Effects of Glutamine on Glycemic Control During and After Exercise in Adolescents With Type 1 Diabetes

A pilot study

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OBJECTIVE — To investigate if oral glutamine ameliorates exercise and postexercise nighttime hypoglycemia in type 1 diabetic adolescents.

RESEARCH DESIGN AND METHODS — Ten adolescents (15.2 ± 1.4 years [SD], A1C 6.9 ± 0.9%) on insulin pumps were studied. The subjects were randomized to receive a glutamine or placebo drink pre-exercise and at bedtime (0.25 g/kg/dose). A 3:00 P.M. exercise session consisted of four 15-min treadmill/5-min rest cycles. Pre-exercise blood glucose was 140–150 mg/dl and was monitored throughout the night. Studies were randomized crossover over 3 weeks.

RESULTS — Blood glucose levels dropped comparably (52%) during exercise on both days. However, the overnight number of hypoglycemic events was higher on glutamine than placebo (≤70 mg/dl, $P = 0.03$ and ≤60, $P = 0.05$). The cumulative probability of nighttime hypoglycemia was increased on glutamine days (80%) versus placebo days (50%) ($P = 0.02$).

CONCLUSIONS — Glutamine increased the cumulative probability of postexercise overnight hypoglycemia compared with placebo in adolescents with type 1 diabetes. Whether glutamine may enhance insulin sensitivity postexercise requires further study in type 1 diabetes.

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We observed a higher incidence of hypoglycemia during exercise and during the night following exercise versus after a sedentary day in adolescents with type 1 diabetes (1,2). Although hypoglycemia decreased by discontinuing the insulin pump during exercise, significant rebound hyperglycemia was observed (3).

Glutamine, the body's most abundant free amino acid, is thought to regulate intestinal protein synthesis and be a major source of carbon for gluconeogenesis (4). However, conflicting reported data suggest it can impair or accelerate recovery from hypoglycemia (5–7). In this pilot study we investigated if oral glutamine could ameliorate hypoglycemia during exercise and in the nighttime after exercise in children with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Written consent was obtained after approval by the Wolfson Children's Hospital Institutional Review Committee. Ten adolescents (five boys and five girls; mean [SD] age 15.2 ± 1.4 years) with type 1 diabetes on insulin pump therapy were recruited. Mean diabetes duration was 6.2 ± 3.3 years; A1C, 6.9 ± 0.9%; with normal BMI, 76.9 ± 12.2 percentile. Subjects were on no other medications or dietary supplements.

Design

Regular dietary intake was maintained for at least 3 days prior to each admission to the clinical research center (CRC) and diabetes was managed as routine. Subjects were admitted mid-day, an intravenous line was placed, and blood glucose was titrated (mid 100 mg/dl) prior to 3:00 P.M. exercise. Children were randomized to receive a drink containing glutamine or placebo (PL, calorie- and nitrogen-free) before exercise and at bedtime (0.25 g/kg/dose). Patients and CRC staff were blinded to the type of drinks consumed. Sessions consisted of four 15-min treadmill cycles (heart rate ~140 bpm) with 5-min rest breaks when blood glucose concentrations were checked for a total of 75 min. If blood glucose was <60 mg/dl, subjects consumed 15–30 g of carbohydrate and were not allowed back on the treadmill until blood >70 mg/dl. Insulin basal rates were continued during exercise. Afterward, subjects ate a snack and then dinner. Blood glucose was monitored hourly overnight from 8:00 P.M. to 8:00 A.M. Blood glucose ≤60 mg/dl prompted treatment with an oral carbohydrate; treatment was repeated as needed until >80 mg/dl. Fasting glutamine and ammonia concentrations were measured 16-h post-exercise the following morning. Subjects were discharged after breakfast and returned within 3 weeks for an identical study with either placebo or glutamine. The caloric/protein intake of the two CRC days was identical; visits were randomized crossover.

Assays

Blood glucose concentrations were measured with a Freestyle meter (Abbott Diabetes Care, Alameda, CA) and by glucose oxidase methods with a Beckman glucose analyzer (Beckman, Brea, CA). Plasma glutamine concentrations were measured by gas chromatography–mass spectrometry and ammonia using an automated chemistry analyzer.

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Statistics

During exercise, hypoglycemia was considered if blood glucose was ≤70 mg/dl; if treated, the most recent previous blood glucose was carried forward 1 h in the calculations. Repeated-measures regression models were performed to compare glutamine concentrations and glucose values prior to exercise and the percentage drop during exercise, the overnight mean glucose, and the percentage of the hypoglycemic values of each visit. Rank scores (van der Waerden) were used to normalize skewed distributions. The proportions of subjects developing hypoglycemia during exercise on both visits were compared using a permutation test as was the time from 10:00 P.M. until the first laboratory glucose value ≤70 mg/dl on the 2 days; all analyses were controlled for a visit effect. SAS version 9.1 (SAS Institute, Cary, NC) and two-sided *t* tests were used.

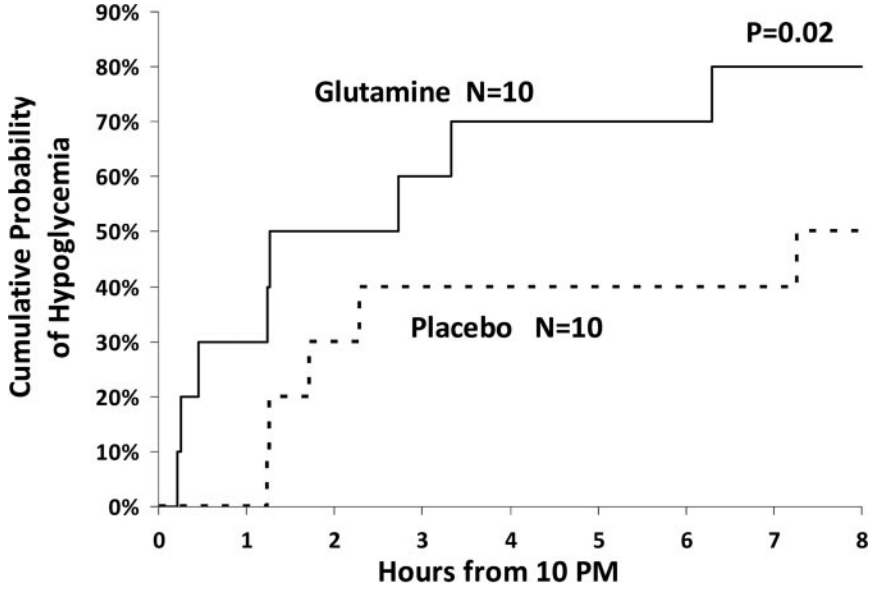

Figure 1—*Cumulative probability of nighttime hypoglycemia (≤70 mg/dl) if the same adolescents with type 1 diabetes took glutamine or placebo before afternoon exercise and at bedtime.*

RESULTS — Plasma glutamine concentrations were >50% higher the morning after glutamine administration (316 μmol/l) as compared with placebo (200 μmol/l, $P < 0.001$).

Exercise

Mean blood glucose concentrations prior to exercise were comparable on the glutamine and placebo day (143 ± 31 mg/dl vs. 162 ± 54, respectively; $P = 0.44$) with a similar percentage drop from baseline during exercise of 52 ± 15% glutamine versus 52% ± 9% placebo ($P = 0.84$). There was a comparable number of subjects that developed hypoglycemia during exercise on the glutamine ($n = 6$) or placebo day ($n = 7$).

Overnight

Mean nighttime postexercise low-glucose levels (≤70 mg/dl or ≤60 mg/dl) were more frequent after glutamine than after placebo (≤70 mg/dl: glutamine, 19%; placebo, 15%; $P = 0.03$; and ≤60 mg/dl: glutamine, 7.7%; placebo, 3.6%; $P = 0.05$). The cumulative probability of overnight hypoglycemia was increased on the glutamine day (80%) compared with the placebo day (50%, $P = 0.02$) (Fig. 1).

Safety

Glutamine is tasteless and odorless, so it was well tolerated. Plasma ammonia concentrations the morning after the studies were similar (glutamine: 40.2 ± 15.3 μmol/l; placebo: 41.2 ± 16.1 μmol/l, P = NS).

CONCLUSIONS — The pilot study data suggest that glutamine supplementation increases the likelihood of nighttime hypoglycemia in adolescents with type 1 diabetes after performing heavy exercise.

Morning glutamine concentrations 16-h post-exercise were >50% higher during the glutamine day versus the placebo day, however these concentrations were still below normal compared with healthy, age-matched control subjects or adolescents with type 1 diabetes measured at rest ($P < 0.001$) (8) and similar to those of healthy adults after prolonged exercise (9). It is possible that glutamine is low due to increased use in gluconeogenesis or use as a buffer or due to increased cortisol secretion, which enhances splanchnic glutamine utilization (10). This relative glutamine depletion after exercise requires further study.

In our study, glutamine did not affect blood glucose levels during exercise but increased the cumulative probability of nighttime hypoglycemia post-exercise. Indirect evidence suggests glutamine may indeed enhance insulin sensitivity in other experimental and clinical situations associated with insulin resistance including in the intensive care unit with trauma patients (11,12) and in children with cystic fibrosis on growth hormone (13). Glutamine increased insulin signaling/sensitivity in skeletal muscle in experimental animals (14), and oral glutamine increased nonoxidative glucose disposal in healthy exercising subjects (15).

Our pilot study, however, has several limitations including its small sample size, the low concentrations of glutamine achieved, and no direct measurement of insulin sensitivity. These results are nonetheless intriguing as the investigation of nutritional, nonpharmacological avenues to improve diabetes control is important and deserves further study, particularly in teenagers who have increased insulin resistance. In the aggregate, these data are congruent with the positive effect of glutamine on insulin sensitivity.

In conclusion, oral glutamine administration was associated with a higher incidence of nighttime post-exercise hypoglycemia as compared with placebo in a pilot group of adolescents with type 1 diabetes. Whether glutamine supplementation affects peripheral and/or hepatic insulin sensitivity requires further study in children with type 1 diabetes.

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N.M. is the principal investigator of the studies. She wrote the grant, recruited the subjects, carried out the experiments, analyzed the data, and wrote the paper. D.X. is the principal biostatistician of the study and helped analyze the data and create the graphs and wrote the statistical section. L.A.F. is a coinvestigator and helped recruit and treat the

patients in the CRC and reviewed and critiqued the manuscript. K.E. is the lead study coordinator in charge of all implementation aspects of the study. D.D. is a co-investigator who assisted N.M. in grant writing, data analysis and interpretation and assisted in the writing of the paper.

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