Optimizing postprandial glycemia in pediatric patients with Type 1 diabetes using insulin pump therapy – impact of glycemic index and prandial bolus type.

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Running title: Optimizing PPG: impact of meal GI/bolus type

Clinical Trial Registry #: ACTRN012605000762651

Received for publication 11 February 2008 and accepted 15 May 2008.
Objective: Postprandial glycemic excursions may contribute to the development of diabetes related complications. Meals of high and low glycemic index (GI) have distinct effects on postprandial glycemia (PPG). Insulin pump therapy offers the potential to tailor insulin delivery to meal composition, however optimal bolus types for meals of different glycemic loads have not been defined. We sought to compare the impact of GI combined with varying prandial bolus types on PPG.

Research Design and Methods: An open cross-over study examining the effects of four different meal and bolus-type combinations on 3 hour PPG (measured by CGMS) was conducted. Twenty young people aged 8-18yrs with type 1 diabetes using insulin pump therapy participated. Meals had equal macronutrient, energy and fibre content and differed only in GI (low vs high). Participants consumed meals of the same GI on consecutive days and were randomised to receive either a standard (100%) or dual-wave (DW- 50:50% over 2 hours) bolus each day. CGMS data from 10 healthy control participants established the ‘target’ response to each meal.

Results: A DW bolus before low GI meals decreased PPG area under curve (AUC) by up to 47% (p=0.004) and lowered the risk of hypoglycemia for the same pre-meal glucose (p=0.005), compared with standard bolus. High GI meals resulted in significant upward PPG excursions with greater AUC (p=0.45), regardless of bolus type.

Conclusion: This data supports the use of a DW bolus with low GI meals to optimize PPG in patients with Type 1 diabetes using insulin pump therapy.
Attention to postprandial glycemia (PPG) is emerging as a key therapeutic strategy in the prevention of adverse outcomes for patients with diabetes. Epidemiological evidence from non-diabetic adults has shown that blood glucose level two hours after a glucose challenge is predictive of both development of cardiovascular disease and mortality (1; 2). In subjects with type 2 diabetes, there is evidence that postprandial hyperglycemia is an independent risk factor for myocardial infarction (3), possibly by inducing endothelial dysfunction and oxidative stress generation. Post-challenge hyperglycemic ‘spikes’ are also more strongly associated with carotid intima-media thickness than fasting plasma glucose or HbA1c (4). Such an association has yet to be defined for type 1 diabetes, however since hyperglycemia can acutely alter normal homeostasis, it is reasonable to hypothesize that this effect will be accentuated in any individual with diabetes.

The DCCT clearly established a continuous relationship between glycemic exposure and the risk of microvascular complications (5). The investigators have however argued that HbA1c alone is insufficient to explain the onset of complications and have suggested that PPG may be implicated (6). Since PPG is a major determinant of HbA1c, efforts that specifically improve PPG have the ability to improve HbA1c (7). How best to integrate such measures into current management strategies is not well defined.

Insulin pump therapy is unique in its ability to tailor prandial insulin delivery to the composition of a meal and its anticipated glycemic effects. Current pump technology allows variation in the speed and duration of prandial insulin delivery; calculation of the pre-meal bolus should therefore be based both on the dose of insulin required and on bolus type. Despite access to these advanced features, there is a paucity of evidence to guide clinicians and patients in their use. Previous studies have shown reduction in late postprandial hyperglycemia with use of a dual-wave (DW) bolus for high-carbohydrate (CHO), high-fat meals (8; 9) and high-fat meals alone (10). The PPG impact of altering pre-meal bolus type for meals of recommended nutritional composition (11) has not yet been examined.

The glycemic index (GI) ranks foods based on acute glycemic impact over a 2-hour period of 50g of available CHO of a test food compared to the reference standard glucose (12). GI is consistent between age groups (13). The glycemic load (GL) considers both the GI and the CHO amount consumed (GL = GI x g of CHO/100) (14). Use of GL to predict glycemic response and insulin demand has been validated in healthy adults (15); whether it can be employed as a predictor of exogenous insulin requirements for different meals in individuals with type 1 diabetes has not previously been examined.

Our hypothesis was that consideration of the GI of a meal when determining the pre-meal bolus type would optimize PPG in patients with type 1 diabetes using insulin pump therapy.

**RESEARCH DESIGN AND METHODS**

We conducted an open cross-over study examining the effects of four different meal- and bolus-type combinations on PPG in children and adolescents with type 1 diabetes using insulin pump therapy. The study received institutional Ethics Committee approval. Inclusion criteria comprised: age 8-18 years, type 1 diabetes for >1 year, use of insulin pump therapy including proficiency with use of a bolus dose calculator for >3 months, HbA1c ≤ 8.5% (PDQ Primus), reliably performing self monitoring of blood glucose (SMBG) at least 4 times daily.
Individuals with eating disorders, concomitant dietary restrictions (e.g., celiac disease or food allergy), use of another medication that lowers blood glucose and those with diabetes-related complications were excluded. Data from healthy young adult control participants were used to establish the normal PPG profiles following each meal type.

During the two weeks prior to participation, SMBG was performed 8 times daily (fasting, pre-meals, 2 hours post meals and overnight) to allow optimization of basal rates, insulin to CHO ratios (ICR) and insulin sensitivity factors. The study was then carried out under supervision in a dedicated research unit. A schematic timeline is shown in Figure 1. Participants arrived fasting at 08.00am and ate a standardized breakfast; this served to negate any confounding ‘second-meal effect’ at the time of the subsequent test meal. The test meal was eaten at lunchtime, 3.5 hours after breakfast. Nutritional composition of all study meals is outlined in Table 1. Test lunchtime meals had equivalent macronutrient (CHO, protein, fat) fibre and energy composition and differed only in their GI and hence GL.

Postprandial glycemia was examined following four different meal- and bolus-type combinations. Participants consumed the same test meal type (either low or high GI) on two consecutive days, using a different pre-meal bolus type on each day; this process was then repeated over a further two day period with the other test meal type. Bolus types used were either a standard bolus delivering 100% of the dose over 3 minutes immediately prior to the meal, or a DW bolus with 50% delivered over 3 minutes immediately prior to the meal and 50% delivered over the subsequent 2 hours. The order of each test meal and bolus-type combination was randomly assigned in advance for each participant. Each participant used their own ICR, as verified during the run-in period, to determine the total dose of insulin to be administered. Before breakfast, if blood glucose level was >10 mmol/l, an additional correction bolus was administered; pre-breakfast insulin was given as a standard bolus over 3 minutes throughout the study. Correction bolus doses were not administered at the test lunchtime meal where total insulin dose was constant in a given individual over the study period for each meal type.

Continuous glucose monitoring using the CGMS Gold (Medtronic, MiniMed, Northridge CA) system was used to monitor changes in PPG for three hours after each test meal-bolus combination. A new subcutaneous sensor was inserted for each two day study block. Controlled conditions were employed throughout the study: insulin aspart was used by all participants, subcutaneous infusion sites were changed on the evening prior to each two-day study block, catheter site (e.g., hip, stomach) remained constant in a given individual over the entire study period, activity was limited to sedentary activities in a research unit. All meals were consumed in their entirety within 20 mins; no additional food or drink was consumed in the 3 hour postprandial period unless required to treat symptomatic hypoglycemia.

**Statistical Analysis:** Primary outcome of interest was area under the curve (AUC), following each of the meal- and bolus-type combinations in participants with diabetes. AUC was defined as the sum of the absolute value of excursions from sensor value at the start of the meal, and was calculated for the 3 hour period following each meal and bolus combination. Data following treated hypoglycemic episodes did not form part of the analysis. To account for this, AUC was calculated in 3 separate ways: i) excluding participants with treated hypoglycemic episodes, ii) extrapolating average values up to time of treatment and iii) carrying forward the last sensor value prior to treatment; separate analyses were performed to ensure
results were consistent. Linear regression was used to investigate the relationship between AUC and bolus type and meal GI, adjusting for sensor value at the start of the meal. Differences in PPG profiles with each of the two bolus types for each of the meals were investigated using logistic regression and chi squared. Analysis was performed using Stata 10 (2007, StataCorp LP, Texas, USA).

RESULTS
Twenty children and adolescents (10 male) with type 1 diabetes participated in the study. Baseline characteristics expressed as mean (range) were as follows: age 11.8 (9.3 – 17.3) years, duration of diabetes 4.9 (2.1 – 8.9) years, duration of insulin pump therapy 0.8 (0.4 – 1.8) years, HbA1c 7.5% (5.9 – 8.5). Ten healthy, non-diabetic young adult controls (4 male) also consumed the study meals on 2 consecutive days under comparable conditions.

Profiles of mean (+/- standard error [SE]) postprandial excursion from pre-meal sensor glucose are shown for control participants following each meal type and for participants with diabetes following each meal type and bolus combination in Figure 2.

Analysis comparing AUC of 3 hour PPG following the low GI meal showed a significant beneficial effect of use of a DW bolus. This effect of lowering AUC was significant using all methods of AUC analysis. Excluding data from those with treated postprandial hypoglycemia, use of a DW rather than a standard bolus resulted in 47% decrease in AUC (p=0.004; see Figure 2 [a]). Similarly, AUC reductions of 31% (p<0.05) and 36% (p=0.03) were found using methods ii) and iii) as described above, respectively. The significant differences in PPG profiles between bolus types for the low GI meal emerged at 25 minutes and persisted thereafter.

In contrast, pre-meal bolus type had no effect on postprandial AUC following the high GI meal (p=0.45). As shown in Figure 2(b), substantial upward glycemic excursion was evident following this meal, regardless of bolus type; mean peak PPG excursion in participants with diabetes was 5.3mmol/l, compared with 1.8mmol/l in control participants. Mean time taken to reach peak glucose excursion was also significantly longer for participants with diabetes relative to control participants: 76 minutes vs 38 minutes respectively (p<0.01), with no difference between bolus types (p=0.75).

Regression analysis was used to establish whether sensor glucose value immediately prior to the test meal had an effect on the subsequent PPG profile. No significant effect of pre-meal glucose on postprandial AUC was evident for either test meal type (p=0.07 and 0.8 for the low GI and high GI meals respectively).

In total, 13 symptomatic hypoglycemic episodes required treatment during the 3 hour postprandial period. Hypoglycemia occurred in participants of all ages. Eleven episodes occurred after low GI meals (standard bolus 7, DW bolus 4); 2 episodes followed the high GI meal with standard bolus. The higher number of episodes following low GI meals did not reach statistical significance (p=0.07). There was, however, a significant effect of pre-meal glucose level for the low GI meal-standard bolus combination, where the odds ratio of symptomatic hypoglycemia increased by 0.6 for every 1mmol/l decrease in pre-meal glucose (p=0.005).

CONCLUSIONS
This study has shown for the first time that consideration of both the GI of a meal and the type of pre-meal insulin bolus has important modifiable effects on PPG. Three hour postprandial AUC was up to 47% lower with use of a DW bolus compared to a standard bolus for a low GI meal. Mean PPG profiles obtained following a low GI meal
with a DW bolus closely mirrored physiological ‘target’ profiles of control participants for the first 90 postprandial minutes. In contrast, high GI meals were followed by significant and prolonged upward PPG excursions in participants with diabetes, irrespective of pre-meal bolus type.

PPG is a relatively new concept in diabetes management and many questions with regard to its assessment remain (16). In practical terms, the measurement of fasting/pre-meal plasma glucose and HbA1c still dominate the assessment of glycemia. Established treatment goals of fasting/pre-meal normoglycemia and HbA1c as near to normal as possible have, however, been challenged by studies which showed that even in patients achieving these goals, postprandial hyperglycemia is common (17). Thus, in light of the recent evidence linking PPG to adverse outcomes (1-4) ‘well-controlled’ patients may remain at increased risk of developing diabetes-associated complications.

Current American Diabetes Association (ADA) nutrition recommendations advocate matching insulin to the CHO content of a meal (11). Traditional prandial insulin dosing, as determined by the amount of CHO in grams or weighed ‘exchanges’, does not account for the very different effects that different types of CHO have on PPG. Although not universally adopted in routine practice, low GI diets have been shown in some studies to have clinically useful effects on lowering HbA1c in type 1 diabetes (18-20) and are acknowledged to produce modest additional benefits to that observed when total CHO is used alone (11; 21). Our centre has previously reported benefits of incorporating use of the GI into routine diabetes management (18) and it continues to be recommended for our patient group.

By definition, low GI foods result in a lower, more gradual rise in PPG; this prompted our hypothesis that a DW bolus may better suit low GI meals. Since GI is defined relative to its PPG impact at 2 hours, we chose to deliver the extended portion of the DW bolus over 2 hours. In the absence of an evidence base a 50:50 split was empirically chosen for both meals to allow for direct comparison. PPG monitoring for 3 hours after the meal allowed for a ‘lag’ time related to exogenous insulin delivery.

Bolus-wizard settings of all participants were verified with 8-point testing over a 2 week run-in period prior to this study; thereafter ICR was consistent in a given individual throughout the study period. Despite this, meals of equivalent CHO amount (g) resulted in markedly different PPG responses (see Figure 2). The striking difference in PPG profiles underscores the inherent difficulty with calculating meal boluses solely based on CHO quantity. Consideration of the nature of the CHO and its anticipated PPG effects (GI) can therefore help to optimize PPG and inform decisions regarding the mode of meal bolus delivery.

Symptomatic hypoglycemic episodes occurred more frequently after low GI meals but this did not reach statistical significance. Of note, however, those with a lower pre-meal glucose were significantly more likely to experience hypoglycemia using a standard bolus rather than a DW bolus for this meal type. This implies that patients attaining their ‘target’ pre-meal glucose may gain additional benefit from reduction in postprandial hypoglycemia with use of a DW bolus for low GI meals. Despite variable age-specific energy requirements and the consistent energy intake of the study meals, hypoglycemia occurred across all age groups.

A concerning finding of this study was the significant upward deviation in PPG following high GI meals in participants with diabetes, where the glycemic response was almost threefold greater than that of non-diabetic controls. Thus, even with use of a rapid acting insulin analog, participants with
diabetes were unable to curtail significant hyperglycemic PPG excursions following high GI meals with boluses initiated immediately before meals. This suggests that in order to optimise PPG, prandial insulin may need to be initiated in advance of a high GI meal; further studies as to the timing of bolus administration with different meal types are now warranted.

This study highlights a number of important practical issues for those who care for patients with type 1 diabetes using insulin pump therapy. The important impact of the GI of any given meal is evident in the PPG profiles following each of the 2 meal types. In addition, clinically significant benefits, including attainment of physiological PPG profiles for the first 90 postprandial minutes, are now apparent with use of a DW bolus for a low GI meal. Our data reinforce the beneficial PPG impact of choosing low GI rather than high GI foods with relevance to commonly eaten mixed meals. Of note, the GI concept also applies to mixed meals of varying macronutrient composition (22). This should guide advice to patients regarding meal choices, informed-use of insulin pump bolus technology and the potential impact on PPG.

We acknowledge that implementation of these findings represents ‘advanced’ insulin pump management which may best be incorporated when basic insulin pumping is established. However, incorporation of GI into routine diabetes care has previously been shown to be easily adopted and accepted in pediatric patients (18). Current nutrition recommendations acknowledge that evidence from well-conducted cohort studies also supports this practice (11, 21). In practical terms, nutritional advice may include basic education with regard to the GI of commonly encountered foods. When a meal contains only low GI foods, a DW bolus should then be administered.

The long-term consequences of postprandial hyperglycemia for patients with type 1 diabetes are unclear, but given the weight of available evidence to date it appears prudent to continue efforts to optimize ‘advanced’ insulin pump techniques to achieve physiologic PPG profiles.

ACKNOWLEDGEMENT

This study was supported by funding from the Australian Novo Nordisk Regional Diabetes Support Scheme.

REFERENCES

6. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 44:968-983, 1995


**Table 1:** Nutritional composition of meals consumed in the study

<table>
<thead>
<tr>
<th></th>
<th>Standardized Breakfast</th>
<th>Low GI test meal</th>
<th>High GI test meal</th>
</tr>
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<tbody>
<tr>
<td>Composition</td>
<td>33g wholewheat cereal</td>
<td>150g boiled spaghetti</td>
<td>280g peeled boiled potato</td>
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<tr>
<td></td>
<td>250ml low-fat milk</td>
<td>120g bolognaise sauce</td>
<td>120g bolognaise sauce</td>
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<tr>
<td></td>
<td>1 slice 9 grain toast</td>
<td>140g red apple</td>
<td>300g watermelon</td>
</tr>
<tr>
<td></td>
<td>5g margarine; 10g jam</td>
<td>300ml water to drink</td>
<td>300ml water to drink</td>
</tr>
<tr>
<td></td>
<td>2 halves tinned pears</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy (kCal)</td>
<td>412</td>
<td>429</td>
<td>430</td>
</tr>
<tr>
<td>Protein (g)</td>
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<td>Fat (g)</td>
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<td>CHO (g)</td>
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</tr>
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<tr>
<td>GL</td>
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<td>20.4</td>
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</tr>
</tbody>
</table>

**Figure 1:** Schematic timeline of each study day.

*Order of lunchtime test meal and pre-meal bolus type was randomly pre-assigned for each patient

1 Breakfast bolus: always given as a standard bolus; additional correction bolus given if BGL>10mmol/L

2 Standard bolus: 100% over 3 minutes immediately prior to meal

3 Dual-wave bolus: 50% immediately prior to meal; 50% over 2 hours. No correction boluses given with test lunch meal.
Figure 2: PPG profiles: mean (+ / - SE) deviation from pre-meal glucose

Optimizing PPG: impact of meal GI/bolus type