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The influence of and optimal insulin therapy for a low glycemic index meal in children with type one diabetes on intensive insulin therapy.

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Running title: Influence of a low glycemic index meal.

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Objective: To quantify the effects of glycemic index (GI) on the postprandial blood glucose excursion (PPGE) in children with type 1 diabetes on multiple daily injections (MDI). To determine optimal insulin therapy for a low GI meal.

Research design and methods: 20 subjects consumed test breakfasts, with equal macronutrient contents on four consecutive days; high and low GI meals (GI: 84 vs. 48) were consumed with preprandial ultra short acting insulin, and the low GI 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 GI meal compared to the high GI meal at 30-180 minutes ($p<0.02$) when preprandial ultra short acting insulin was administered. The maximum difference occurred at 60 minutes (4.2 mmol/l $p<0.0001$).

Regular insulin produced a 1.1 mmol/l higher PPGE at 30 minutes compared to ultra short acting insulin ($p=0.015$) when the low GI meal was consumed.

Postprandial ultra short acting insulin produced a higher PPGE at 30 and 60 minutes compared to preprandial administration when the low GI meal was consumed. The maximum difference was 2.5 mmol/l at 60minutes ($P<0.0001$).

Conclusions: Low GI meals produce a lower PPGE compared to high GI meals. Preprandial ultra short acting insulin is the optimal therapy for a low GI 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 the most important dietary determinant of postprandial glucose control (3).

Published educational programs regarding intensive insulin therapy do not consider the influence of carbohydrate type on metabolic control (4-7). Glycemic index (GI) ranks carbohydrate containing foods based on their ability to raise blood glucose levels (BGLs) for a standardized amount of carbohydrate (8). GI is dependent on the chemical structure of the carbohydrate and preparation methods which influence the speed of carbohydrate digestion and absorption.

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

Newer intensive regimes using ultra short acting insulin analogues have been shown to improve postprandial glycemic rise (14). The potential additional benefits of low GI 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 GI meals.

Preprandial regular insulin, which has a more delayed onset, lower peak concentration and longer duration of action compared to ultra short acting insulin (15, 16), may better match the absorption profile of low GI foods. However, postprandial ultra short acting insulin has been demonstrated to produce higher PPGEs compared to preprandial administration (17, 18), and this may be another alternative approach to optimizing insulin therapy for a low GI 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 GI of a meal on postprandial glucose control in children with type 1 diabetes on multiple daily injection therapy. The secondary aim was to assess if preprandial ultra short acting insulin remains optimal insulin therapy for a low GI meal.

RESEARCH DESIGN AND METHOD

Children and adolescents with type 1 diabetes diagnosed for ≥1 year and using multiple daily injection therapy (≥4 injections per day) for greater than 6 months were recruited from the John Hunter Children's Hospital Diabetes Clinic. Eligibility criteria included age between 7 to 17 years inclusive, non-obese and recent HbA1C ≤ 8.5% (Primus, PDQ A1c Analyzer [Primus Corp. Kansas City, MO]). Exclusion criteria included complications of diabetes such as gastroparesis or co-existing 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.

Study Design: Participants and their families were contacted by telephone two weeks prior to 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 less than 3.5 mmol/l.

Four test conditions were administered to each child at breakfast on four consecutive days in a randomized way using a permuted block method with block size of four, stratified by test condition:

1. Low GI meal (GI 48), preprandial ultra short acting insulin
2. High GI meal (GI 84), preprandial ultra short acting insulin
3. Low GI meal (GI 48), preprandial regular insulin
4. Low GI meal (GI 48), postprandial ultra short acting insulin.

Due to an increased risk of sensor failure on day 4, test conditions one and two were randomized on the first two days to ensure conservation of these results. Test conditions three and four were randomized on the final two days.

Preprandial injection of insulin was administered immediately prior to meal consumption. Postprandial insulin was administered 15 minutes after meal commencement. A kitchen timer was supplied to each participant to ensure accuracy. Each child received their normal breakfast insulin dose based on the amount of carbohydrate in the test meal. If the preprandial BGL was above 16 mmol/l the subject was instructed to add a correction dose of insulin and was asked to repeat the study.

Participants were provided with four pre-made test meals. Each meal was consumed at breakfast after a minimum 10 hour 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 four hour postprandial period. A food and activity diary was kept by each subject/parent to determine adherence to this protocol.

***Test Meals*:** The low GI test meal (GI 48) and the high GI test meal (GI 84) consisted of a ham sandwich and a drink (Table 1). A concentrated yeast extract spread (Vegemite) sandwiches were offered as a vegetarian option, which two participants accepted. The carbohydrate, fat, protein and fiber amount was standardized for both meals (Table 1). The GI of foods was obtained from published tables (20) where available and confirmed by manufacturers. The GI of each meal was calculated using methods previously described (21).

Food was weighed using Salter kitchen scales which measure to +/- 1g (model 323. Kent, UK). Liquids were measured using a 250mL measuring jug and a 10mL disposable syringe.

All meals were supplied in an insulated bag the afternoon prior to 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 prior to consumption.

Blood Glucose Measurement: A Continuous Glucose Monitoring System was used (CGMS; Medtronic, MiniMed, Northridge, CA). The sensor was inserted in the abdominal subcutaneous tissue the afternoon prior to study commencement. Subjects were instructed to enter 4 BGLs per day into the monitor at a time when BGLs were stable for calibration. They were asked to enter a ‘meal marker’ into the CGMS immediately prior to meal consumption.

Only subjects who had acceptable traces for each 4 test conditions were accepted for analysis. If sensor failure occurred, then the test condition was repeated using a new sensor.

Statistical Analysis: The four hour postprandial period was analyzed using SPSS 15 software. A one way repeated measures ANOVA analyzed the following parameters:

- Blood glucose excursions at 30 minute increments
- Incremental area under the curve as previously described (22)
- Peak blood glucose level
- Time to peak BGL
- 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 pair wise comparisons. Results are presented as means with 95% confidence intervals.

RESULTS

Subjects: Thirty-four participants were recruited. Two withdrew before study commencement due to personal reasons and one participant was excluded due to an inappropriate HbA1c. Of the 31 children who participated, the results of 11 participants were excluded from analysis due to:

- Sensor failure (n=4)
- Inappropriate starting BGL on test days (n=2)
- Prolonged hypoglycemia (n=2)
- Failure to comply to protocol (n=1)
- Diagnosis during study period of a medical condition that would interfere with study protocol (n=1)
- 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 (range 1.0-13.6) years and had good metabolic control (HbA1c; 7.4 ±0.7 [range 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).

Low GI vs. high GI meal with preprandial ultra short acting insulin: The high GI meal resulted in a significantly higher PPGE at all time points between 30-180 minutes compared to the low GI meal (LSD $p<0.02$, figure 1a). The maximum difference between the PPGE following each test condition occurred at 60 minutes; the high GI meal was 4.2 mmol/l higher than the low GI meal (7.1 [5.2-9.0] mmol/l vs. 2.9 [1.5-4.3] mmol/l, LSD $p<0.0001$).

The AUC and peak blood glucose excursion were greater for the high GI meal compared to the low GI meal (LSD $p<0.0001$, table 2). The high GI meal took significantly longer to return to baseline BGL (LSD $p=0.011$, table 2). There was no difference in time to peak BGL for the two test conditions (table 2).

Preprandial ultra short acting insulin vs. preprandial regular insulin for a low GI meal: Administering preprandial regular insulin compared to ultra short acting insulin resulted in a 1.1 mmol/l higher blood glucose excursion at 30 minutes only (3.4 [2.4-4.4] mmol/l vs. 2.3[1.3-3.3] mmol/l, LSD $p=0.015$ figure 1b). Ultra short acting insulin reduced the AUC compared to administration of regular insulin (LSD $p=0.046$, table 2). There was no difference in the peak blood glucose excursion, time to peak or time to baseline between the two test conditions (table 2).

Preprandial vs. postprandial ultra short acting insulin for a low GI meal: Administration of preprandial ultra short acting insulin resulted in a significantly lower PPGE compared to postprandial administration at 30 and 60 minutes (figure 1c). At 60 minutes the blood glucose excursion was 2.5 mmol/l lower following

administration of preprandial insulin compared to postprandial insulin (2.9 [1.5-4.3] mmol/l vs. 5.4 [4.2-6.6] mmol/l, LSD p< 0.0001).

Preprandial administration resulted in a lower AUC for 0-1 (1.9 [1.0-2.7] mmol.hr/l vs 3.5 [2.8-4.2] mmol.hr/l, LSD p<0.0001) and 0-2 hours (4.4 [1.8-7.0] mmol.hr/l vs 7.1 [4.8-9.4] mmol.hr/l, 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 Bonferroni's correction led to a p=0.02. Almost all the p-values in the analysis remained significant using this threshold and this adjustment did not change the conclusions.

CONCLUSION

To our knowledge this study is the first to examine if changing the GI of a mixed meal alters the PPGE in children on multiple daily injections. The low GI meal produced a significantly lower PPGE for 30-180 minutes, a lower AUC, a smaller peak blood glucose excursion and reduced time to reach baseline BGLs compared to the high GI meal when preprandial ultra short acting insulin was administered (LSD p<0.02).

Previous studies in children on conventional insulin therapy and in adults on intensive insulin therapy (11, 23, 24) support our findings. Furthermore, Nansel et al (13) recently postulated that reduction in postprandial excursions may be responsible for the improved daytime glycemic control they found in youths consuming low GI diets. However, one study in children failed to show a difference in the PPGE when the GI 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 not applicable to children on intensive insulin therapy regimes.

It may be hypothesized that the substantial differences demonstrated in the postprandial glucose excursion and AUC between the low and high GI test meals in this study should extrapolate to an improved HbA1c. This is supported by Brand-Miller's meta-analysis, which detected a 10.6% reduction in the HbA1c of adults and children with T1DM when a low GI diet was consumed over a two to 52 week period (10).

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

After considering the effect of GI on PPGEs the question remains if insulin type (regular insulin or ultra short acting insulin) or timing of insulin administration should be altered when a low GI meal is consumed.

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 minutes (p=0.015). Therefore the use of preprandial regular insulin did not offer an advantage over preprandial ultra short acting insulin when a low GI 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) . As such we believe

postprandial administration of ultra short acting insulin should not be recommended as it potentates deviations from normoglycemia.

Dietary focus remains on carbohydrate counting as a dietary 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 GI dietary advice into medical nutrition therapy for children and adolescents with type 1 diabetes on multiple daily injections. Preprandial ultra short acting insulin remains optimal insulin therapy when a low GI meal is consumed and postprandial injection of insulin is not recommended as a standard management technique.

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Table 1. Nutritional Information for Low and High GI Test Meals.

Food		Weight (g)	Energy (Kcal)	Carbohydrate[1] (g)	Fat (g)	Protein (g)	Fiber (g)	GI
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)	250mL	107.1	26.5	<1	<1g	<1g	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
	Totals		375.9	60.1	9.4	10.6	3	48
High GI Meal	Regular white bread (Tip Top Sunblest 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
	Totals		359.0	60	9.3	10.6	1.8	84

GI= glycemic index, Tr= trace amounts.
1 Available carbohydrate including sugars and starch and excluding fiber

Table 2. Mean fasting BGL, mean peak BGL, mean time to peak BGL, mean time to baseline BGL and mean AUC for each test condition, presented where appropriate with 95% confidence intervals.

Test meal	Mean fasting BGL (mmol/l)	Mean peak blood glucose excursion (mmol/l)	Mean time to peak BGL (mins)	Mean time to fasting BGL (mins)	Mean AUC (mmol.hr/L)
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)

*denotes statistically different when compared with result of low GI meal, preprandial ultra short acting insulin (LSD, $p<0.05$).

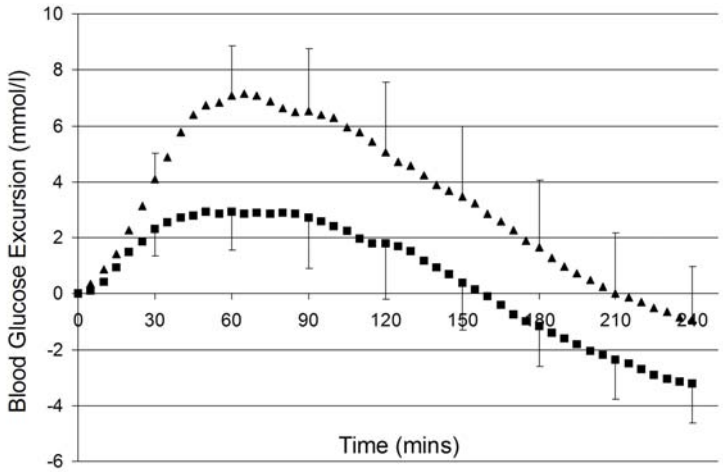
Figure legend:

Figure 1a. Low vs. high glycemic index meal with preprandial ultra short acting insulin. Black squares= low GI meal, preprandial ultra short acting insulin. Black triangles= high GI meal, preprandial ultra short acting insulin. Mean postprandial glucose excursions of 20 patients after a low GI meal and high glycemic index meal with preprandial ultra short acting insulin. Error bars represent 95% confidence intervals. The results are significantly different for 30-180 minutes (LSD, $p<0.02$).

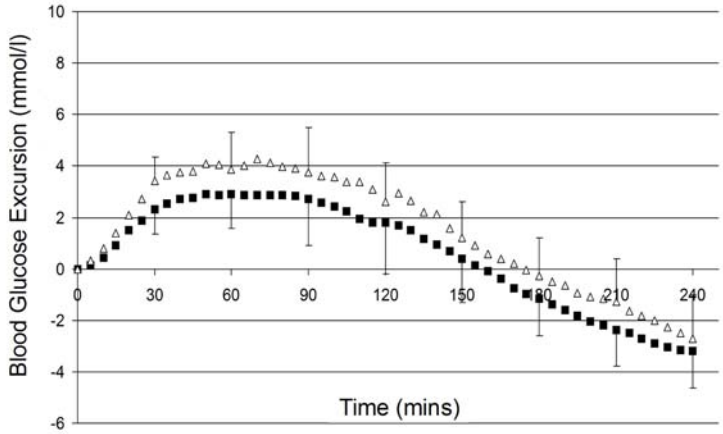
Figure 1b. Preprandial ultra short acting insulin vs. preprandial regular insulin for a low GI meal. Black squares= low GI meal, preprandial ultra short acting insulin. White triangles= low GI meal, preprandial regular insulin. Postprandial glycemic excursions after administering ultra short acting insulin and regular insulin before a low glycemic index meal. The results are significantly different at 30 minutes only (LSD, $p<0.02$).

Figure 1c. Preprandial vs. postprandial ultra short acting insulin for a low glycemic index meal. Black squares=low GI meal, preprandial ultra short acting insulin. Black circles=low GI meal, postprandial ultra short acting insulin. Postprandial glycemic excursions after administering preprandial and postprandial ultra short acting insulin with a low GI meal. The results were significantly different at 30 and 60 minutes (LSD, $p<0.02$).

1a


Blood Glucose Excursion (mmol/l)
10
8
6
4
2
0
-2
-4
-6
0
30
60
90
120
150
180
210
240
Time (mins)

1b


Blood Glucose Excursion (mmol/l)
10
8
6
4
2
0
-2
-4
-6
0
30
60
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120
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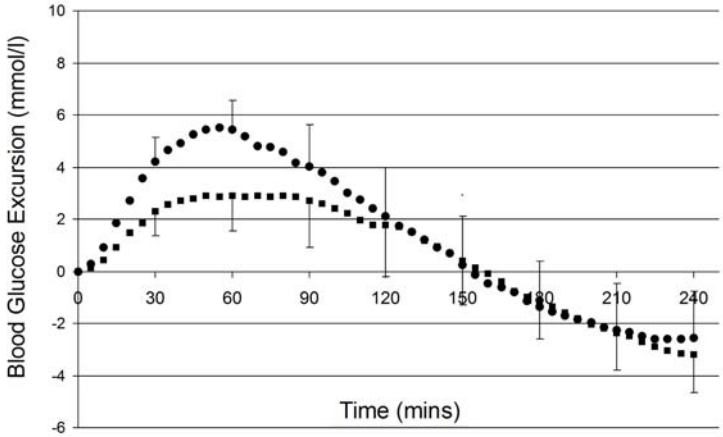
180
210
240
Time (mins)

1c


Blood Glucose Excursion (mmol/l)
10
8
6
4
2
0
-2
-4
-6
0
30
60
90
120
150
180
210
240
Time (mins)