Influence of and Optimal Insulin Therapy for a Low–Glycemic Index Meal in Children With Type 1 Diabetes Receiving Intensive Insulin Therapy

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OBJECTIVE — The purpose of this study was to quantify the effects of glycemic index on postprandial glucose excursion (PPGE) in children with type 1 diabetes receiving multiple daily injections and to determine optimal insulin therapy for a low–glycemic index meal.

RESEARCH DESIGN AND METHODS — Twenty subjects consumed test breakfasts with equal macronutrient contents on 4 consecutive days, high– and low–glycemic index meals (glycemic index 84 vs. 48) were consumed with preprandial ultra-short-acting insulin, and the low–glycemic index meal was also consumed with preprandial regular insulin and postprandial ultra-short-acting insulin. Each child’s insulin dose was standardized. Continuous glucose monitoring was used.

RESULTS — The PPGE was significantly lower for the low–glycemic index meal compared with the high–glycemic index meal at 30–180 min (P < 0.02) when preprandial ultra-short-acting insulin was administered. The maximum difference occurred at 60 min (4.2 mmol/l, P < 0.001). Regular insulin produced a 1.1 mmol/l higher PPGE at 30 min compared with ultra-short-acting insulin (P = 0.015) when the low–glycemic index meal was consumed. Postprandial ultra-short-acting insulin produced a higher PPGE at 30 and 60 min compared with preprandial administration when the low–glycemic index meal was consumed. The maximum difference was 2.5 mmol/l at 60 min (P < 0.0001).

CONCLUSIONS — Low–glycemic index meals produce a lower PPGE than high–glycemic index meals. Preprandial ultra-short-acting insulin is the optimal therapy for a low–glycemic index meal.

The results of the Diabetes Control and Complications Trial (DCCT) established that intensive insulin therapy optimizes glycemic control and reduces the risk of long-term complications in people with type 1 diabetes (1). Subjects who matched carbohydrate amount and insulin dose demonstrated a further improvement in glycemic control (2). Consequently, carbohydrate amount is considered to be the most important dietary determinant of postprandial glucose control (3).

Established dietary recommendations for children with type 1 diabetes advocate the consideration of glycemic index (9). Some evidence suggests that a low–glycemic index diet may improve the long-term glycemic control of people with type 1 diabetes (10) and that postprandial glucose excursion (PPGE) is improved when children receiving treatment with conventional insulin regimens consume low–glycemic index meals (11, 12). A recent article demonstrated improved daily glycemic profiles when children receiving intensive therapy consumed low–glycemic index diets (13). However, the effect of glycemic index on the postprandial glucose response requires further exploration in children receiving intensive insulin therapy.

Newer intensive regimens using ultra-short-acting insulin analogs have been shown to improve postprandial glycemic rise (14). The potential additional benefits of low–glycemic index meals are uncertain within this context. Moreover, the time action profile of ultra-short-acting insulin may be inappropriate for the prolonged and lower glycemic rise of low–glycemic index meals.

Preprandial regular insulin, which has a more delayed onset, lower peak concentration, and longer duration of action compared with ultra-short-acting insulin (15,16), may better match the absorption profile of low–glycemic index foods. However, postprandial ultra-short-acting insulin has been demonstrated to produce higher PPGEs compared with preprandial administration (17,18), and this may be another alternative approach to optimizing insulin therapy for a low–glycemic index meal, as suggested by the British Dietetics Association in its 2005 consensus statement (19).

Therefore, the primary aim of this study was to determine the effect of altering the glycemic index of a meal on post-
Influence of a low–glycemic index meal

Table 1—Nutritional information for low– and high–glycemic index test meals

| Test meal                                      | Weight (g) | Energy (kcal) | Carbohydrate (g)* | Fat (g) | Protein (g) | Fiber (g) | Gl  |
|------------------------------------------------|------------|---------------|-------------------|---------|-------------|-----------|-----|
| Low-GI meal                                    |            |               |                   |         |             |           |     |
| Low-GI white bread (Tip Top UP EnerGI white bread) | 75         | 186.4         | 33.6              | 2.3     | 6.2         | 3         | 54  |
| Apple juice (Berri)                            | 250 ml     | 107.1         | 26.5              | <1      | <1          | <1        | 40  |
| Low-fat ham                                    | 26         | 26.7          | Tr (<1)           | 0.8     | 4.4         | 0.0       | NA  |
| Margarine                                      | 9          | 55.7          | Tr (<1)           | 6.3     | Tr (<1)     | 0.0       | NA  |
| Total                                          | 375.9      | 60.1          |                   | 9.4     | 10.6        | 3         | 48  |
| High-GI meal                                   |            |               |                   |         |             |           |     |
| Regular white bread (Tip Top Sunbest white bread) | 60         | 148.1         | 27.1              | 1.4     | 5.6         | 1.8       | 71  |
| Glucose-based energy drink (Lucozade Energy)   | 184 ml     | 133.2         | 32.9              | 0.0     | Tr          | 0.0       | 95  |
| Low-fat ham                                    | 30         | 30.8          | Tr (<1)           | 0.9     | 5.0         | 0.0       | NA  |
| Margarine                                      | 10         | 61.9          | Tr (<1)           | 7.0     | Tr (<1)     | 0.0       | NA  |
| Total                                          | 359.0      | 60.1          |                   | 9.3     | 10.6        | 1.8       | 84  |

*Available carbohydrate including sugars and starch and excluding fiber. GI, glycemic index; NA, not applicable; Tr, trace amounts.

RESEARCH DESIGN AND METHODS — Children and adolescents with type 1 diabetes diagnosed for ≥1 year and using multiple daily injection therapy (≥4 injections/day) for >6 months were recruited from the John Hunter Children’s Hospital Diabetes Clinic. Eligibility criteria included age between 7 and 17 years inclusive, that subjects not be obese, and recent A1C ≤8.5% (Primus PDQ A1c Analyzer; Primus, Kansas City, MO). Exclusion criteria included complications of diabetes such as gastroparesis or coexisting medical disorders such as celiac disease. Recruitment continued until a sample size of 20 was reached.

Ethics approval was obtained by the Hunter New England Human Research Ethics Committee in December 2006. Written consent was obtained from all participants and/or their parents.

Participants and their families were contacted by telephone 2 weeks before study commencement to review BGLs and adjust insulin therapy to optimize waking BGLs (4–8 mmol/l) and minimize the risk of hypoglycemia, defined as symptomatic or BGL <3.5 mmol/l. Four test conditions were randomly assigned on the first 2 days to ensure conservation of these results. Test conditions 3 and 4 were randomly assigned on the final 2 days.

The preprandial injection of insulin was administered immediately before meal consumption. Postprandial insulin was administered 15 min after meal commencement. A kitchen timer was supplied to each participant to ensure accuracy. All children received their normal breakfast insulin dose based on the amount of carbohydrate in the test meal. If the preprandial BGL was >16 mmol/l, the subject was instructed to add correction dose of insulin and was asked to repeat the study.

Participants were provided with four premade test meals. Each meal was consumed at breakfast after a minimum 10-h overnight fast. Evening meals and suppers the preceding nights were standardized for carbohydrate amount and type to limit the impact of these meals on the analysis of breakfast PPGE. Participants were supplied with measuring cups to facilitate compliance with preparation of these meals.

Children were required to fast and standardize their activity during the 4-h postprandial period. A food and activity diary was kept by each subject/parent to determine adherence to this protocol.

Test meals

The low–glycemic index test meal (glycemic index 48) and the high–glycemic index test meal (glycemic index 84) consisted of a ham sandwich and a drink (Table 1). Sandwiches with a concentrated yeast extract spread (Vegemite) were offered as a vegetarian option, which two participants accepted. The carbohydrate, fat, protein, and fiber amounts were standardized for both meals (Table 1). The glycemic index of each food was obtained from published tables (20) where available and confirmed by manufacturers. The glycemic index of each meal was calculated using methods described previously (21).

Food was weighed using Salter kitchen scales (model 323; Salter, Kent, U.K.), which measure to ±1 g. Liquids were measured using a 250-ml measuring jug and a 10-ml disposable syringe.

All meals were supplied in an insulated bag the afternoon before study commencement. Sandwiches and drinks were individually wrapped and labeled with the day of consumption and instructions to refrigerate the drinks and freeze the sandwiches, defrosting them the night before consumption.

Blood glucose measurement

A continuous glucose monitoring system was used (Medtronic; MiniMed, Northridge, CA). The sensor was inserted in the abdominal subcutaneous tissue the afternoon before study commencement. Subjects were instructed to enter four BGLs per day into the monitor at a time when BGLs
excursions at 30-min increments, Chicago, IL). A one-way repeated-
ure occurred, then the test condition was repeated using a new sensor.
traces for each of the four test conditions were stable for calibration. They were asked
ated before meal consumption.
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were recruited. Two participants withdrew before study commencement for personal reasons, and one participant was excluded because of an inappropriate A1C. Of the 31 children who participated, the results of 11 participants were excluded from analysis because of sensor failure (n = 4), inappropriate starting BGL on test days (n = 2), prolonged hypoglycemia (n = 2), failure to comply with the protocol (n = 1), diagnosis during the study period of a medical condition that would interfere with study protocol (n = 1), and sensor misplaced (n = 1).
were stable for calibration. They were asked to enter a “meal marker” into the continuous glucose monitoring system immediately before meal consumption.
thesis was analyzed repeatedly using a new sensor.
only subjects who had acceptable traces for each of the four test conditions were accepted for analysis. If sensor failure occurred, then the test condition was repeated using a new sensor.

**Statistical analysis**
The 4-h postprandial period was analyzed using SPSS software (version 15; SPSS, Chicago, IL). A one-way repeated-measures ANOVA was used to analyze the following parameters: 1) blood glucose excursions at 30-min increments, 2) incremental area under the curve (AUC) as described previously (22), 3) peak blood glucose level, 4) time to peak BGL, and 5) time to return to baseline.

If significance was reached (P < 0.05) the test of least significant differences (LSD) was applied as the post hoc test. Sensitivity analysis was performed using Bonferroni correction to adjust for multiple pairwise comparisons. Results are presented as means with 95% CIs.

**RESULTS**—Thirty-four participants were recruited. Two participants withdrew before study commencement for personal reasons, and one participant was excluded because of an inappropriate A1C. Of the 31 children who participated, the results of 11 participants were excluded from analysis because of sensor failure (n = 4), inappropriate starting BGL on test days (n = 2), prolonged hypoglycemia (n = 2), failure to comply with the protocol (n = 1), diagnosis during the study period of a medical condition that would interfere with study protocol (n = 1), and sensor misplaced (n = 1).

The mean age of participants was 13.6 ± 2.7 (range 8.3–17.7) years. The subjects had been diagnosed with type 1 diabetes for 5.2 ± 3.8 (1.0–13.6) years and had good metabolic control (A1C 7.4 ± 0.7 [6.1–8.5] %). The starting BGL for each of the four test conditions was not significantly different (one-way repeated-measures ANOVA P > 0.05) (Table 2).

**Preprandial versus postprandial ultra-short-acting insulin for a low–glycemic index meal**
Administration of preprandial ultra-short-acting insulin resulted in a significantly lower PPGE compared with postprandial administration at 30 and 60 min (Fig. 1C). At 60 min the blood glucose excursion was 2.5 mmol/l lower after administration of preprandial insulin compared with postprandial insulin (2.9 [range 1.5–4.3] vs. 5.4 [4.2–6.6] mmol/l; LSD, P < 0.0001).

Preprandial administration resulted in a lower AUC for 0–1 h (1.9 [range 1.0–2.7] vs. 3.5 [2.8–4.2] mmol·h⁻¹·l⁻¹; LSD, P < 0.0001) and 0–2 h (4.4 [1.8–7.0] vs. 7.1 [4.8–9.4] mmol·h⁻¹·l⁻¹; LSD, P = 0.012); however, the total AUC was not significantly different. The peak BGL was 1.7 mmol/l lower when preprandial insulin was administered (LSD, P = 0.003) (Table 2). There was no difference in the time to peak BGL or time to return to baseline between the two test conditions (Table 2).

Adjusting for multiple comparisons using the Bonferroni correction led to a P = 0.02. Almost all of the P values in the analysis remained significant using this threshold, and this adjustment did not change the conclusions.

**CONCLUSIONS**—To our knowledge, this study is the first to examine whether changing the glycemic index of a mixed meal alters the PPGE in children receiving multiple daily injections. The low–glycemic index meal produced a significantly lower PPGE for 30–180 min, a lower AUC, a smaller peak blood glucose excursion, and reduced time to reach baseline BGLs compared with the high–glycemic index meal when preprandial ultra-short-acting insulin was administered (LSD, P < 0.02).

Previous studies in children receiving conventional insulin therapy and in parameter of a medical condition that would interfere with study period of a medical condition that would interfere with study protocol (n = 1), and sensor misplaced (n = 1).

**Table 2—Fasting BGL, peak BG excursion, time to peak BGL, time to fasting BGL, and AUC for each test condition**

| Test Condition                        | Fasting BGL (mmol/l) | Peak BG excursion (mmol/l) | Time to peak BGL (min) | Time to fasting BGL (min) | AUC (mmol·h⁻¹·l⁻¹) |
|---------------------------------------|----------------------|----------------------------|------------------------|---------------------------|-------------------|
| Low-GI meal, preprandial ultra-short-acting insulin | 8.8 (7.3–10.4) | 4.6 (3.0–6.2) | 70 (45–95) | 137 (99–175) | 2.5 (–2.9–7.8) |
| High-GI meal, preprandial ultra-short-acting insulin | 7.7 (6.3–9.1) | 8.1 (6.2–10.1)* | 75 (61–88)* | 179 (150–209) | 13.8 (6.4–21.2)* |
| Low-GI meal, preprandial regular insulin | 9.1 (7.0–11.2) | 5.7 (4.3–7.1) | 73 (54–92) | 136 (100–172) | 6.4 (1.9–10.9)* |
| Low-GI meal, postprandial ultra-short-acting insulin | 8.9 (7.5–10.2) | 6.3 (5.1–7.5)* | 63 (52–74) | 160 (133–186) | 5.9 (0.7–11.1) |

Data are means (95% CI). *Statistically different when compared with result for the low-GI meal, preprandial ultra-short-acting insulin (LSD, P < 0.05).
adults receiving intensive insulin therapy (11,23,24) support our findings. Furthermore, Nansel et al. (13) recently postulated that reductions in postprandial excursions may be responsible for the improved daytime glycemic control they found in youths consuming low-glycemic index diets. However, one study in children failed to show a difference in the PPGE when the glycemic index of a test breakfast was altered (25). This study was influenced by numerous confounders, including failure to standardize fiber and macronutrient content. Additionally, the results were

Figure 1—A: Low– versus high–glycemic index meal with preprandial ultra-short-acting insulin. ■, low–glycemic index meal, preprandial ultra-short-acting insulin; ▲, high–glycemic index meal, preprandial ultra-short-acting insulin. Mean PPGEs of 20 patients after a low–glycemic index meal and high–glycemic index meal with preprandial ultra-short-acting insulin. Error bars represent 95% CI. The results are significantly different for 30–180 min (LSD, P < 0.02). B: Preprandial ultra-short-acting insulin versus preprandial regular insulin for a low–glycemic index meal. ■, low–glycemic index meal, preprandial ultra-short-acting insulin; ▲, low–glycemic index meal, preprandial regular insulin. PPGEs after administration of ultra-short-acting insulin and regular insulin before a low–glycemic index meal. The results are significantly different at 30 min only (LSD, P < 0.02). C: Preprandial versus postprandial ultra-short-acting insulin for a low–glycemic index meal. ■, low–glycemic index meal, preprandial ultra-short-acting insulin; ▲, low–glycemic index meal, postprandial ultra-short-acting insulin. PPGEs after administering preprandial and postprandial ultra-short-acting insulin with a low–glycemic index meal. The results were significantly different at 30 and 60 min (LSD, P < 0.02).
not applicable to children receiving intensive insulin therapy.

It may be hypothesized that the substantial differences demonstrated in the postprandial glucose excursion and AUC between the low- and high-glycemic index test meals in this study should extrapolate to improved HbA1C. This theory is supported by Brand-Miller’s meta-analysis, which detected a 10.6% reduction in the A1C of adults and children with type 1 diabetes when a low–glycemic index diet was consumed over a 2- to 52-week period (10).

The test meals in this study had significantly different glycemic index values (glycemic index 48 vs. 84). A limitation of the study is that more moderate differences in glycemic index values may result in less significant alterations in PPGE. In addition, as discussed by Mohammed and Wolever (24), the shape of the postprandial blood glucose curve may be different if a starchy food of the same glycemic index value was substituted for the fruit juice given in this study. Further studies in mixed meals are warranted to explore these issues.

After consideration of the effect of glycemic index on PPGEs, the question of whether insulin type (regular insulin or ultra-short-acting insulin) or timing of insulin administration should be altered when a low–glycemic index meal is consumed remains. Administration of preprandial ultra-short-acting insulin and regular insulin produced clinically similar PPGEs. Administration of regular insulin produced a 1.1 mmol/l higher blood glucose excursion at 30 min (P = 0.015). Therefore, the use of preprandial regular insulin did not offer an advantage over that of preprandial ultra-short-acting insulin when a low–glycemic index meal was consumed.

This study demonstrated that postprandial administration of ultra-short-acting insulin produced significantly higher postprandial blood glucose levels. These findings are supported by the results of other studies in adults (17,18). Thus, we believe that postprandial administration of ultra-short-acting insulin should not be recommended, as it poten-
tiates deviations from normoglycemia.

Dietary focus remains on carbohydrate counting as a strategy to reduce the risk and progression of long-term complications in the context of intensive insulin therapy. The current study supports the integration of low–glycemic index dietary advice into medical nutrition therapy for children and adolescents with type 1 dia-

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