Prevention of Hypoglycemia During Exercise in Children With Type 1 Diabetes by Suspending Basal Insulin

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

OBJECTIVE — Strategies for preventing hypoglycemia during exercise in children with type 1 diabetes have not been well studied. The Diabetes Research in Children Network (DirecNet) Study Group conducted a study to determine whether stopping basal insulin could reduce the frequency of hypoglycemia occurring during exercise.

RESEARCH DESIGN AND METHODS — Using a randomized crossover design, 49 children 8–17 years of age with type 1 diabetes on insulin pump therapy were studied during structured exercise sessions on 2 days. On day 1, basal insulin was stopped during exercise, and on day 2 it was continued. Each exercise session, performed from ~4:00–5:00 P.M., consisted of four 15-min treadmill cycles at a target heart rate of 140 bpm (interspersed with three 5-min rest breaks over 75 min), followed by a 45-min observation period. Frequently sampled glucose concentrations (measured in the DirecNet Central Laboratory) were measured before, during, and after the exercise.

RESULTS — Hypoglycemia (≤70 mg/dl) during exercise occurred less frequently when the basal insulin was discontinued than when it was continued (16 vs. 43%; $P = 0.003$). Hyperglycemia (increase from baseline of ≥20% to ≥200 mg/dl) 45 min after the completion of exercise was more frequent without basal insulin (27 vs. 4%; $P = 0.002$). There were no cases of abnormal blood ketone levels.

CONCLUSIONS — Discontinuing basal insulin during exercise is an effective strategy for reducing hypoglycemia in children with type 1 diabetes, but the risk of hyperglycemia is increased.

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Although children and adolescents with type 1 diabetes are encouraged to exercise regularly, plasma glucose concentrations are often difficult to manage during prolonged periods of physical activity. In patients maintained on fixed basal/bolus insulin regimens, exercise-induced increases in glucose utilization can lead to hypoglycemia (1,2).

The examination of variables contributing to hypoglycemia during and after exercise in youth with diabetes has been the subject of increasing research (2–4). These studies illustrate that the type, duration, and timing of exercise, as well as its temporal relation to meals and premeal insulin doses, may affect the glucose-lowering effects of exercise in children with type 1 diabetes. However, few recent studies have examined the most effective means to prevent hypoglycemia during exercise in children.

A previous Diabetes Research in Children Network (DirecNet) study of 50 children with type 1 diabetes found that plasma glucose concentrations fell during moderate-intensity treadmill exercise in almost all patients, decreasing >25% in 83%, and 30% of subjects required treatment for hypoglycemia (2,5). Because the subjects received the same fixed basal insulin rates on both days, such maintenance of basal insulin may have contributed to the development of hypoglycemia.

The present study was undertaken to determine whether complete suspension of basal insulin infusion could effectively prevent hypoglycemia during exercise in children with type 1 diabetes on insulin pump therapy.

RESEARCH DESIGN AND METHODS

Consent procedures

The DirecNet Data and Safety Monitoring Board and the institutional review boards at each DirecNet center approved the study protocol, consent form, and assent form. A parent or guardian and each subject gave written consent and assent, respectively.

Eligibility criteria and assessment

To be eligible for the study, the subject had to *1*) be between 8 and 18 years of age, *2*) have a clinical diagnosis of type 1 diabetes of ≥18 months' duration, *3*) have a stable insulin regimen using an insulin pump for at least 1 month prior, *4*) have an HbA_{1c} (A1C) ≤10.0% measured with the DCA 2000 (Bayer Diagnostics, Tarrytown, NY), *5*) have a BMI between the 5th and 95th percentile for age and sex (6), *6*) have a body weight ≥39.5 kg, and *7*) have normal thyroid function. Subjects were not eligible if they *1*) had asthma that was medically treated in the prior year, *2*) were currently using glucocorticoids or β-blockers, *3*) anticipated a significant change in exercise regimen between admissions, or *4*) had a medical condition or were using a medication that in the judgment of the investigator could affect completion of the exercise protocol.

Study procedures

The study consisted of two 75-min exercise sessions in the late afternoon, separated by 6–36 days. For one of the visits (labeled "basal-stopped"), the insulin pump was turned off at the beginning of

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*A complete list of DirecNet Study Group members can be found in the APPENDIX.

Abbreviations: DirecNet, Diabetes Research in Children Network.

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

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the exercise session and restarted 45 min after exercise (~2 h total). For the other visit, the basal rate was continued during the exercise (labeled "basal-continued"). The order of the basal-stopped and basal-continued visits was determined at random using a crossover design.

Management of insulin and meals was as similar as possible during the basal-continued and basal-stopped visits. On both days, the subject arrived at the clinic's clinical research center before 12:00 P.M. and remained until ~6:30 P.M. Lunch was served in the clinical research center at approximately noon using the prelunch bolus and correction factor the subject usually used at home. Glucose was checked using a home glucose meter (see below) at 1:00, 2:00, and 3:00 P.M., with the goal of having the subject's glucose concentration between 120 and 200 mg/dl just before the start of exercise (~4:00 P.M.). An intravenous bolus of regular insulin (0.05–0.1 units/kg) was given because of its short half-life and duration of action if the investigator felt the subject's glucose level would likely be >200 mg/dl at 4:00 P.M., or 15–30 g carbohydrate was given orally if the investigator felt the subject's 4:00 P.M. glucose would likely be <120 mg/dl. If at 4:00 P.M. the subject's glucose was not within 120–200 mg/dl or the subject had been given intravenous insulin within the previous hour, then the exercise session was delayed. The glucose was checked every 15 min, and if not in range by 5:00 P.M., the visit was rescheduled (three basal-stopped and two basal-continued visits were rescheduled).

Exercise procedures and postexercise period. The exercise session consisted of 15 min of brisk walking on a treadmill at a heart rate of ~140 bpm (estimated to be equivalent to 55% Vo_{2max} [7]) followed by a 5-min rest period. A heart rate monitor was worn throughout exercise, and treadmill speed and/or incline were adjusted as necessary to achieve the target heart rate. This cycle was repeated three more times for a total of four 15-min exercise periods with 5-min rest periods in-between (75 min total).

Venous samples were used for the home glucose meter (FreeStyle Flash [8], "Freestyle"; Abbott Diabetes Care, Alameda, CA) and central laboratory (at the DirecNet Central Biochemistry Laboratory at the University of Minnesota using a hexokinase enzymatic method [9,10]) glucose determinations before starting exercise, during each of the three rest periods, immediately after exercise, and at 15, 30, and 45 min after completion of the exercise session. All results are expressed as plasma glucose concentrations. If during exercise the home glucose meter glucose dropped ≤65 mg/dl, further exercise was delayed until the glucose level was >70 mg/dl. Before starting and at the completion of the exercise session, blood ketones were checked by finger stick using a Precision Xtra meter (Abbott Diabetes Care).

Statistical analysis

The sample size was estimated to be 55 subjects to have 80% power with an α level of 5% to detect a halving (42 vs. 21%) of the hypoglycemia rate. During the study period of May to December 2005, 57 subjects were enrolled, but 7 dropped out before completing both exercise sessions because of scheduling conflicts ($n = 2$), problems with the IV during the first visit ($n = 1$), lost to follow-up ($n = 1$), and other reasons ($n = 3$). These subjects did not differ from the others in terms of age, sex, A1C, duration of diabetes, or BMI. One subject was excluded because the two visits were 116 days apart, leaving 49 subjects for analysis.

Hypoglycemia was considered to have occurred when a central laboratory glucose concentration was ≤70 mg/dl. Except where otherwise stated, the definition of hypoglycemia also included cases (one basal-stopped and one basal-continued) in which hypoglycemia treatment was given based on a Freestyle meter glucose value, but a confirmatory central laboratory glucose value ≤70 mg/dl was not present. Analyses using only central laboratory–confirmed hypoglycemia cases are indicated as such.

The proportions of subjects developing hypoglycemia on the basal-continued visits were compared with those on the basal-stopped visits using generalized estimating equations controlling for baseline glucose, period (first versus second visit), and repeated measures from the same subject. Baseline glucose was treated as a continuous covariate.

Hyperglycemia was defined as a plasma glucose concentration ≥200 mg/dl that had increased from baseline by at least 20%. Development of hyperglycemia was analyzed using a similar generalized estimating equation regression model.

Drop in glucose was defined as the baseline minus the nadir glucose concentration during exercise. Because subjects were treated when the glucose dropped ≤65 mg/dl, the nadir glucose was truncated at 65 mg/dl for calculation of the drop in glucose. The percent drop in glucose was defined as the drop divided by the baseline concentration. Both of these outcomes were analyzed using a repeated-measures, least-squares regression model adjusting for baseline glucose and period effects.

RESULTS — The mean age of the 49 subjects was 14.5 ± 2.0 years (range 8–17); 43% were female; and 94% were Caucasian, 2% Hispanic, 2% Asian, and 2% reported more than one race. The mean BMI of the subjects was 22.3 ± 3.0 kg/m^2 (range 15.8–30.1) The mean duration of diabetes was 7.2 ± 3.8 years, and the mean A1C was 7.5 ± 0.9%. A severe episode of hypoglycemia (resulting in seizure or loss of consciousness) in the 6 months before the study was reported by three subjects (6%). A total of 26 subjects completed the basal-continued visit first and 23 completed the basal-stopped visit first. The median time between the two visits was 14 days (25th, 75th percentile: 8, 20 days [range 6–36]).

Completion of exercise protocol

The full exercise session was completed at 95 (97%) of the 98 visits. In three sessions (one basal-continued and two basal-stopped), at least the first two cycles were completed, but the subject could not complete the session because of hypoglycemia. On 6 of the other 95 visits (2 basal-continued and 4 basal-stopped), the subject failed to achieve the target heart rate of 140 bpm for one of the four cycles (heart rate achieved ranged from 128 to 137 bpm).

Pre-exercise glucose concentrations

Baseline glucose concentrations before the start of the exercise measured at the central laboratory ranged from 115 to 230 mg/dl (all but one of the Freestyle values were within the specified range of 120–200 mg/dl). Baseline values were similar on basal-continued and basal-stopped visits (means [±SD] 156 ± 27 vs. 161 ± 24 mg/dl, respectively; $P = 0.30$).

Drop in plasma glucose and hypoglycemia

As seen in Fig. 1 and Table 1, the drop in glucose from baseline during exercise was less during the basal-stopped visit than during the basal-continued visit (absolute change 44 ± 38 vs. 63 ± 33 mg/dl, $P <$

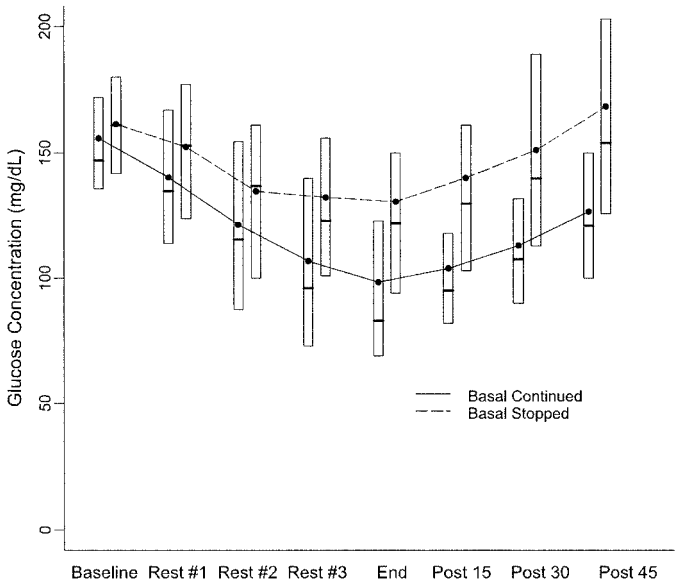

Figure 1—*Plasma glucose concentrations during/after exercise (n = 98 visits from 49 subjects). Black dots denote mean values, and boxes denote median and 25th and 75th percentiles.*

0.001; relative change 28 ± 23 vs. 41 ± 19%, $P < 0.001$), as was the frequency of hypoglycemia (16 vs. 43%, $P = 0.003$). Hypoglycemia occurred only on the basal-continued visit in 15 subjects (31%), only on the basal-stopped visit in 2 subjects (4%), on both visits in 6 (12%), and on neither visit in 26 (53%). For the two subjects with hypoglycemia on the basal-stopped days, one had similar baseline glucose concentrations on the 2 days (127 vs. 131 mg/dl) and one had a higher baseline glucose concentration on the basal-continued day (185 vs. 127 mg/dl). Four subjects who did not become hypoglycemic during the exercise became hypoglycemic within 45 min of exercise completion (all on the basal-continued visit). The lower incidence of hypoglycemia on the basal-stopped visits was consistent in subgroups based on A1C, age, sex, and frequency of exercise performed at home. As can be seen in Fig. 2*A*, hypoglycemia during exercise was unusual in the basal-stopped but not the basal-continued visit, when the baseline glucose level was >130 mg/dl (9 vs. 46%). Hypoglycemia occurred more often on the first compared with the second visit, but the difference was not statistically significant (37 vs. 22%; $P = 0.12$). There was no evidence of a treatment by period interaction ($P = 0.30$).

Subjects were treated with 15–30 g carbohydrates for hypoglycemia during or after exercise on 29 visits (22 basal-continued and 7 basal-stopped). A second treatment was necessary for seven of these subjects (all basal-continued), two of whom required a third treatment and one required third and fourth treatments. Three subjects were still ≤70 mg/dl 45 min after exercise (63, 69, and 69 mg/dl). There were no cases of severe hypoglycemia during this study.

Hyperglycemia

During exercise, glucose concentrations increased from baseline by 20% or more to ≥200 mg/dl in six subjects on the basal-stopped visit and two subjects on the basal-continued visit (12 vs. 4%; $P = 0.11$). The relationship between baseline and end-of-study (~120 min) glucose levels is shown in Fig. 2*B*. At 120 min, plasma glucose levels had risen above baseline values in 21 (43%) of basal-stopped subjects, 13 (27%) of whom had become hyperglycemic (increased ≥20% from baseline to ≥200 mg/dl), compared with a rise in 8 (16%) basal-continued subjects, 2 (4%) of whom became hyperglycemic ($P < 0.001$ and $P = 0.002$, respectively). No abnormal blood ketone levels were observed during exercise (all values ≤0.4 mmol/l).

CONCLUSIONS— In the present study, we demonstrated that stopping the basal insulin infusion at the start of a prolonged period of moderate aerobic exercise in the late afternoon was an effective strategy for reducing the risk of hypoglycemia during the exercise period. While this maneuver did not completely eliminate the risk of hypoglycemia, a fall in glucose that required treatment was infrequently observed if the pre-exercise plasma glucose level was >130 mg/dl. Moreover, the response to treatment of hypoglycemia with oral carbohydrate was more effective under basal-stopped conditions, since none of the subjects required more than one treatment with carbohydrate snacks compared with approximately one-third of the subjects during the basal-continued visit. Discontinuation of basal infusion was associated with a modest increased risk of hyperglycemia (12 vs. 4%, $P = 0.11$) dur-

Table 1—*Change in glucose* and development of hypoglycemia during and after exercise*

	Basal-continued	Basal-stopped	*P*
n	49	49	
Baseline	156 ± 27	161 ± 24	0.30
During exercise			
Glucose drop†	63 ± 33	44 ± 38	<0.001
Percent glucose drop‡	41 ± 19	28 ± 23	<0.001
Hypoglycemia§‖	21 (43)	8 (16)	0.003
Hyperglycemia¶	2 (4)	6 (12)	0.11
Additional events after exercise#			
Hypoglycemia§	4	0	
Hyperglycemia¶	1	7	
During or after exercise			
Hypoglycemia§	25 (51)	8 (16)	<0.001
Hyperglycemia¶	3 (6)	13 (27)	0.008

Data are means ± SD or *n* (%) unless otherwise indicated. *Glucose values are milligrams per deciliter. †Baseline glucose minus nadir. ‡Glucose drop divided by baseline glucose. §Glucose ≤70 mg/dl. ‖Includes two visits (one basal-stopped and one basal-continued) where treatment was given for hypoglycemia based on a meter glucose value, but the central laboratory value was >70 mg/dl (85 and 71 mg/dl). $P = 0.001$ for analysis restricted to laboratory confirmed cases. ¶Glucose increased ≥20% from baseline to ≥200 mg/dl. #Glucose measured 15, 30, and 45 min after completion of exercise.

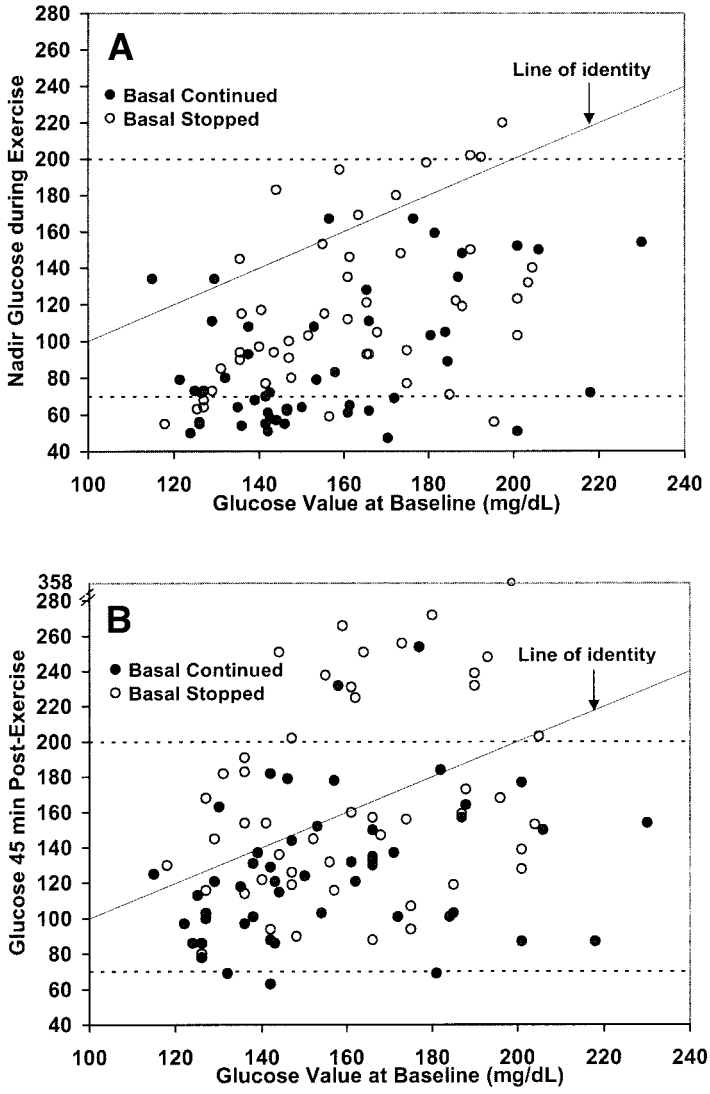

Figure 2— *Nadir and postexercise plasma glucose concentrations by baseline level* (n = *98 visits from 49 subjects). The nadir glucose concentration during exercise* (A) *and glucose concentration 45 min after completion of exercise* (B) *are shown by baseline level. Dashed lines denote the hypo- and hyperglycemia thresholds of 70 and 200 mg/dl, respectively. Note different scales on the horizontal and vertical axes.*

ing exercise, but blood ketone levels remained suppressed.

Because children and adolescents with type 1 diabetes may have periods of exercise and rest that extend beyond 75 min (e.g., an afternoon at the beach), we monitored the subjects for 45 min after exercise on both study days. During the basal-continued visit, four subjects who had not been hypoglycemic during exercise became hypoglycemic and one subject became hyperglycemic, compared with no subjects becoming hypoglycemic and seven becoming hyperglycemic during the basal-stopped visit. At the end of the study (~120 min from the start of the study), a much greater rise in plasma glucose was observed on the basal-stopped day than on the basal-continued day, with hyperglycemia being present in 27 and 4% of subjects, respectively. The effect of delaying the restarting of insulin after exercise (as was done in the study) versus restarting it immediately after exercise warrants further study.

The duration and intensity of exercise in this study reflect the current national recommendation of at least 60 min of daily moderate to vigorous activity for children (11). We chose to study the effects of exercise at ~4:00 P.M., since this is when children and adolescents often engage in after-school physical activities. Recent work using an objective monitoring system suggests that youth are most active from 3:00 to 7:00 P.M. (12). However, we recognize that a structured exercise program such as the one used in this study is not the same as real-life exercise performed by children. We plan to conduct future studies with the use of accelerometry to better address the effect of "real-life exercise" on glucose levels.

Because the last premeal bolus dose of insulin was given ~4 h earlier, the subcutaneous depot of rapid-acting insulin analog was likely to be quite small in our subjects at baseline (13). While discontinuation of basal infusion was very effective in preventing episodes of exercise-induced hypoglycemia under these conditions, alterations in premeal bolus doses might be a more effective strategy to reduce the risk of hypoglycemia during bouts of exercise that occur shortly after a meal. This question was addressed by Schiffrin and Parikh (14) in a study that predated the introduction of insulin analogs. These investigators examined the effect of altering premeal insulin doses before a 45-min exercise session in seven adolescents on insulin pumps and six on multiple daily injections. Subjects were tested one time resting and four times during exercise after administering varied proportions of their usual insulin doses (0, 50, 67, and 100%). Under these conditions, a 50% reduction in the premeal dose provided an effective means to reduce the risk of hypoglycemia. A recent study comparing 50% basal insulin versus basal stopped during morning exercise in 10 adolescents with type 1 diabetes found no difference in acute hypoglycemia or fall in blood glucose (15). Hypoglycemia developed during 2 of the 10 basal-stopped sessions and during 2 of the 10 basal-continued sessions. The authors concluded that discontinuing the basal rate did not prevent hypoglycemia. A small sample size, shorter exercise session (40–45 min), timing of the exercise 2 h after the breakfast meal and premeal bolus dose reduction in the first study, and 50% reduction in basal insulin on the control visit in the latter study may explain why those results differ from the present study.

Because of its complexity, trial and error remains the principal method of regulating plasma glucose levels during exercise. However, the results of the present study can be used to guide recommendations for managing youth receiving insulin pump treatment during similar late-afternoon exercise. The plasma glucose should be checked before exercise,

and 15–30 g of carbohydrate should be taken if the glucose is <130 mg/dl, or a small correction bolus should be given if the glucose is >200 mg/dl. Although in most patients the pump can then be safely suspended or disconnected for up to 2 h, glucose levels should be measured every 60–90 min during and after exercise and insulin administered when needed. The child and parents can also be informed that if hypoglycemia develops during exercise, it will be easier and more consistently treated with 15–30 g carbohydrate if the basal insulin infusion has been temporarily interrupted. The ability to suspend or reduce basal insulin during increased physical activity is another example of the flexibility of insulin pump therapy that distinguishes it from multiple daily injection regimens that use long-acting insulin analogs for basal insulin replacement.

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APPENDIX

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