The Effects of Aerobic Exercise on Glucose and Counterregulatory Hormone Concentrations in Children With Type 1 Diabetes

THE DIABETES RESEARCH IN CHILDREN NETWORK (DIRECNET) STUDY GROUP*

OBJECTIVE — To examine the acute glucose-lowering effects of aerobic exercise in children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Fifty children and adolescents with type 1 diabetes (ages 10 to <18 years) were studied during exercise. The 75-min exercise session consisted of four 15-min periods of walking on a treadmill to a target heart rate of 140 bpm and three 5-min rest periods. Blood glucose and plasma glucagon, cortisol, growth hormone, and norepinephrine concentrations were measured before, during, and after exercise.

RESULTS — In most subjects (83%), plasma glucose concentration dropped at least 25% from baseline, and 15 (30%) subjects became hypoglycemic (≤60 mg/dl) or were treated for low glucose either during or immediately following the exercise session. The incidence of hypoglycemia and/or treatment for low glucose varied significantly by baseline glucose, occurring in 86 vs. 13 vs. 6% of subjects with baseline values <120, 120–180, and >180 mg/dl, respectively ($P < 0.001$). Exercise-induced increases in growth hormone and norepinephrine concentrations were marginally higher in subjects whose glucose dropped ≤70 mg/dl. Treatment of hypoglycemia with 15 g of oral glucose resulted in only about a 20-mg/dl rise in glucose concentrations.

CONCLUSIONS — In youth with type 1 diabetes, prolonged moderate aerobic exercise results in a consistent reduction in plasma glucose and the frequent occurrence of hypoglycemia when preexercise glucose concentrations are <120 mg/dl. Moreover, treatment with 15 g of oral glucose is often insufficient to reliably treat hypoglycemia during exercise in these youngsters.

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The benefits of exercise in children and adolescents with type 1 diabetes have long been recognized. Nevertheless, exercise has potential acute adverse effects that are related to hypo- and hyperglycemic excursions. Hypoglycemia during exercise in a child can be dangerous and decreases a young person's performance during sports or other activities. Conversely, excessive snacking before or during exercise can result in hyperglycemia and negate some metabolic and vascular benefits of exercise. Despite the prominent role that sports and physical activity play in the lives of many youth with type 1 diabetes, standard recommendations that could guide families and clinicians in the management of glycemia during exercise are lacking.

There are a variety of conditions that need to be considered in understanding hypoglycemia during exercise, including the type and duration of exercise, glucose concentrations before starting exercise, and the relation of exercise to meals and insulin doses. Guelfi et al. (1) compared the effects of exercise on a bicycle ergometer over a 30-min period with and without brief maximal sprints in seven children with type 1 diabetes. Exercise, which was performed in the late morning when the blood glucose was ~200 mg/dl following breakfast and a prebreakfast insulin dose, resulted in an ~25-mg/dl-greater fall in blood glucose when exercise did not include the interspersed sprints. There was a larger increase in counterregulatory hormone concentrations that may have blunted the fall in glucose concentrations when exercise included the sprints. Plasma glucose concentrations <72 mg/dl were observed in 3 of 14 exercise tests.

We conducted a study to examine the acute glucose-lowering effects of aerobic exercise in 50 youth with type 1 diabetes. In contrast to the Guelfi study, our subjects exercised in the late afternoon 4 h after lunch over a 75-min period at moderate intensity, at the time of day of after school physical activity. In a prior publication, we reported that the mean overnight glucose was lower (131 vs. 154 mg/dl, $P = 0.003$) and the overnight incidence of hypoglycemia greater on the exercise day compared with a control sedentary day (48 vs. 28%, $P = 0.009$) (2). Herein, we report the changes in glucose and counterregulatory hormones during the exercise session compared with those during a control day without exercise.

RESEARCH DESIGN AND METHODS

— Details of the protocol are reported elsewhere (2). Major eligibility criteria included *1*) age 10 to <18 years, *2*) diagnosis of type 1 diabetes of at least 18 months duration, *3*) stable insulin regimen involving either use of an insulin pump or use of insulin glargine and short-acting insulin for at least 1 month (NPH or Lente, if part of regimen, used only in the morning), *4*) HbA_{1c} (A1C) ≤10.0%, *5*) BMI between the 5th and 95th percentile for age and sex (3), and *6*) no severe hypoglycemia episodes within the past 2 weeks.

The study consisted of two randomized 24-h clinical research center admissions separated by 1–4 weeks: one with a

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*A list of DirecNet Study Group members appears in the appendix to ref. 2. See the APPENDIX for members of the writing committee.

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

75-min exercise session in the late afternoon (exercise day) and one without exercise (sedentary day). Insulin management on both study days were as similar as possible and followed the routine that the subject followed at home on a day without exercise.

On the morning of the exercise day, the subjects walked on a motorized treadmill for 5–15 min to determine the settings needed to achieve a steady-state heart rate of 140 bpm. These treadmill settings were used for the start of the afternoon exercise session at ~4:00 P.M. A heart rate of 140 bpm is ~70% of maximal heart rate, equivalent to 60% maximum aerobic effort. This level of exertion in children and adolescents is considered moderate and aerobic (4). Subjects were assumed to have a normal cardiovascular response to exercise due to their age and limited duration of diabetes. At 2:00 and 3:00 P.M. on both the exercise and sedentary days, the glucose concentrations in blood were measured with a One Touch Ultra meter (LifeScan, Milpitas, CA). These values are expressed as equivalent concentrations in plasma or serum, comparable to central laboratory measurements (5). At the discretion of the investigator, small correction doses of rapid-acting insulin analog were allowed for high glucose (six subjects received a correction dose on both days, three others on the exercise day, and five others on the sedentary day) and 15–30 g of carbohydrate for low glucose concentrations with the aim of achieving 4:00 P.M. glucose concentrations between 80 and 200 mg/dl. On the exercise day at 4:00 P.M., if the glucose concentration was <80 mg/dl, the subject was given a snack, and the start of the exercise was deferred until the glucose was ≥80 mg/dl. No extra insulin was given if the 4:00 P.M. glucose concentration was >200 mg/dl. In insulin pump patients, the usual basal rate was continued during the exercise session and was the same rate of infusion as on the sedentary day. Six children were receiving NPH insulin in the morning with the same dose on both days.

The exercise protocol consisted of four 15-min periods walking on a treadmill at a heart rate of ~140 bpm (target range 133–147 bpm) separated by a 5-min seated rest period. A heart rate monitor (Polar Electro, Kempele, Finland) was worn throughout the exercise session.

Blood samples for central laboratory determination of glucose and counterregulatory hormone concentrations (with plasma and serum separated promptly) were obtained from an intravenous catheter before starting exercise, during each of the three rest periods, immediately following exercise completion, and 30 min after exercise completion. Glucose concentrations were also checked using the Ultra meter at each time point during and at 15-min intervals following completion of exercise. If the meter glucose concentration dropped to <60 mg/dl, the subject was given 15 g of carbohydrate, and after 5–15 min the glucose concentration was rechecked. Exercise did not resume until the glucose concentration was >70 mg/dl. On the sedentary day, glucose determinations were made with the Ultra meter at 4:00 and ~6:00 P.M.

Serum glucose was measured by the DirecNet Central Laboratory (University of Minnesota) using a hexokinase enzymatic method, which has been proposed as the reference method for measuring glucose (6,7). Glucagon was measured by a radioimmunoassay (Linco Research, St. Charles, MO) with the primary antibody from guinea pig and secondary from goat. Lower limit of detection was 20 pg/ml. Coefficients of variation (CVs) were 6.5–8.8% on three control subjects. Cortisol was assayed with a competitive chemiluminescence assay (Bayer Advia Centaur; Bayer HealthCare, Tarrytown, NY) using a polyclonal rabbit antibody and mouse monoclonal antibody coupled with paramagnetic particles. Lower limit of detection was 0.5 μg/dl. CVs were 11–12% on two control subjects. Growth hormone was measured by a sandwich chemiluminescence assay (DPC Immulite). Monoclonal mouse antibody was coated on the bead with a rabbit polyclonal antibody in the reagent. Lower limit of detection was 0.1 ng/ml. CVs were 5.9–9.1%.

Norepinephrine and epinephrine were measured at the Mayo Clinic Laboratory (Rochester, MN) using a reverse-phase (C18) high-performance liquid chromatography column to separate norepinephrine and epinephrine, which were detected coulometrically, using an ESA Coulochem II instrument. Lower limit of detection is 10 pg/ml. CVs were 7–11% and 6–7%, respectively, on three control subjects. Unlike norepinephrine, many baseline epinephrine values were below the assay's detection limit, which may have been due in part to the fact that plasma samples were not collected in tubes containing preservatives. Consequently, only norepinephrine results will be reported.

Statistical analysis

Hypoglycemia was defined as a laboratory glucose concentration ≤60 mg/dl and/or treatment for low glucose based on the Ultra meter concentration available at the time. Laboratory glucose concentrations were used for analysis whenever available. When a laboratory glucose was unavailable, the Ultra meter concentration was used instead. Two subjects were excluded from the analysis of glucose change during exercise because a snack was given before the start of exercise (due to an Ultra concentration <80 mg/dl), and a baseline glucose concentration was not recorded after the snack.

Exercise versus sedentary day glucose concentrations were compared separately at 4:00 and 6:00 P.M. using a repeated-measures regression including a period effect. Logistic regression was used to identify factors associated with hypoglycemia and/or treatment for low glucose during exercise. Factors considered in these models included: baseline glucose, age, sex, insulin route (pump versus injections), A1C, BMI, self-reported days with at least 1 h of exercise during a typical week, and estimated level of cardiovascular fitness. To assess the latter, we predicted the oxygen uptake (milliliters per kilogram per minute) during the exercise session at the target heart rate of 140 bpm using the American College of Sports Medicine metabolic equation for graded walking that has been validated for adults (we assume it is approximate for children as well) (8).

Repeated-measures regression treating time as a linear continuous factor was used to test for changes in the concentrations of growth hormone, norepinephrine, cortisol, and glucagon. ANCOVA was used to compare changes between subjects whose glucose did versus did not drop ≤70 mg/dl during exercise adjusting for the baseline concentrations. Logarithm transformation was used for norepinephrine and cortisol and a square root transformation for growth hormone to reduce the skewness of the distributions.

RESULTS — Fifty subjects participated in the study. Their average age was 14.8 ± 1.7 years and they were 44% female and 90% Caucasian, 4% African American, 2% Hispanic, and 4% Asian. Duration of diabetes was 7.0 ± 3.7 years.

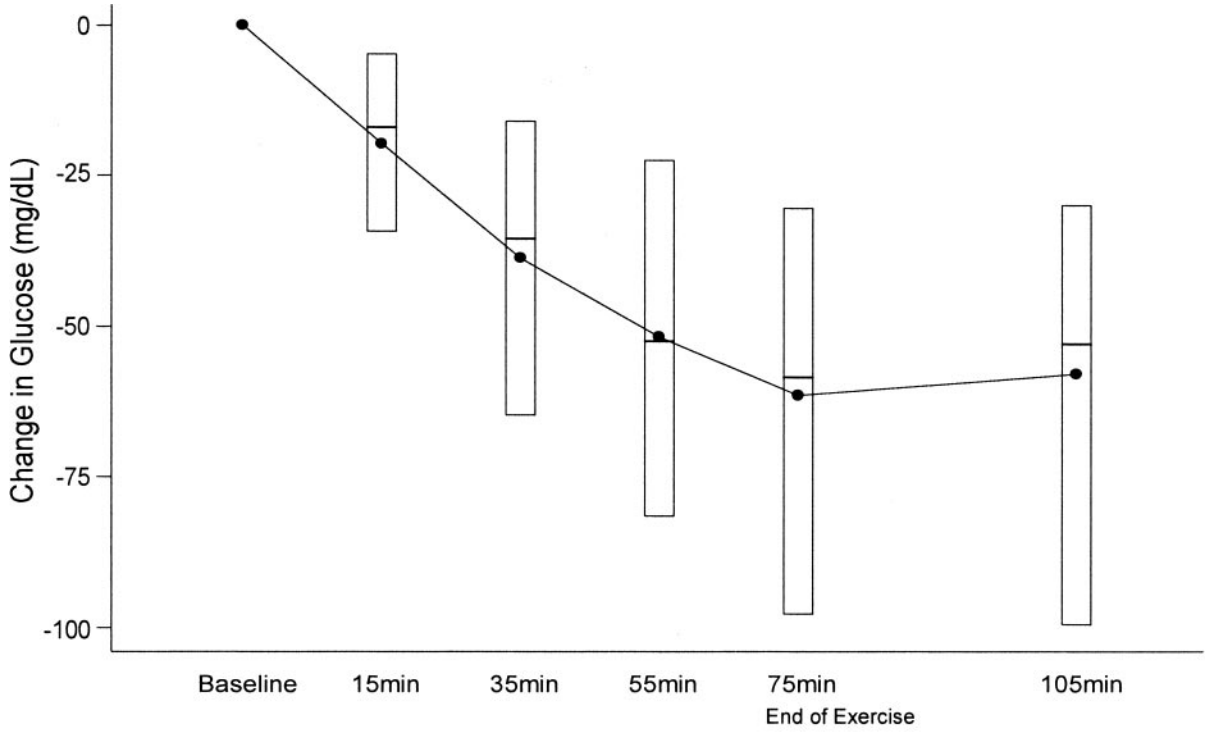

Figure 1—*Change in glucose concentrations during exercise* (n = *48). Two subjects excluded because baseline glucose was unavailable (see* RESEARCH DESIGN AND METHODS*). Black dots denote mean values and boxes denote median (25th, 75th percentiles).*

Fifty-four percent used an insulin pump and 46% used glargine and short-acting insulin (26% of those using glargine were also taking NPH in the morning). A1C was 7.8 ± 0.8%.

Treadmill settings and adherence to protocol

The median treadmill speed needed to achieve the target heart rate of 140 bpm was 3.5 mph (25th, 75th percentiles = 3.4, 4.0 mph; range 2.7–4.0) and the median incline was 6.8° (3.0, 8.0; 0–10.0). Predicted oxygen uptake had a median value of 22.9 ml · kg^{-1} · min^{-1} (19.1, 25.9; 12.9–33.5).

The full four-cycle exercise session was completed by 46 (92%) of 50 subjects. Three subjects completed the first three cycles and part of a fourth, and the remaining subject completed two cycles fully and two partially. One subject achieved the target heart rate in three of the four exercise cycles and the other 49 subjects achieved target for all four cycles. Median time (25th, 75th percentiles) required to achieve 140 bpm from the start of each cycle was 3 min (2,4) ranging from <1 to 11 min.

Glucose changes during exercise

Mean baseline glucose concentration at 4:00 P.M. before exercise was 159 ± 61 mg/dl, similar to the 4:00 P.M. glucose concentrations on the sedentary study day (167 ± 95 mg/dl; $P = 0.45$). Glucose concentrations fell rapidly, beginning in the first 15 min of exercise and extending throughout the 75-min period (Fig. 1). The mean glucose concentration at 6:00 P.M., ~45 min after completion of the exercise and before dinner, was lower than it was on the sedentary day (112 ± 58 vs. 159 ± 78 mg/dl, $P < 0.001$).

The relationship between baseline and nadir glucose concentrations during exercise in individual subjects is shown in Fig. 2. Most had a decline in the glucose concentration irrespective of the baseline concentration, with 83% experiencing a drop in the glucose concentration ≥25%.

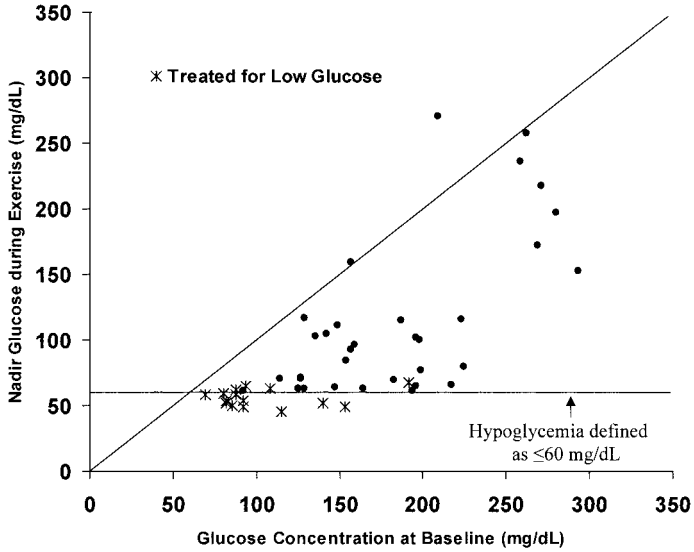

Figure 2—*Nadir glucose during exercise versus baseline concentration* (n = *48). Two subjects excluded because baseline glucose was unavailable (see* RESEARCH DESIGN AND METHODS*). Diagonal represents the line of identity.*

Eleven (23%) subjects became hypoglycemic (laboratory glucose ≤60 mg/dl) either during or immediately following exercise, and four additional subjects were treated for hypoglycemia due to an Ultra meter glucose ≤60 mg/dl but had central laboratory glucose concentrations between 62 and 68 mg/dl. Eleven subjects had a laboratory glucose concentration between 61 and 70 mg/dl (overall 26 of 50, 52% with a concentration ≤70 mg/dl). Only one subject had a meaningful increase in the glucose concentration. Among the 15 subjects who developed and/or were treated for hypoglycemia, hypoglycemia occurred after the first 15-min cycle in 3, second cycle in 2, third cycle in 5, and fourth cycle in 5.

The drop in glucose from baseline to nadir averaged 34 ± 14 mg/dl when the baseline glucose was <120 mg/dl, 58 ± 29 mg/dl when the baseline was 120–180 mg/dl, and 91 ± 55 mg/dl when the baseline was >180 mg/dl. The incidence of hypoglycemia and/or treatment for low glucose varied significantly by baseline glucose, occurring in 86 vs. 13 vs. 6% of subjects with baseline concentrations <120, 120–180, and >180 mg/dl, respectively ($P < 0.001$). Corresponding percentages for ≤70 mg/dl were 100 vs. 44 vs. 28% ($P < 0.001$). After controlling for baseline glucose, no other factors were associated with the risk of hypoglycemia including age ($P = 0.71$), sex ($P = 0.64$), BMI ($P = 0.38$), duration of diabetes ($P = 0.52$), A1C ($P = 0.39$), insulin route (multiple daily injections versus pump, $P = 0.65$), treadmill workload required to raise heart rate to 140 bpm ($P = 0.49$), and self-reported days of exercise in a typical week ($P = 0.91$).

Hormone changes during exercise

In the group as a whole, exercise induced a sharp rise in circulating concentrations of growth hormone (mean change baseline to peak: 12.0 ng/ml, $P < 0.001$) and norepinephrine (278 pg/ml, $P < 0.001$), but no statistically significant changes in plasma cortisol (baseline 9 vs. peak 12 μg/dl, $P = 0.54$) or plasma glucagon (72 vs. 82 pg/ml, $P = 0.16$). There were trends toward higher growth hormone ($P = 0.08$) and norepinephrine ($P = 0.04$) concentrations in subjects whose glucose dropped ≤70 mg/dl (Fig. 3).

Treatment of hypoglycemia

Based on the Ultra concentrations available at the time, 15 subjects were treated for hypoglycemia (mean 56 ± 5 mg/dl)

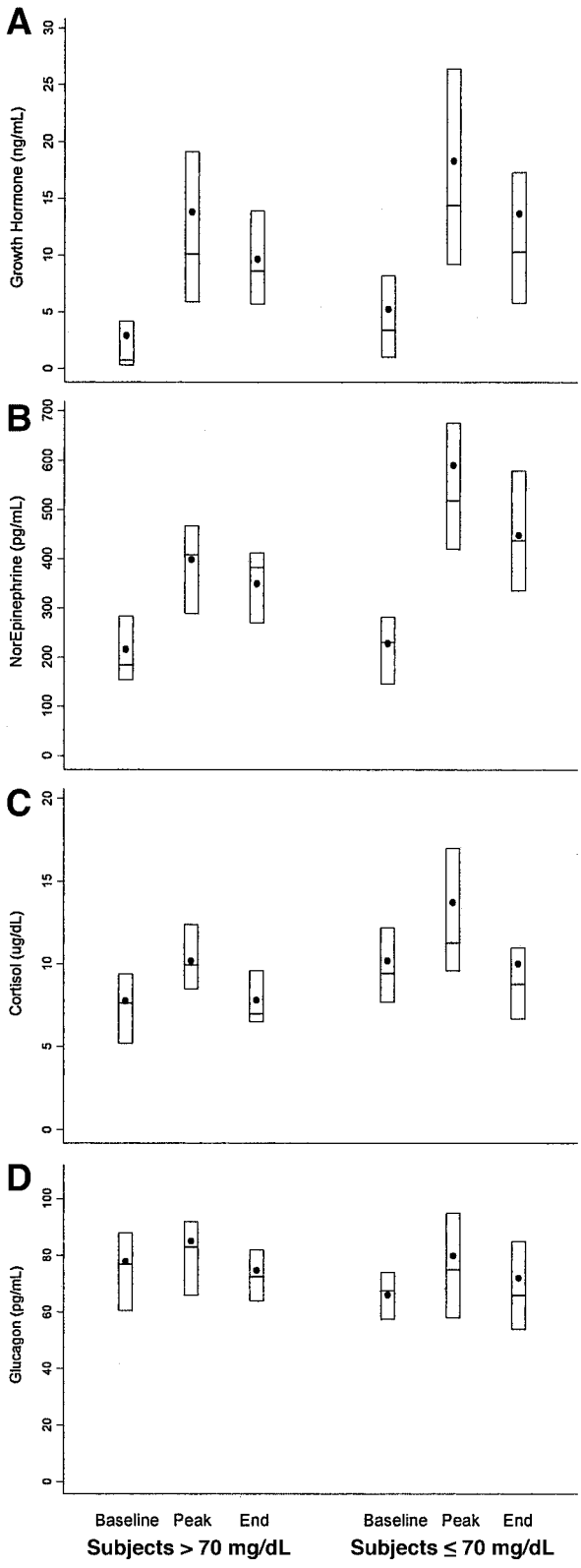

Figure 3—*Hormone concentrations during exercise. Distributions given for growth hormone* (A)*, norepinephrine* (B)*, cortisol* (C)*, and glucagon* (D)*. Black dots denote means and boxes denote median (25th, 75th percentiles). Hormone data available for* n = *45 subjects* (n = *23 whose glucose fell ≤70 mg/dl during exercise vs.* n = *22 whose glucose stayed >70 mg/dl). Norepinephrine data available for* n = *30 subjects (16 of whom had their glucose fall ≤70 mg/dl).*

during exercise. Glucose concentrations increased modestly ~10 min after 15 g of carbohydrate (to 77 ± 15 mg/dl, range 57–102). Four subjects required a second 15 g to raise the glucose >70 mg/dl and two required a second 15 g at the end of exercise for recurrent hypoglycemia.

CONCLUSIONS — The present study demonstrated that a prolonged period of aerobic exercise at the time of day for after school physical activity and consistent with federal recommendations for health-related physical activity (9) produced an average fall in plasma glucose of ~40% of baseline values. Treatment for hypoglycemia during exercise was required by ~30% of subjects. The baseline glucose concentration was a strong predictor of hypoglycemia risk (i.e., plasma glucose ≤60 mg/dl), since the majority of episodes occurred in children with preexercise concentrations <120 mg/dl and only one occurred with a baseline glucose >180 mg/dl (192 mg/dl). An American Diabetes Association Work Group recently recommended that hypoglycemia be defined biochemically as a plasma glucose concentration ≤70 mg/dl (10). By this standard, all of our subjects with baseline concentrations <120 mg/dl became hypoglycemic, 44% when the baseline concentration was 120–180 and 28% when the baseline concentration was >180 mg/dl. These data suggest that it is advisable to achieve a blood glucose level that is at least 120 mg/dl if not higher before the start of exercise and that monitoring for hypoglycemia during exercise is important even when the preexercise glucose is >180 mg/dl. Other important clinical factors (A1C, BMI, age, and insulin route) were not associated with hypoglycemia under these experimental conditions.

The reduction in glucose observed in our study following prolonged exercise in the late afternoon was larger than that observed by Guelfi et al. (11) following several short bursts of intense exercise after breakfast but was slightly less than was observed under similar conditions with moderate sustained exercise (1). These differences emphasize that the type, duration, and timing of exercise, as well as its relation to meals and insulin doses, need to be considered in assessing the metabolic effects of exercise in diabetic children.

Exercise stimulates growth hormone and catecholamine responses in diabetic and nondiabetic children (12), and our subjects showed the expected increases in growth hormone and norepinephrine concentrations. However, these counterregulatory hormone responses failed to prevent the fall in glucose during exercise in our subjects, indicating that exercise-induced increases in glucose utilization were not being compensated for by appropriate increases in endogenous glucose production. It is noteworthy that the development of hypoglycemia during exercise did not appear to enhance the rise in counterregulatory hormone levels over and above the responses that were stimulated by exercise alone. Reductions in glucose ≤70 mg/dl (a threshold value for stimulation of anti-insulin hormones in nonexercising children) (13) were only marginally associated with larger growth hormone and norepinephrine responses. Guelfi et al. noted significantly higher norepinephrine responses when exercise included several short sprints compared with sustained moderate exercise and similar trends in this direction for epinephrine and growth hormone (1).

In nondiabetic subjects, the initial response to falling plasma glucose concentrations is a prompt suppression of endogenous insulin secretion. Since we did not adjust the basal rate of insulin during exercise, it is possible that maintenance of basal insulin contributed to the inability of the liver to meet the increased metabolic demands of prolonged physical activity in our subjects. Temporary reduction or suspension of the basal rate can be readily accomplished with continuous subcutaneous insulin infusion. Further studies are needed to carefully determine whether such alterations in basal infusion doses at the start of exercise can prevent hypoglycemia without causing hyperglycemia and metabolic decompensation. Strategies are also needed to prevent nocturnal hypoglycemia on nights following exercise, since subjects in this study had an increased frequency of hypoglycemia during the night after exercise than on the sedentary night (2).

Because of its complexity, trial and error remains the principal method of managing glycemic excursions during exercise in individual patients. Nevertheless, studies such as ours can provide an evidence-based framework to guide the empirical decision-making process. Our findings underscore the importance of checking glucose concentrations before exercise to determine whether a preexercise snack is required to prevent hypoglycemia. Ingestion of 15 g of carbohydrate is a commonly recommended treatment for mild to moderate hypoglycemia in nonexercising children (14). However, in our subjects, treatment of hypoglycemia with 15 g of oral glucose resulted in only about a 20-mg/dl rise in glucose concentrations, and more than a third of those subjects needed a second 15 g to complete the exercise regimen. Consequently, 30–45 g of oral glucose may be a more appropriate amount of carbohydrate to treat hypoglycemia during exercise in children and adolescents with type 1 diabetes.

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APPENDIX

DirecNet Study Group

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