or significantly reduced (30) when compared with that of nondiabetic subjects exercising at the same [insulin]. In support of the latter, plasma glucose uptake has been shown to be restored to normal only if [insulin] is approximately fourfold higher in IDDM compared with healthy individuals (41). In line with these findings of impaired glucose uptake in insulin-treated IDDM, our study shows that orally ingested Gluexo oxidation is lower in IDDM compared with healthy controls, despite [insulin] values that are threefold higher.

The reduced Gluexo oxidation in the subjects with IDDM may be explained by several possible factors. First, a lower rate of gastrointestinal absorption of glucose may have limited Gluexo oxidation during exercise. Delays in gastric emptying time and gastric electrical abnormalities at rest have been associated with poor glycemic control in children with IDDM (13). Furthermore, hyperglycemia impedes gastric emptying in IDDM (34), and experimental hyperinsulinemia reduces carbohydrate absorption at least in healthy individuals (15). Although we did not measure plasma glucose enrichment in our subjects to assess glucose absorption, our subjects with IDDM who were both hyperglycemic and hyperinsulinemic would be expected to have impaired Gluexo absorption. These potential impairments in glucose absorption in our subjects may have resulted in a lower Gluexo oxidation. Second, it appears from the elevated glycemic (Fig. 3) and insulin (Fig. 4) concentrations that our subjects with IDDM have some degree of insulin resistance that may limit plasma glucose uptake and oxidation. Indeed, adolescents with IDDM are especially prone to insulin resistance and poor diabetes management (2). A reduction in skeletal muscle glucose-transporter density (specifically the GLUT-4 isoform) has been associated with insulin resistance in IDDM (20). A lower density of GLUT-4 isoform or an inability to activate the transporter mechanism (29) may reduce Gluexo uptake and oxidation in IDDM even if [insulin] values are elevated. Interestingly, however, no relationships between either individual glycosylated hemoglobin levels ($r = -0.10$) or [insulin] ($r = -0.12$) and Gluexo oxidation were found. Because we did not measure plasma glucose uptake in our study, we are unsure whether a lower Gluexo oxidation was a result of a reduced skeletal muscle uptake of glucose. Third, Gluexo oxidation may be impaired in insulin-treated individuals with IDDM because of an impairment in a key regulatory enzyme of glucose oxidation [i.e., pyruvate dehydrogenase (PDH) complex]. In healthy adults, the oxidation of ingested carbohydrate may be regulated by the activation of the PDH complex (36) and an impairment in this activation (16) may reduce Gluexo oxidation in IDDM. Although we did not measure PDH activity directly in this study, the elevated [FFA] observed at rest in the subjects with IDDM would be expected to inactivate the PDH complex, according to the glucose-fatty acid cycle as proposed by Randle et al. (32). Indeed, elevations in [FFA] associated with diabetes appear to lower skeletal muscle glucose uptake and oxidation (4). Conceivably, these potential impairments in gastrointestinal glucose absorption, insulin sensitivity, skeletal muscle glucose transport, and PDH activation may help to explain the reduction in Gluexo oxidation in our subjects with IDDM.

In addition to the lower rate of Gluexo oxidation compared with controls, our subjects with IDDM tended to utilize less total carbohydrate and more fat both at rest and during exercise (Table 3). This finding is in agreement with a recent study examining substrate utilization during moderate and intense exercise in adults with IDDM (30). In our study, the difference in Gluexo and Fattot oxidation during exercise between IDDM and healthy boys was not statistically significant; however, possibly because of our small sample sizes. Interestingly, although [insulin] was elevated compared with controls, [FFA] was also somewhat elevated (Fig. 5). The elevated [FFA], along with lower RER during rest and exercise in IDDM, indicates a greater reliance on fat oxidation compared with that in the healthy boys. Furthermore, it appears that individuals with IDDM lack the expected increase in [glycerol] and [FFA] normally observed with prolonged exercise without carbohydrate intake (Fig. 5). These findings indicate that substrate utilization and the metabolic response to exercise are not restored to normal with subcutaneous insulin administration.

The use of $^{13}$C glucose tracer allows for an indirect estimation of Gluendo during exercise. In this study, Gluendo was lower in the GT compared with the CT (Fig. 2, Table 3), indicating that Gluexo ingestion spares endogenous glycogen stores by ~12% in adolescents with and without IDDM. A similar Gluendo sparing effect with Gluexo intake has also been shown in healthy adults (24). In line with these findings, glucose intake appears to reduce hepatic glucose output (25) and may lower muscle glycogen utilization if the dose of glucose is large enough or if the exercise is of an intermittent type (8, 18, 39). However, other investigations have found no muscle glycogen-sparing effect with Gluexo intake (7, 11, 17). Because of methodological limitations in this study, we are unsure what source of Gluendo was spared with Gluexo intake.
Blood [glucose] in the individuals with IDDM decreased significantly during exercise with water ingestion, but this drop was attenuated with Gluexo ingestion (Fig. 3). The attenuation of the hypoglycemic effect of exercise with Gluexo intake matched with Glu tot utilization elevated after subcutaneous insulin injection in these nondiabetic boys even though plasma insulin levels were not change significantly during exercise with water ingestion but was slightly elevated with Gluexo intake. A small decrease in glycemia has been reported after the onset of postprandial exercise in healthy 8- to 11-yr-old boys and girls (14).

In conclusion, the oxidation rate of exogenous glucose during prolonged moderate-intensity exercise is impaired in boys with IDDM compared with healthy nondiabetic boys even though plasma insulin levels are elevated after subcutaneous insulin injection in these patients. Gluexo ingestion matched with Glu tot utilization contributes from 9 to 12% of the total energy provision of exercise in adolescent boys with and without IDDM and is effective in attenuating the drop in blood glucose in boys with IDDM.

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