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A randomized comparison of three prandial insulin dosing algorithms for children and adolescents with Type 1 diabetes

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Abstract

Aim To compare systematically the impact of two novel insulin-dosing algorithms (the Pankowska Equation and the Food Insulin Index) with carbohydrate counting on postprandial glucose excursions following a high fat and a high protein meal.

Methods A randomized, crossover trial at two Paediatric Diabetes centres was conducted. On each day, participants consumed a high protein or high fat meal with similar carbohydrate amounts. Insulin was delivered according to carbohydrate counting, the Pankowska Equation or the Food Insulin Index. Subjects fasted for 5 h following the test meal and physical activity was standardized. Postprandial glycaemia was measured for 300 min using continuous glucose monitoring.

Results 33 children participated in the study. When compared to carbohydrate counting, the Pankowska Equation resulted in lower glycaemic excursion for 90–240 min after the high protein meal ($p < 0.05$) and lower peak glycaemic excursion ($p < 0.05$). The risk of hypoglycaemia was significantly lower for carbohydrate counting and the Food Insulin Index compared to the Pankowska Equation (OR 0.76 carbohydrate counting vs. the Pankowska Equation and 0.81 the Food Insulin Index vs. the Pankowska Equation). There was no significant difference in glycaemic excursions when carbohydrate counting was compared to the Food Insulin Index.

Conclusion The Pankowska Equation resulted in reduced postprandial hyperglycaemia at the expense of an increase in hypoglycaemia. There were no significant differences when carbohydrate counting was compared to the Food Insulin Index. Further research is required to optimize prandial insulin dosing.

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Introduction

Postprandial glycaemic variability remains a clinical challenge in optimizing glucose control in Type 1 diabetes. Carbohydrate quantification is traditionally recommended for prandial insulin dose estimation. However, there is growing evidence that other macronutrients should also be taken into account when determining the prandial insulin dose (1–7). In particular, high fat and high protein meals have been shown to increase postprandial glycaemia for at least 5 h (2,6,8). These findings suggest that additional insulin may be required for meals with high fat or protein content.

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Novel algorithms have been proposed which take into account the glycaemic impact of fat and protein. The Pankowska equation defines a 'Fat Protein Unit' as 100 kcal of fat or protein and provides additional insulin as an extended bolus in addition to the insulin dose estimated according to carbohydrate content delivered as a standard bolus (3–5). The Food Insulin Index is a measure of postprandial insulin responses in healthy subjects to a reference food. The insulin bolus is calculated using both the Food Insulin Index and the serving size of the meal and adjusted according to the individualized insulin-to-carbohydrate ration (ICR) (9). Currently there are no clinical studies comparing the acute postprandial glycaemic impact of using carbohydrate counting, the Pankowska Equation and the Food Insulin Index for meals high in fat and protein.

What's new?

- This is the first study to compare three prandial insulin dosing algorithms (carbohydrate counting, the Pankowska Equation and the Food Insulin Index).
- The study found no significant difference in any outcome between carbohydrate counting and the Food Insulin Index for a high protein or a high fat meal.
- While the Pankowska Equation reduced postprandial hyperglycaemia, there was a significant increase in hypoglycaemic events, suggesting some children and adolescents may need clinical modification of this algorithm to avoid hypoglycaemia.
- Regardless of the algorithm used participants spent a significant amount of the postprandial period in hyperglycaemia (at least 18.6% of time following a high protein meal and 31.0% of time following a high fat meal) suggesting a need for further research into optimal insulin-dosing algorithms for meals of different macronutrient content.

The aim of this study was to compare systematically the impact of two novel insulin-dosing algorithms (the Pankowska Equation and the Food Insulin Index) to the usual standard insulin-dosing algorithm (carbohydrate counting) on postprandial glucose excursions following a high fat and a high protein meal. It was hypothesized that the 5-h postprandial glucose excursions would be similar when carbohydrate counting was used to calculate mealtime insulin dosing, compared with using the Pankowska Equation or the Food Insulin Index.

Participants and Methods

Study design

The study was conducted at two Paediatric Diabetes centres in Australia, the John Hunter Children's Hospital, Newcastle, NSW, and the Princess Margaret Hospital, Perth, WA. Institutional Ethics committee approval was obtained from each site. The study was registered with the Australia New Zealand Clinical Trials Register (ACTRN: ACTRN12617000292370).

Inclusion criteria were Type 1 diabetes diagnosed for at least one year, insulin pump therapy for at least 6 months, age between 7–17 years, and HbA1c < 64 mmol/mol (8%). Exclusion criteria were known complications of diabetes or other medical conditions including celiac disease and treatment with oral hypoglycaemic agents.

A lead-in period of one week was used to optimize the participants' ICR and insulin pump settings. Participants and their families were contacted daily by a member of the research team and their blood glucose (BG) levels were reviewed.

The study had a randomized, crossover design and involved the provision of two sets of test meals given on two sets of 3 consecutive days in the same study participants. Figure 1 depicts the study design. The order of the test meal and insulin algorithms was determined by computer-generated randomization.

Participants attended the clinic the day prior to weeks one and two of the study for insertion of Dexcom continuous glucose monitoring (CGM) and review of BG levels, and were asked to return to the clinic on the day following completion of the study for review. At each clinic visit the insulin pump was downloaded and the CGM data reviewed. Participants were also required to keep a BG, food and activity diary for the study period to confirm compliance with study protocol.

Procedure for calculating and delivering mealtime insulin

Three insulin algorithms were used: carbohydrate counting, the Food Insulin Index and the Pankowska Equation. Two test meals of different protein and fat content, but with similar carbohydrate amounts, were provided at breakfast: high protein (spaghetti bolognese: 1983 kJ, 48 g carbohydrate, 34 g protein, 13 g fat, Food Insulin Demand [FID] 67) and high fat (chicken nuggets and chips: 2085 kJ, 47 g carbohydrate, 16 g protein, 27 g fat, FID 83).

Insulin dose was determined using the algorithm method described in the literature. For carbohydrate counting, the subject's individualized ICR, expressed as insulin units per 10 g carbohydrate portion, was used to calculate insulin dose. The meals contained 47 g and 48 g carbohydrate, respectively, and the insulin dose was calculated based on this amount. In order to standardize insulin split and duration across algorithms, and because evidence for optimal split and duration of combination bolus was limited at the commencement of this study, a combination bolus split of 60:40% and a duration of 4 h were used for all carbohydrate-counting doses.

The Food Insulin Index insulin dose was calculated from the Food Insulin Demand (FID) of the meal as described by Bell *et al.* (10). The FID is the mathematical product of the Food Insulin Index and the energy content (kJ) per serving divided by 1000 (FID = Food Insulin Index x kJ per serving/1000). The FID was scaled up by a factor of 100/59 (FID of 1000 kJ of pure glucose/grams of carbohydrate in 1000 kJ of pure glucose) so that insulin could be dosed in the same ratio as each participants' individualized insulin: carbohydrate ratio (e.g. 1 unit: 10 g carbohydrate is equivalent to 1 unit: 10 scaled FID points). There is no evidence of the ideal combination bolus split and duration for the Food Insulin Index, so a 60:40% combination bolus split over 4 h was used for all the Food Insulin Index doses to keep it consistent across algorithm types and to reduce confounding.

For the Pankowska Equation, the insulin dose was calculated as described by Pankowska *et al.* (3). The dose

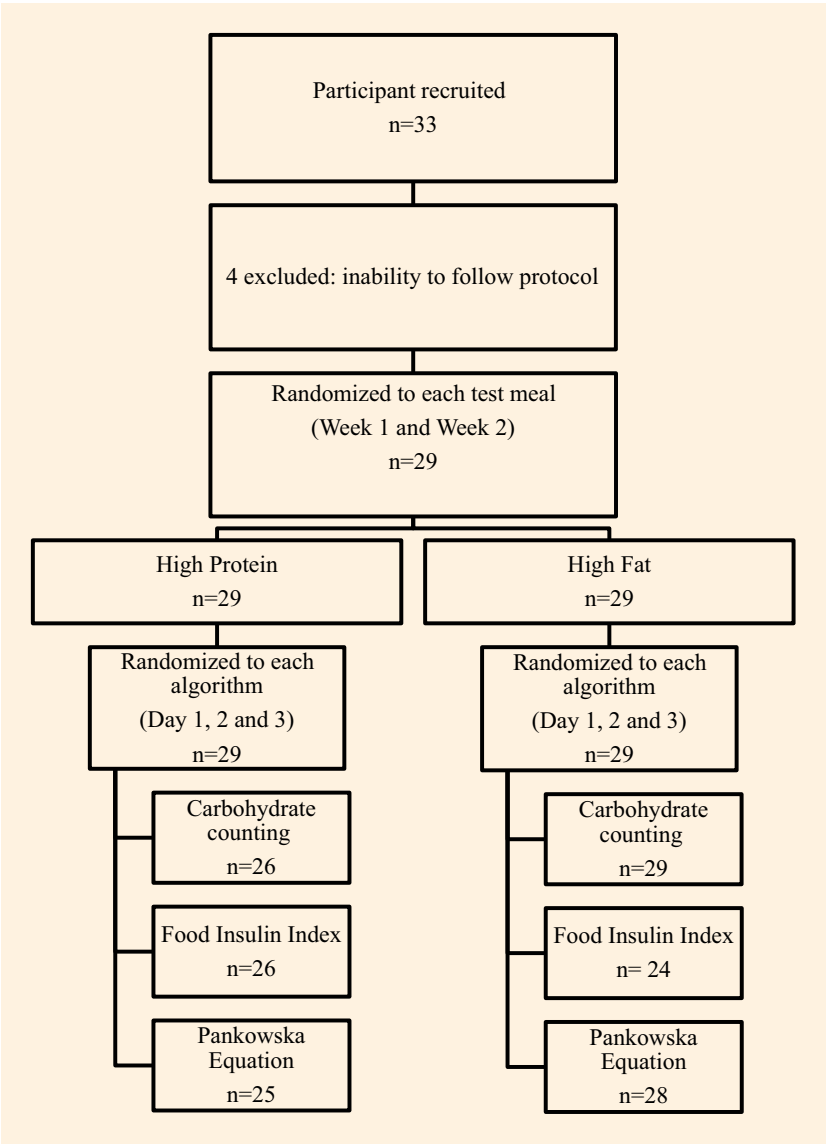

FIGURE 1 Flow diagram of randomized, crossover study design.

of insulin in the standard bolus was calculated based on the number of carbohydrate units, while the dose for the extended bolus was counted as the number of fat–protein units (FPUs) multiplied by insulin ratios (dose of insulin that covers 10 g of carbohydrate or 100 kcal from fat/protein products). The insulin dose was programmed for carbohydrate portions in the standard bolus and for FPU in the extended bolus. The total insulin dose was calculated as the sum of the standard bolus and extended bolus components. The extended boluses should be given for 4 h for 2 FPU and 5 h for 3 FPU according to Pankowska *et al.* (3). As the high protein meal had 2.5 FPUs, the extended bolus component of the insulin dose was delivered over 4 h. As the high fat meal had 3 FPUs, the extended bolus component of the insulin dose was delivered over 5 h. Insulin was administered as a combination insulin bolus commencing 15 min prior to eating the test meal. The duration of the insulin bolus was determined according to the algorithm. Participants were required to fast for five h following the test meal. Physical activity was limited and standardized on the study days.

Measurement of glycaemia

Postprandial glycaemia was measured for 300 min using Dexcom CGM, (Dexcom Inc, 6340 Sequence Drive, San Diego, CA, USA).

Glucose levels were measured using CGM at baseline and at 5-min increments over the 5-h postprandial period. Glucose levels following treated hypoglycaemic episodes were excluded from analysis for the remainder of the study period. The following

outcomes were evaluated following each test meal over 300 min: mean glucose excursions at 5-min increments, defined as the change in glucose levels from baseline; mean glucose levels at 5-min increments; and hypoglycaemic event, defined as a BGL drop to < 3.9 mmol/l, confirmed on fingerstick. Data was excluded for the times after the participant had a hypoglycaemic event for the rest of the study period.

Statistical analysis

A sample size of 30 children was needed to provide 80% power to detect a difference in glucose excursions of 2.5 mmol/l at 240 min between the algorithms at the 2.5% significance level, assuming a with-in person SD of differences in glucose levels of 3.5 mmol/l.

A generalized linear mixed model was used to estimate the difference in continuous outcomes [blood glucose excursion, time within and above target (target range 3.9–10.0 mmol/l), and peak glucose excursion] between meal types and dosing algorithms. The outcome in the model was the continuous measure and the model included the predictor variables representing meal type and dosing algorithm. A random intercept was included in the model to handle the repeated measurements on individuals. Differences in the risk of a hypoglycaemic event within the 5-h postprandial period was tested using a logistic regression model fitted within a generalized estimating equation framework to handle the repeated measurements on individuals. The outcome in the model was whether or not the subject had a hypoglycaemic event within 5 h after the test meal, and the model included the predictor variables of meal type and dosing algorithm.

P values < 0.05 were considered statistically significant. No adjustments were made for multiple comparisons.

Results

Thirty-three children and adolescents participated in the study (13 boys/young men). Four were excluded due to inability to eat the study meals within a 20-min time frame, leaving 29 participants for analysis. 21/29 participants successfully completed all study sessions. The total number of participants successfully completing each study condition were, respectively, 26/29 for high protein meal using carbohydrate counting, 26/29 for high protein meal using Food Insulin Index, 25/29 for high protein meal using the Pankowska Equation, 29/29 for high fat meal using carbohydrate counting, 24/29 for high fat meal using food insulin index, and 28/29 for high fat meal using the Pankowska Equation (Figure 1). Study sessions were not completed due to inability to consume the test meals within the allotted time and one episode of pre-meal hyperglycaemia. Table 1 shows the demographic data of study participants. Participants had a mean age of 12.3 years (7–17 years), mean HbA1c 56 mmol/mol (7.3%) (SD ± 0.7), mean duration of diabetes 7.0 years (1.2–9.5 years), mean duration of insulin pump therapy of 5.6 years (1.0–9.5 years), mean ICR of 1.3 units per 10 g carbohydrate (SD ± 0.7), mean total daily insulin dose of 0.9 units/kg/day (SD ± 0.2) and mean BMI z-score of 0.2 (SD ± 1.0).

Mean insulin doses for each meal type are shown in Table 2. The mean insulin dose for carbohydrate counting was constant across both meals for each individual. The mean insulin dose for the Pankowska Equation was higher than carbohydrate counting for both meal types. The mean insulin dose for the Food Insulin Index was higher than carbohydrate counting for the high fat meal, but lower for the high protein meal.

Mean glucose excursion

Figure 2 shows mean glucose excursions (± SD) for each meal type for 300 min following the test meal.

For the high protein meal, blood glucose excursion was statistically significantly higher with carbohydrate counting compared with the Pankowska Equation from 90–240 min after the test meal; however, there was no statistically significant difference for carbohydrate counting vs. the Food Insulin Index. At 90 min after the test meal, mean blood glucose excursion was 2.31 mmol/l for carbohydrate counting vs. 0.43 mmol/l for the Pankowska Equation (p = 0.04) and 2.60 mmol/l for the Food Insulin Index. At 120 min after the test meal, mean blood glucose excursion was 2.6 mmol/l

Table 1 Demographic data for study participants at John Hunter Children's Hospital, Newcastle, and Princess Margaret Hospital, Perth

	Combined	JHCH	PMH
Number	29	22	7
Age (years)	12.3 (± 3.6)	11.8 (± 2.6)	13.9 (± 3.1)
Diabetes duration (years)	7.0 (± 3.1)	7.6 (± 2.7)	5.3 (± 1.4)
Insulin pump use duration (years)	5.6 (± 2.8)	6.2 (± 2.6)	4.0 (± 1.9)
HbA1c [mmol/mol (%)]	56 (7.3) (± 0.7)	55 (7.2) (± 0.7)	58 (7.5) (± 0.6)
ICR (units/10 g)	1.3 (± 0.7)	1.4 (± 0.7)	1.0 (± 0.5)
Total daily insulin dose (units/kg/day)	0.9 (± 0.2)	0.7 (± 0.2)	0.9 (± 0.2)
BMI z score (%)	0.2 (± 1.0)	0.1 (± 1.1)	0.5 (± 1.0)

JHCH, John Hunter Children's Hospital; PMH, Princess Margaret Hospital; ICR, Insulin-to-Carbohydrate ratio. Data are presented as means ± SD.

Table 2 Mean insulin doses by algorithm for high protein and high fat meals

		Meal type	
		High protein	High fat
Algorithm	**CC**	5.9 (± 3.0) units	5.9 (± 3.2) units
	PE	7.3 (± 3.5) units	6.9 (± 3.9) units
	FII	4.3 (± 2.0) units	6.1 (± 2.9) units

CC, carbohydrate counting; PE, Pankowska Equation; FII, Food Insulin Index. Data are presented as means ± SD.

for carbohydrate counting vs. 0.6 mmol/l for the Pankowska Equation (p = 0.04) and 3.04 mmol/l for the Food Insulin Index. At 300 min after the test meal, blood glucose excursion was 0.05 mmol/l for carbohydrate counting vs. -1.11 mmol/l for the Pankowska Equation (p = 0.08) and 1.33 mmol/l for the Food Insulin Index (Table 3).

For the high fat meal, there were no significant differences in glucose excursion at any time point following the test meal. The mean glucose excursion was < 2.6 mmol/l for each of the three algorithms. For carbohydrate counting, the peak glucose excursion was 2.45 mmol/l at 180 min after the test meal. For the Food Insulin Index, the peak glucose excursion was 2.34 mmol/l at 120 min after the test meal. For the Pankowska Equation, the peak glucose excursion was 1.54 mmol/l at 150 min after the test meal (Table 3).

Peak glucose excursion

Peak glucose excursion is the highest glucose excursion for each subject for the 300-min period for each algorithm. After adjusting for meal type, there was no significant difference in mean peak glucose excursion for carbohydrate counting compared to the Food Insulin Index [mean difference = 0.07 (95% CI, -1.04, -1.19, p = 0.898)]. Peak glucose excursion was higher for both carbohydrate counting and the Food Insulin Index compared to the Pankowska Equation [mean difference carbohydrate counting vs. the Pankowska Equation = 1.28 (95% CI, 0.26, -2.29, p < 0.02), mean difference for the Food Insulin Index vs. the Pankowska Equation = 1.34 (0.29–2.39, p < 0.02)].

Percentage of time in glucose target range (3.9–10 mmol/l)

Table 4 shows the percentage of time in blood glucose target range (3.9–10 mmol/l) for 300 min after each test meal. Following the high protein meal, participants spent less time within the target range using carbohydrate counting (54.4%) or the Food Insulin Index (51.0%) than the Pankowska Equation (74.9%). Following the high fat meal, participants using carbohydrate counting spent 56.3% of time within the target range compared to 57.3% for the Food Insulin Index and 64.4% for the Pankowska Equation. After adjusting for meal type, participants spent less time within the target range when using carbohydrate counting and the Food Insulin Index compared to the Pankowska Equation [mean difference (95% CI) for carbohydrate counting vs. the Pankowska Equation = 13.6 (2.3, -24.8), (p = 0.018); mean difference (95% CI) for the Food Insulin Index vs. the Pankowska Equation = 15.3 (3.6, -27.0), (p = 0.010)]. There was no significant difference in time spent within the target range for carbohydrate counting vs. the Food Insulin Index [mean difference (95% CI) for carbohydrate counting vs. the Food Insulin Index 1.7 (-9.9, -13.3), (p = 0.73)].

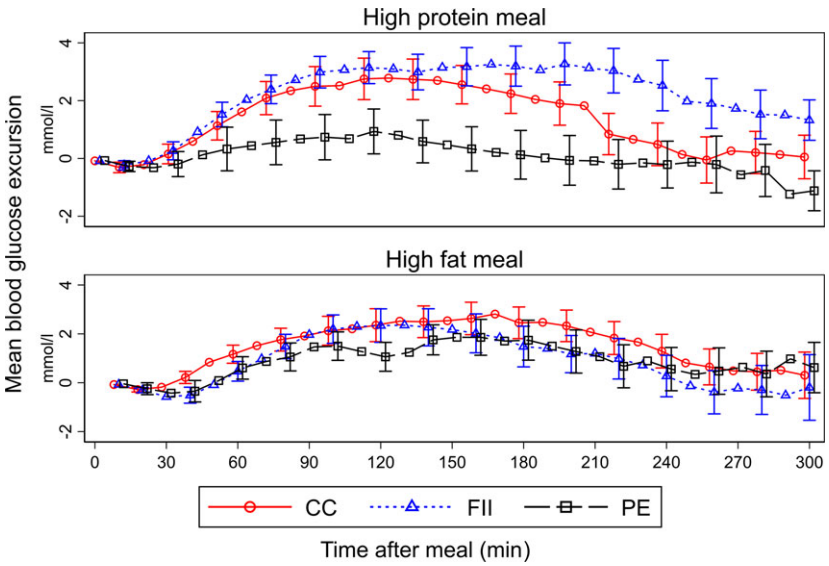

FIGURE 2 Blood glucose excursion (mmol/l) (± SD) from 0–300 min following a high protein and a high fat meal with insulin dose determined according to carbohydrate counting (CC), the Pankowska Equation (PE) or the Food Insulin Index (FII).

Table 3 Mean glycaemic excursion (mmol/l) by algorithm following (a) a high protein and (b) a high fat meal

	Algorithm			
Time (min)	CC	FII	PE	p value (CC vs. PE)
(a)				
30	−0.19 (1.15)	−0.05 (1.24)	−0.39 (1.31)	0.6306
60	1.15 (2.33)	1.49 (2.19)	0.11 (3.34)	0.1855
90	2.31 (3.09)	2.60 (2.56)	0.43 (3.51)	0.0386
120	2.62 (3.53)	3.04 (2.89)	0.62 (3.32)	0.0393
150	2.53 (3.44)	3.24 (2.92)	0.16 (3.15)	0.0068
180	2.13 (3.29)	3.23 (3.18)	−0.09 (3.46)	0.0061
210	1.66 (3.71)	3.12 (3.38)	−0.38 (3.60)	0.0092
240	0.32 (3.47)	2.39 (3.96)	−0.58 (3.31)	0.0319
270	0.01 (3.15)	1.77 (3.61)	−0.86 (3.53)	0.0691
300	0.05 (3.11)	1.33 (2.71)	−1.11 (2.19)	0.0830
(b)				
30	−0.21 (1.03)	−0.57 (1.14)	−0.50 (2.03)	0.6236
60	1.01 (2.14)	0.47 (1.93)	0.51 (2.38)	0.5829
90	1.79 (2.76)	1.97 (2.64)	1.19 (3.19)	0.5899
120	2.21 (3.58)	2.34 (3.29)	0.79 (3.37)	0.1822
150	2.36 (3.58)	2.18 (3.76)	1.54 (3.58)	0.6927
180	2.45 (3.49)	1.48 (3.91)	1.51 (3.87)	0.5619
210	2.07 (3.42)	1.20 (3.77)	0.82 (3.93)	0.4672
240	1.29 (3.51)	0.27 (3.98)	0.29 (3.74)	0.5615
270	0.49 (3.70)	−0.23 (3.92)	0.78 (3.30)	0.7038
300	0.31 (3.79)	−0.19 (4.84)	0.97 (3.31)	0.7819

CC, carbohydrate counting; FII, Food Insulin Index; PE, Pankowska Equation. Data are presented as means ± SD.

Percentage of time above target range (> 10 mmol/l)

After adjusting for meal type, subjects spent more time with BG levels > 10 mmol/l following carbohydrate counting or the Food Insulin Index compared with the Pankowska Equation [mean difference (95% CI) for the Pankowska Equation vs. carbohydrate counting = -17.7 (-29.2, -6.1), (p = 0.003); mean difference (95% CI) for the Pankowska Equation vs. the Food Insulin Index = -16.4 (-28.3, -4.4), (p = 0.007)]. There was no significant difference in time spent with BG levels > 10 mmol/l for carbohydrate counting compared with the Food Insulin Index [mean difference (95% CI) for carbohydrate counting vs. the Food Insulin Index = 1.6 (-10.1, -13.3), (p = 0.789)] (Table 4).

Hypoglycaemic events (< 3.9 mmol/l)

Table 4 shows the number and percentage of hypoglycaemic events for each algorithm according to meal type. After adjusting for meal type, there was no significant difference in odds of a hypoglycaemic event between the carbohydrate counting and the Food Insulin Index algorithms (p = 0.172). The odds of a hypoglycaemic event were significantly lower for carbohydrate counting and the Food Insulin Index compared with the Pankowska Equation [odds ratio carbohydrate counting vs. the Pankowska Equation = 0.76 (95% CI, 0.66 to 0.87), p < 0.001; the Food Insulin Index vs. the Pankowska Equation = 0.81 [95% CI, 0.70 to 0.95), p < 0.01].

Discussion

This is the first study to compare traditional mealtime insulin dose estimation (carbohydrate counting) with two novel insulin-dosing algorithms (the Pankowska Equation and the Food Insulin Index) for meals of mixed macronutrient composition. A reduced mean glucose excursion, peak glucose excursion, and an increased time within target range were reported, but an increased risk of hypoglycaemia using the Pankowska Equation compared with carbohydrate counting. There was no difference in any outcome measure for carbohydrate counting compared with the Food Insulin Index.

When insulin was dosed according to the Pankowska Equation, the insulin dose was approximately 24% higher for a high protein, and 17% higher for a high fat meal, than for carbohydrate counting. This increase in insulin dose resulted in a significantly lower blood glucose excursion for the high protein meal for 90–240 min as well as a higher rate of hypoglycaemia following the Pankowska Equation for both high fat and high protein meals. This is consistent with Kordonouri *et al.* who found a high rate of hypoglycaemia of up to 43% for the Pankowska Equation (11). However, Blazik and Pankowska, in their trial of insulin pump software that calculates prandial insulin using the Pankowska Equation, reported no difference in hypoglycaemic events when the Pankowska Equation was compared to carbohydrate counting (5). However, their study used a 2-h postprandial period as the primary end-point, which may

Table 4 Glycaemic outcomes by algorithm following a high protein and a high fat meal

		Mean percent time in target range (3.9–10 mmol/l)		Mean percent time above target range (> 10 mmol/l)		Participants reporting hypoglycaemic events number (%)	
		Meal type		Meal type		Meal type	
Algorithm		**High protein**	**High fat**	**High protein**	**High fat**	**High protein**	**High fat**
	CC	54.4	56.3	44.8	41.3	1 (3.9)	2 (6.7)
	PE	74.9	64.4	18.6	31.0	5 (21.7)	13 (44.8)
	FII	51.0	57.3	45.8	35.9	2 (7.8)	5 (20.8)

CC, carbohydrate counting; PE, Pankowska Equation; FII, Food Insulin Index.

explain the reduced number of hypoglycaemic events. Pankowska *et al*., in a study of voice recognition software using the Pankowska Equation, found that 6/12 participants using the software had an increased rate of hypoglycaemia (12). The results of the current study support this and earlier findings, that the additional insulin needs for a high fat, high protein meal should be calculated on an individual basis, with average incremental increases starting as low as 15% to avoid the risk of hypoglycaemia (1).

The current study did not demonstrate a difference in any outcome measure of glycaemic control when carbohydrate counting was compared with the Food Insulin Index. For the Food Insulin Index, the insulin dose used in the current study was similar to carbohydrate counting for the high fat meal, but significantly lower than carbohydrate counting for a high protein meal. Meals containing carbohydrate with added protein have been shown to increase postprandial glycaemic excursions from 120 min after consumption (13). This would suggest that additional insulin may be required for a high protein meal with carbohydrate, and that the Food Insulin Index algorithm may not provide sufficient insulin. This may be because the Food Insulin Index is based on 2-h insulin demand, whereas studies have shown that glucose levels rise 3–5 h following meals high in fat and protein (2,8). In a single test meal study containing moderate amounts of fat and protein, Bao *et al*. reported that the Food Insulin Index improved the mean amplitude of blood glucose excursion across a 180-min postprandial period when compared with carbohydrate counting (9). However, there was an increased rate of hypoglycaemia following the Food Insulin Index test condition. The Food Insulin Index has also been shown to result in lower mean BGL, and change in mean BGL than carbohydrate counting, across six high protein meals in people with Type 1 diabetes, but this was accompanied by a clinically significant number of hypoglycaemic episodes (approximately 50%) (10). However, the results of the current study did not support a benefit of the Food Insulin Index over carbohydrate counting for high protein or high fat meals.

The percentage of time spent within a target range of 3.9–10 mmol/l was suboptimal for all three different algorithms for both meal types, despite optimizing the insulin:carbohydrate ratio during the run-in period. Studies have reported wide inter-individual differences in the additional insulin required to optimize postprandial glycaemic control (6,14), ranging from 17–124% in one study based on 10 individuals with Type 1 diabetes (14). Currently, this type of individualized approach to insulin dosing for high protein or high fat meals is advised with tailoring of the dose according to structured postprandial glucose monitoring or CGM.

In the current study a postprandial observation period of 300 min was chosen. As the impact of added protein and fat continues for at least 300 min (13), a longer period of observation may be required to assess the effect of insulin dosing on meals high in protein or fat. Additionally, Smart *et al*. demonstrated an additive impact of fat and protein, and it is likely for meals containing both fat and protein that insulin requirements will be higher than for meals solely high in either fat or protein (2). Further research is required to optimize blood glucose control for high fat and high protein meals, with particular attention being paid to reducing glycaemic excursions in the late postprandial period.

The ideal insulin bolus shape for high fat and protein meals is yet to be determined and will impact the effectiveness of the insulin-dosing algorithm. In the present study insulin was delivered as a combination bolus for each algorithm. Combination insulin boluses have been shown to be beneficial for high fat and protein meals (3,4,16–19). However, the optimal split and duration of the combination bolus have not yet been determined. Lopez *et al*. found that at least 60% of the total insulin dose should be given in the standard bolus component of a combination bolus to control early postprandial glycaemia (16). Furthermore, to optimize glycaemic control for up to 300 min after a test meal, at least 70% of the total insulin dose was required in the extended bolus component, suggesting a need for increased insulin for a high fat and protein meal (16). In contrast, Bell *et al*., in a closed loop study in adults found that the optimal combination bolus delivery pattern was a 30:70 split and 2.4 h bolus duration. However, the optimal pattern for individuals ranged from a 10:90 to 50:50 split (14). This indicates the optimal combination bolus pattern needs to be individualized and may differ according to the age of participants, amount of food consumed, as well as its macronutrient composition.

Carbohydrate estimation is established as integral to management of Type 1 diabetes (20). Most people with Type 1 diabetes and their caregivers are able to accurately estimate meal carbohydrate content (21). Fat and protein estimation adds complexity to insulin dose estimation; hence, optimal insulin-dosing algorithms should be developed prior to recommending this for routine care. Similar to carbohydrate counting, the Pankowska Equation requires the user to estimate the quantity of fat and divide it by the fat and protein ratio. The Food Insulin Index requires the user to refer to a list of foods with determined food insulin values. Further studies of these algorithms over a longer time period in real life situations are required to fully assess the user-friendliness of these algorithms.

In summary, this is the first study to compare three prandial insulin-dosing algorithms. The Pankowska Equation resulted in lower peak glucose excursion and percentage of time above the target range when compared with carbohydrate counting. However, this was at the expense of a significantly increased risk of hypoglycaemia. There were no significant differences in any outcome measure between carbohydrate counting and the Food Insulin Index. Regardless of the algorithm used, each resulted in a significant amount of the 5-h postprandial period in hyperglycaemia. These findings suggest that while additional insulin may be required for high fat and protein meals, the ideal meal bolus algorithm has yet to be determined. Currently, an individualized approach to insulin dosing is best

practice for people with Type 1 diabetes. This study provides supportive evidence for lower starting levels of 15% additional insulin for high fat and protein meals with upper limits of 40% to minimize the risk of postprandial hypoglycaemia. The effectiveness of the insulin-dosing approach for the individual should be confirmed with CGM or structured postprandial glucose testing.

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Competing interests

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References

1 Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care* 2015; **38**: 1008–1015.

2 Smart C, Evans M, O'Connell S, McElduff P, Lopez P, Jones T *et al.* Both Dietary Protein and Fat Increase Postprandial Glucose Excursions in Children With Type 1 Diabetes, and the Effect Is Additive. *Diabetes Care* 2013; **36**: 3897–3902.

3 Pankowska E, Szypowska A, Lipka M, Szpotanska M, Blazik M, Groele L. Application of novel dual wave meal bolus and its impact on glycated haemoglobin A1c level in children with type 1 diabetes. *Pediatr. Diabetes* 2009; **10**: 298–303.

4 Pankowska E, Blazik M, Groele L. Does the fat-protein meal increase postprandial glucose level in type 1 diabetes patients on insulin pump: The conclusion of a randomised study. *Diabetes Technol Ther* 2012; **14**: 16–22.

5 Blazik M, Pankowska E. The effect of bolus and food calculator Diabetics on glucose variability in children with type 1 diabetes treated with insulin pump: the results of RCT. *Pediatr. Diabetes* 2012; **13**: 534–539.

6 Wolpert H, Atakov-Castillo A, Smith S, Steil G. Dietary fat acutely increases glucose concentrations and insulin requirements in patients with Type 1 Diabetes: Implications for carbohydrate-based bolus dose calculation and intensive diabetes management. *Diabetes Care* 2013; **36**: 810–816.

7 Paterson MA, Bell KJ, O'Connell SM, Smart CE, Shafat A, King B. The Role of Dietary Protein and Fat in Glycaemic Control in Type 1 Diabetes: Implications for Intensive Diabetes Management. *Curr Diab Rep* 2015; **15**: 61.

8 Paterson MA, Smart CE, Lopez PE, McElduff P, Attia J, Morbey C *et al.* Influence of dietary protein on postprandial blood glucose levels in individuals with Type 1 diabetes mellitus using intensive insulin therapy. *Diabet Med* 2016; **33**: 592–598.

9 Bao J, Gilbertson H, Gray R, Munns D, Howard G, Petocz P *et al.* Improving the estimation of mealtime insulin doses in adults with type 1 diabetes: The Normal Insulin Demand for Dose Adjustment (NIDDA) study. *Diabetes Care* 2011; **34**: 2146–2151.

10 Bell KJ, Gray R, Munns D, Petocz P, Howard G, Colagiuri S *et al.* Estimating insulin demand for protein-containing foods using the food insulin index. *Eur J Clin Nutr* 2014; **68**: 1055–1059.

11 Kordonouri O, Hartmann R, Remus K, Blasig S, Sadeghian E, Danne T. Benefit of supplementary fat plus protein counting as compared with conventional carbohydrate counting for insulin bolus calculation in children with pump therapy. *Pediatr. Diabetes* 2012; **13**: 540–544.

12 Pankowska E, Ladyzynski P, Foltynski P, Mazurczak K. A Randomized Controlled Study of an Insulin Dosing Application That Uses Recognition and Meal Bolus Estimations. *J Diabetes Sci Technol* 2017; **11**: 43–49.

13 Paterson MA, Smart CEM, Lopez PE, Howley P, McElduff P, Attia J *et al.* Increasing the protein quantity in a meal results in dose-dependent effects on postprandial glucose levels in individuals with Type 1 diabetes mellitus. *Diabet Med* 2017; **34**: 851–854.

14 Bell KJ, Toschi E, Steil GM, Wolpert HA. Optimized Mealtime Insulin Dosing for Fat and Protein in Type 1 Diabetes: Application of a Model-Based Approach to Derive Insulin Doses for Open-Loop Diabetes Management. *Diabetes Care* 2016; **39**: 1631–1634.

15 Campbell MD, Walker M, King D, Gonzalez JT, Allerton D, Stevenson EJ *et al.* Carbohydrate counting at meal time followed by a small secondary postprandial bolus injection at 3 hours prevents late hyperglycemia, without hypoglycemia, after a high-carbohydrate, high-fat meal in type 1 diabetes. *Diabetes Care* 2016; **39**: e141–e142.

16 Lopez PE, Smart CE, McElduff P, Foskett DC, Price DA, Paterson MA *et al.* Optimizing the combination insulin bolus split for a high-fat, high-protein meal in children and adolescents using insulin pump therapy. *Diabet Med* 2017; **34**: 1380–1384.

17 Chase H, Saib S, MacKenzie T, Hansen M, Garg S. Post-prandial glucose excursions following four methods of bolus insulin administration in subjects with type 1 diabetes. *Diabet Med* 2002; **19**: 317–321.

18 Lee S, Cao M, Sajid S, Hayes M, Choi L, Rother C *et al.* The dual-wave bolus feature in continuous subcutaneous insulin infusion pumps controls prolonged post-prandial hyperglycaemia better than standard bolus in Type 1 diabetes. *Diabetes Nutr Metab* 2004; **17**: 6.

19 Jones S, Quarry J, Caldwell-McMillan M, Mauger D, Gabbay R. Optimal insulin pump dosing and postprandial glycaemia following a pizza meal using the continuous glucose monitoring system. *Diabetes Technol Ther* 2005; **7**: 8.

20 Smart C, Annan F, Bruno L, Higgins L, Acerini C. International Society for Paediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines: Chapter 10 Nutrition. *Pediatr. Diabetes* 2014; **15**(suppl 20): 135–153.

21 Smart C, Hopley L, Burgess D, Collins C. Biting off more than you can chew: Is it possible to precisely count carbohydrate? *Nutr Diet* 2011; **68**: 4.

