Target-Seeking Behavior of Plasma Glucose With Exercise in Type 1 Diabetes

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OBJECTIVE — To investigate the reproducibility of the plasma glucose (PG) response to exercise in subjects with type 1 diabetes on a nonintensive insulin regimen.

RESEARCH DESIGN AND METHODS — Subjects cycled for 45 min at 50% $V_{O2\max}$ on two occasions (studies 1 and 2) either 1 h after lunch and usual insulin (protocol A) or after overnight fasting without morning insulin (protocol B). Identical diet, activity, and insulin (twice daily neutral and intermediate) were maintained before and during each study day. A total of 13 type 1 diabetic subjects (6 men and 7 women, BMI 24.0 ± 0.9 kg/m² [means ± SE], age 42.6 ± 2.7 years, diabetes duration 14.1 ± 2.8 years) completed protocol A, and 7 (3 men and 4 women, BMI 23.8 ± 1.3 kg/m², age 39.7 ± 1.3 years, diabetes duration 14 ± 4.4 years) completed protocol B.

RESULTS — In protocol A (fed), the fall in PG during exercise was 4.5 ± 1.0 and 5.0 ± 0.8 mmol/l in studies 1 and 2, respectively, whereas in protocol B (fasted), it was 0.6 ± 0.8 and 3.4 ± 1.6 mmol/l. Regression analysis of the change in PG in protocol A in study 1 versus study 2 showed poor reproducibility ($r^2 = 0.12, P = 0.25$) despite uniform conditions. In protocol B, the fall in PG was more reproducible ($r^2 = 0.81, P = 0.006$). In fed subjects, there was better ($P = 0.01$) and clinically useful reproducibility of the PG at exercise completion ($r^2 = 0.77, P = 0.0001$) compared with preexercise.

CONCLUSIONS — These results indicate poor reproducibility of the change in PG during exercise after feeding in type 1 diabetes on nonintensive insulin regimens but reasonable reproducibility when fasting. Exercise apparently decreases the glycemic variability after feeding, so that PG concentrations after exercise seek a reproducible “target.” Thus, the absolute PG level after a typical bout of exercise in the fed state should be a good guide to carbohydrate or insulin adjustment on subsequent occasions.

Hypoglycemia is a common complication of exercise in type 1 diabetes. Despite adjustments of insulin and carbohydrate intake, many patients still suffer from hypoglycemia during and up to 24 h after exercise (1). The Diabetes Control and Complications Trial (2) indicated that tight glycemic control prevents or delays microvascular complications, which has significant implications for management of exercise in type 1 diabetes. With tighter glycemic control, it is important to improve understanding of plasma glucose (PG) fluctuations with exercise.

Patients are usually instructed to adjust carbohydrate intake and/or insulin dose based on results of a trial bout of exercise (3). This assumes that under comparable exercise conditions, a similar glycemic response will occur. However, this assumption has only been tested once in adolescent boys with a starting PG of 18 mmol/l 1 h after breakfast using a some-

what atypical exercise protocol (4). We aimed to test, under controlled conditions, the reproducibility of the glycemic response to exercise in type 1 diabetes in both the fed and fasted states by examining duplicate bouts of exercise.

RESEARCH DESIGN AND METHODS — Subjects with confirmed type 1 diabetes (including unrecordable C-peptide) were recruited via St. Vincent’s Hospital Diabetes Clinic and publications of Diabetes Australia. Subject details are shown in Table 1 (as our service is not proximate to a pediatric hospital, most subjects had adult-onset type 1 diabetes). All subjects used a nonintensive insulin regimen: morning and evening regular and intermediate (in six subjects), evening intermediate at bedtime). This study was conducted before general availability of rapid-acting insulin analogs in Australia. The subjects had a range of normal activity, but competitive athletes were excluded. The subjects underwent medical examination to exclude those at risk of adverse events during exercise (those with cardiovascular disease, nephropathy, and more-than-minimal retinopathy). Those aged >35 years had a resting electrocardiograph (ECG) and, if abnormal, an exercise ECG; patients with abnormalities in the exercise ECG were excluded. The nature, purpose, and possible risks were explained, and written consent was obtained. The study was approved by the Research Ethics Committee of St. Vincent’s Hospital.

Exercise protocol
A total of 13 subjects were studied to test the reproducibility of the PG response to exercise, 1 h after a standard meal (fed group), and 7 subjects (4 of whom had participated in the fed study) were studied while fasting.

Both groups (fed and fasted) exercised for 45 min at the same workload in an air-conditioned room on two occasions (interval between studies 3–30 days). The fed group exercised for 1 h after a meal that was identical on the two study occasions (chicken sandwiches; 44% carbohydrate, 34% fat, and 22%...
protein) consumed over 20 min; the subjects estimated how many sandwiches were needed for lunch followed by exercise on the basis of past experience. Study of the fasted group began at 0800 after a 12-h fast, with the previous evening’s intermediate-acting insulin reduced by 2 units and without injection of morning insulin. All subjects were asked to eat the same food at the same time for the meals on the day of and the day preceding the study, to ensure that the timing and dosage of insulin were identical, and not to undertake exercise in the preceding 24 h. Subjects injected insulin subcutaneously into the abdomen. Exercise was on a cycle ergometer (Monark, Stockholm) at a heart rate (HR) corresponding to 50% \( V_{O_2\text{max}} \) according to the formula: HRtarget = 0.5 \times ([220 – age] – HRresting) + HRresting (5).

Blood samples were taken 15 min before exercise and then every 15 min for 90 min via a 20-gauge catheter (Deseret) in a forearm vein. A constant infusion of isotonic saline maintained patency of the intravenous cannula. For safety, blood glucose concentrations were monitored during the studies, a ectance meter (Boehringer- Mannheim, Mannheim, Germany). A blood glucose reading <5 mmol/l was deemed too low to commence, and exercise was stopped if blood glucose fell below 2.5 mmol/l.

**Sample analysis**

Samples for PG were collected in oxalate/fluoride tubes; glucagon (at 0 and 30 min) in tubes containing heparin/protamine (kept on ice); and insulin (at –15, 0, 30, and 45 min) in plain glass tubes before centrifugation, separation, and storage at \( -20^\circ \text{C} \) until assay. PG levels for final analysis were determined using an immobilized glucose oxidase method (coefficient of variation <3%) (model 23AM glucose analyzer; Yellow Springs Instruments, Yellow Springs, OH).

Serum-free insulin, performed on polyethylene glycol supernatants of plasma after incubation at 37°C for 2 h, was determined by double-antibody radioimmunoassay using a homologous insulin standard (crystalline human insulin, catalogue no. 470; Novo) and 3-(\( ^{125}\text{I} \)) iodotyrosyl A14 insulin (Amer sham) as tracer. Plasma glucagon was determined by radioimmunoassay using a porcine glucagon standard (Novo, CSL Australia) and porcine \( ^{125}\text{I} \) glucagon (Amersham).

**Statistical methods**

Statistical analyses were performed with Staview SE+ Graphics using a simple regression analysis and paired t test. Regression slopes are presented with their SEs. Correlation coefficients were compared using Fisher’s Z-transformation. In all analyses, a \( P \) value <0.05 was regarded as significant. Results are shown as means ± SE. The values for PG and insulin at –15 and 0 min were averaged to provide baseline, designated time 0.

**RESULTS** — In the fed group of 13 subjects (Table 1), mean duration of diabetes was 14.1 ± 2.8 years, BMI 24.0 ± 0.9 kg/m\(^2\), age 42.6 ± 2.7 years (range 21–56), and total daily insulin 37 ± 4 units. In the fasted group of seven subjects, BMI was 25.8 ± 1.3 kg/m\(^2\), age 39.7 ± 1.3 years, duration of diabetes 14.0 ± 4.4 years, and insulin dose 42.5 ± 5 units.

**Exercise performance**

Subjects completed two 45-min bouts of exercise in both fasted and fed studies without undue fatigue. In four subjects in the fed group, a PG ≤2.5 mmol/l occurred during exercise in study 1. These studies were aborted (results not included) and further studies performed with adjustment of prior carbohydrate intake. No subjects approached hypoglycemia in the fasted studies, in which morning insulin was omitted.

**PG response to exercise**

**Fed subjects.** The PG fell in all subjects in both studies after 45 min exercise. There was substantial between-subject variation, but the mean change in study 1 (–4.5 ± 0.9 mmol/l, range –0.8 to 3.3 mmol/l) was significantly different from the fasted group.

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**Table 1—Subject characteristics**

<table>
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<th>Study type</th>
<th>Subject</th>
<th>Sex</th>
<th>Age (years)</th>
<th>BMI (kg/m(^2))</th>
<th>Type 1 diabetes duration (years)</th>
<th>Insulin dose (units/day)</th>
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<td>Thyrinone (125 ( \mu )g), budesonide (500 ( \mu )g), salbutamol (as required)</td>
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Fasted subjects. PG did not change significantly in either study after 45 min exercise. Change in PG was $-0.6 \pm 0.8$ mmol/l in study 1 and $-3.4 \pm 1.6$ mmol/l in study 2.

Reproducibility of PG concentrations in the two studies

Fed subjects. The fall in PG was clearly not reproducible between the two studies. The change in PG after 45 min was calculated for each subject as absolute fall from basal and percentage change in the first and second studies. Analysis showed no significant relationship in either case ($r^2 = 0.12$ and 0.27, respectively, $P > 0.05$). Regression analysis of the absolute fall is shown in Fig. 1A. The data was also evaluated excluding subjects who had an interval between studies $>7$ days (seven subjects) to determine whether that variable affected the reproducibility. Analysis showed that the fall in PG was still not reproducible ($r^2 = 0.01$, $P = 0.80$).

The mean absolute difference in PG between the two replicate bouts of exercise was taken and the SE calculated for each time point in the two studies (Fig. 2A). At baseline, there was wide variation in the PG concentration within individuals; the mean difference was $3.0 \pm 0.6$ mmol/l between the two studies. However, as exercise continued, the absolute difference decreased significantly ($P = 0.03$) until, after 45 min exercise, the difference was only $1.2 \pm 0.4$ mmol/l.

Simple regression analysis was also used to compare the PG in the two bouts of exercise at each time point (Fig. 2B). There was a moderate correlation between the preexercise PG concentrations in each study ($r^2 = 0.52$, $P = 0.01$). The correlation was higher after 45 min exercise ($r^2 = 0.77$, $P = 0.0001$). Variability decreased during exercise ($P = 0.03$) and increased during recovery ($P = 0.002$) (repeated measures of $\Delta$PG from 0 to 45 min and 45 to 90 min).

Fasted subjects. Regression analysis of the fall in PG in study 1 compared with study 2, calculated as absolute change (Fig. 1B) and as percentage fall, was far more reproducible ($r^2 = 0.81$ and 0.86, respectively, $P < 0.01$) than in fed subjects.

There was wide variation in starting PG concentrations between the two studies ($3.9 \pm 0.8$ mmol/l) (Fig 2A) that was not significantly greater than for the fed subjects ($P = 0.33$). As in the fed subjects, during exercise, the absolute difference decreased significantly ($P = 0.04$) until after 45 min exercise; the difference in PG between the two studies was $1.9 \pm 0.6$ mmol/l (again not significantly different from the fed group, $P = 0.33$) (Fig 2A).

Simple regression analysis (Fig 2B) comparing PG in the two studies showed an increase in the correlation after 45 min exercise ($P = 0.04$) from an initial $r^2$ of 0.25 ($P = 0.25$) to an $r^2$ of 0.45 ($P = 0.001$) at 45 min. Fasted subjects did not experience a significant increase in variability in PG during recovery ($P = 0.27$).

The hormonal responses in exercise and recovery (fed and fasted subjects)

The concentrations of PG and serum-free insulin are shown in Fig. 3. The glucagon concentrations for fed subjects at 0 and 30 min were $86 \pm 7$ and $87 \pm 9$ ng/l, respectively, in the first study and $128 \pm 31$ and $114 \pm 21$ ng/l, respectively, in the second study. For fasted subjects, they were $125 \pm 26$ and $141 \pm 32$ ng/l in the first and $138 \pm 26$ and $143 \pm 27$ ng/l in the second study.

The values for PG, insulin, or glucagon-
gon were not significantly different between the two bouts of exercise, and regression analysis did not show a statistical relationship between the PG concentration and levels of insulin or glucagon in either the fasted or fed group.

CONCLUSIONS — The major finding of this study is that the change in PG after exercise in the fed state is not usefully reproducible. One explanation for lack of reproducibility in the fall in PG in the fed state could be insufficient uniformity of experimental conditions between bouts of exercise. This is unlikely. First, regarding varying subject fitness between studies (which might alter relative exercise intensity), subjects were asked to maintain a uniform pattern of physical activity and, although the interval between studies varied from <1 week to 1 month, reproducibility of responses was not affected by excluding subjects with an interval exceeding 1 week. Second, fasted subjects exercised under exactly the same protocol; however, there was significant reproducibility of the fall in PG in the fasted group. This suggests that any non-reproducibility was not solely a product of differences in experimental conditions. In any case, the reproducibility of conditions in this study is likely to be greater than when subjects with type 1 diabetes normally exercise; the results obtained under “field conditions” are therefore likely to be less reproducible than in this study.

The lack of reproducibility in the fall in PG after 45 min exercise in the fed group may be explained by effects of continuing gut absorption of carbohydrate (6). While strenuous exercise (>75% $V_{O_2\text{max}}$) decreases rate of gastric emptying of solid food, as well as slows the transit rate through the small intestine, exercise in the range of 50–70% $V_{O_2\text{max}}$ has been shown to not affect the rate of gastric emptying (7). Gut absorption continuing throughout exercise may explain why starting PG was a poor predictor of final PG concentration at the end of exercise in the fed group and why the fall in PG was more reproducible in the fasted state, in which there was no contribution to the blood glucose pool from gut absorption.

The other major finding is that while PG concentrations were initially quite variable in both groups, exercise decreased the variability such that PG concentrations after 45 min exercise were reproducible between study bouts to a clinically useful extent. This similar finding in both fed and fasted groups may be accounted for by the nature of glucose transport in exercising muscle. Glucose transporters translocate to the membrane in response to insulin or exercise, as well as facilitate glucose transport (8). In type 1 diabetes, where insulin levels are not suppressed with exercise, GLUT4 translocation will be enhanced by synergistic actions of insulin and exercise (9). A higher starting PG concentration would then result in greater glucose transport into muscle. Thus, subjects commencing exercise with a higher PG would have a greater rate of fall in PG during exercise (if transport is not saturated), explaining the similar PG values at the end of exercise despite dissimilar starting PG.

Our results differ from the only previous study investigating reproducibility of the PG response to exercise in type 1 diabetes in the fed state, which reported that intrasubject PG responses to prolonged moderate-intensity exercise were reliable and repeatable under consistent conditions of exercise, insulin, and carbohydrate intake (4). However, that study protocol did not correspond to conditions under which people with type 1 diabetes usually exercise. Subjects exercised in six 10-min bouts with 5-min rest periods in which supplemental beverage carbohydrate was consumed. Additionally, the adolescent subjects had poor glycemic control on study days with preexercise PG ~18 mmol/l, a level that some consider a contraindication to exercise (1). The conditions of our protocol and the starting PG concentrations correspond more closely to those seen in “real-

Figure 2 — Reproducibility of PG levels before, during, and after exercise. A: Absolute difference in PG between bouts of exercise (study 1 versus study 2) in fed (○) and fasted subjects (●). In both cases, progressive reduction in the between-study difference during exercise is shown. B: The $r^2$ values relating PG concentrations in study 1 to study 2 in fed and fasted subjects.
life” exercise, in type 1 diabetic subjects under reasonable to good control.

This report applies to the situation of a nonintensive insulin regimen using regular plus intermediate insulin. Further study is needed of type 1 diabetic subjects on intensive regimens and using rapid-acting analogs. Nevertheless, the results have implications for clinical management of exercise in type 1 diabetes. Contrary to current belief, the absolute fall in PG in the fed state under these circumstances is not reproducible to a useful extent. This may explain some of the difficulties in controlling glycemia during exercise, despite following current recommendations. While the absolute fall in PG in the fasted state is relatively reproducible, the “end point PG” reached after exercise provides a more useful guide in the fed state for exercise planning. We suggest that people with type 1 diabetes, exercising in the nonfasting state, use the previously determined PG at completion of exercise for guidance with carbohydrate supplementation, rather than the preexercise PG or the expected fall.

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References
5. Schneider SH, Ruderman NB: Exercise and NIDDM. Diabetes Care 15:30–34, 1992

Figure 3—The mean PG and insulin concentrations during exercise and recovery in fed (A) and fasted subjects (B).