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Original research

Protein and fat meal content increase insulin requirement in children with type 1 diabetes – Role of duration of diabetes

M. van der Hoogt [a], J.C. van Dyk [b], R.C. Dolman [a], M. Pieters [a,*]

[a] Centre of Excellence for Nutrition, North-West University, Potchefstroom 2520, South Africa
[b] Life Groenkloof Hospital, Pretoria 0181, South Africa

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ABSTRACT

Background and objective: Hyperglycaemia remains a challenge in type 1 diabetes since current regimes used to determine meal insulin requirements prove to be ineffective. This is particularly problematic for meals containing high amounts of protein and fat. We aimed to determine the post-prandial glycaemic response and total insulin need for mixed meals, using sensor-augmented insulin pumps in children with type 1 diabetes.

Methods: Twenty-two children with type 1 diabetes, aged 4–17 years on insulin pump therapy completed this home-based, cross-over, randomised controlled trial. Two meals with identical carbohydrate content – one with low fat and protein (LFLP) and one with high fat and protein (HFHP) contents – were consumed using normal insulin boluses. Blood glucose monitoring was done for 10 h post-meal, with correction bolus insulin given two-hourly if required.

Results: The HFHP meal required significantly more total insulin (3.48 *vs.* 2.7 units) as a result of increased post-meal correction insulin requirement (1.2 *vs.* 0.15 units) spread over a longer duration (6 *vs.* 3 h). The HFHP meals significantly increased the time spent above target glucose level. Duration of diabetes and total daily insulin use significantly influenced the post-prandial blood glucose response to the two meals.

Conclusion: When consuming carbohydrate-based mixed meals, children with type 1 diabetes on insulin pump therapy, required significantly more insulin over a longer period of time than the insulin requirement calculated using current regimes. This additional amount required is influenced by the duration of diabetes and total daily insulin use.

Introduction

For many people with type 1 diabetes, post-prandial hyperglycaemia remains one of the major challenges in diabetes care and contributes greatly to glucose variability and overall glycaemic control [1]. Even in the presence of a near normal glycosylated haemoglobin (HbA1c), diabetes complications can still develop [1]. Therapy includes lifetime management of exogenous insulin delivery either by injection or by subcutaneous insulin infusion, also known as insulin pump therapy, dietary and exercise management, as well as blood glucose monitoring with finger pricks and, for some, continuous glucose monitoring (CGM) systems [2].

Current practices for determining meal-time bolus insulin whether on multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) (insulin pump therapy) involve carbohydrate counting, usually advanced (Level 3) carbohydrate counting where individualised insulin-to-carbohydrate ratios are used [2]. This and other methods of carbohydrate counting assume that only carbohydrates affect the post-prandial glucose rise in children with type 1 diabetes. However, many studies have indicated that factors such as the type of carbohydrate, the glycaemic index of the meal, and the fat, fibre and protein content of the meal play an important role in delaying post-prandial hyperglycaemia, and these factors should be considered when trying to optimise post-prandial glucose levels [3–5].

When using CSII, most pumps offer three modes to deliver bolus or meal-time insulin: the normal or standard bolus, the dual-wave or multi-wave bolus, and the square-wave or extended bolus. The use of only normal or standard boluses and carbohydrate counting alone, where all bolus insulin is delivered immediately and the

* Corresponding author at: Centre of Excellence for Nutrition, North-West University, Potchefstroom Campus, Private Bag X6001, Potchefstroom 2520, South Africa.
E-mail address: marlien.pieters@nwu.ac.za (M. Pieters).

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dose is determined by the current blood glucose reading and carbohydrate content of the meal, can be ineffective in optimising post-prandial blood glucose levels for mixed meals as fat and protein have shown independent effects on post-prandial hyperglycaemia [3–5]. Consequently, Pańkowska et al. [6] developed a method of quantifying meal insulin based on all macronutrients of the meal (carbohydrate, fat and protein (CFP) counting). However, CFP counting may pose a risk for increased post-prandial hypoglycaemic events in the early hours post meal [3,6] and may be challenging to implement in the paediatric diabetes population. In 2014, the *Guide for nutritional management in children and adolescents with diabetes*, developed by the International Society for Paediatric and Adolescent Diabetes (ISPAD), indicated that randomised controlled trials, aimed at developing methods to better manage post-prandial hyperglycaemia after fat and protein rich meals, are needed [2].

The aim of this study was to determine the post-prandial glycaemic response and total insulin need for mixed meals with known, constant carbohydrate content but different fat and protein contents, using insulin pump therapy and CGM in children with type 1 diabetes.

Subjects

In total, 32 children with type 1 diabetes aged 4–17 years were recruited. The inclusion criteria were: use of sensor-augmented pump therapy for longer than one month; HbA1c $\leq$ 9.6% (81 mmol/mol) for the last three months; World Health Organization BMI/age z-score of -1 to below 3, thus not including wasted or obese individuals; and total daily insulin use of $\geq$0.5 u/kg to avoid inclusion of participants in the remission phase of diabetes.

The exclusion criteria were: smoking; coeliac disease; cystic fibrosis; concurrent conditions that can be associated with delayed gastric emptying or altered digestion; and the use of any medication or supplements that could influence gastric emptying, digestion or glucose levels, such as glucocorticoids or oral antidiabetic drugs. Participants had to be free of any acute illnesses at the start of the study.

The study was conducted in accordance with the Helsinki Declaration. Ethical approval was obtained from the Health Research Ethics Council of North-West University, South Africa (NWU-00042-15-S1).

Materials and methods

Study design

A home-based, cross-over, randomised controlled trial was performed. For all participants, optimal basal insulin rates, carbohydrate ratios and sensitivity factors were revised and adjusted by a paediatric endocrinologist before enrolment. Participants were randomised to treatment. The two meals were consumed at dinner time (18:00) under parental supervision, at least a day apart and within a month of one another, to ensure that factors which could potentially change HbA1c values such as illness, radical changes in diet or activity, or stress did not interfere with the results. Participants maintained their normal, habitual activity levels during the two study days. Pump settings, including basal rates and bolus wizard settings, had to remain unchanged from enrolment until after data collection was completed. Upon enrolment, participants received detailed study instructions, a cooler bag with their two individual study meals, three Enlite sensors (Medtronic, Inc., MN, USA), a blood glucose meter (Bayer Contour 2.4 Next Link 2.4 blood glucose meter; Bayer Indianapolis, IN, USA) and 30 strips for the meter.

Sensor-compatible insulin pumps used in the study included the 554 Veo, 754 Veo, 722 Paradigm and 640G from Medtronic (Medtronic, Inc., MN, USA). For CGM, Medtronic Enlite Sensors were used with two different transmitters, the Gaurdian Link and Gaurdian Connect, as different pump models were used. Study meals could only be taken on days 2–5 of the sensor lifespan as a sensor is least accurate on day 1 and day 6 [7]. All participants used rapid-acting insulin Novorapid (Novo Nordisk, Copenhagen, Denmark) in their pumps.

Test meals

Each participant received two different meals with the same carbohydrate content. One meal was high in fat and protein (HFHP) and the other low in fat and protein (LFLP). Meals consisted of smoked, skinless and boneless chicken breast, pre-prepared plain, white long-grain rice, ready prepared chicken gravy, and olive oil. The meals only required pre-heating in the microwave; no cooking was allowed. The fat and protein content was manipulated by the portion sizes of the chicken breast and the amount of gravy and olive oil. The rice was a low glycaemic index (GI) food.

The macronutrient content of the meals was calculated as follows: the total daily energy requirement for each participant was individually calculated using an age, weight and gender specific World Health Organization energy expenditure recommendation [8]. The total carbohydrate per day was then calculated at 50% of total energy, since 50–55% is recommended for children with type 1 diabetes [6]. Of the total daily carbohydrates, 25% was allocated to each study meal. The amount of carbohydrates for both meals was kept constant in order for the LFLP meal to be used as the control for the HFHP meal. The fat and protein content per meal, calculated as percentage energy, were as follows: LFLP meal carbohydrates 60%, fat 25%, and protein 15%; HFHP meal carbohydrates 40%, fat 35% and protein 25%.

Meal consumption procedures and capillary blood glucose testing

A pre-prandial blood glucose level of 4–11 mmol/L was required before the study meal could be taken. If the level was not in the specified range, the participant was allowed to give a correction bolus and then have the study meal 30–60 min later, if the capillary test then fell within the recommended range. The blood glucose level and indicated carbohydrate content of the meal were entered into the bolus wizard feature of the pump and a normal insulin bolus was then delivered 10 min prior to eating each meal. To limit variability of gastro intestinal clearance affected by fluid intake, participants were not allowed to have more than two to three glasses of water 30 min pre-meal to two hours post-meal. Meals had to be consumed within 20 min. Consuming the study meal was not permitted on an evening where the participant experienced a hypoglycaemic event (<4 mmol/L) during that day. Participants were allowed a breakfast and a low fat, light lunch meal of their choice but were not allowed to have any food two hours prior to the study. The entire process was repeated for the second meal on a different night.

After consumption of the study meal, in addition to CGM, capillary blood testing was performed by a parent at 30 min post-meal and then every two hours after the start of the meal for 10 h. Each blood glucose value was entered into the pump and a correction bolus (calculated by the pump) was delivered when required (also at 2-h intervals). All hypoglycaemic events and carbohydrate treatments were entered into the pump. In the case of a blood glucose value dropping below 4 mmol/L, the study was terminated as additional food had to be given, but the time of the hypoglycaemic events was still recorded and used for data analysis.

In the case of a child not finishing a meal, not wearing the sensor for the required amount of time or not adhering to the study protocol, the meal missed was repeated and given on another day (n = 4). If this resulted in an altered meal order, it was recorded accordingly.

Insulin infusion

Before initiating the study, sensor and pump infusion sites were checked by a paediatric endocrinologist for, among others, swelling, infection and lipodystrophy, and changed if necessary. Participants were encouraged to consume study meals on days where infusion sets were changed and not to wear infusion sets longer than three days to limit the risk of poor insulin infusion.

Outcome measures

Pump downloads to obtain the study data were done using Medtronic Carelink Software Professional version (Medtronic, Inc., MN, USA). Main outcomes measured for the two meals were: peak sensor glucose value post-meal i.e. maximum post-meal glucose excursion above 6 mmol/L; time to peak sensor glucose excursion i.e. the time it took, following consumption of the meal, to reach the maximum post-meal glucose excursion; time of first and largest correction bolus – times at which first and largest correction bolus insulin were required; total correction insulin – the total of additional (correction) insulin required post-meal; total meal insulin – the total amount of insulin needed for the meal, this includes meal bolus and correction boluses; additional insulin required – correction bolus as a percentage of total bolus insulin; area under the sensor glucose response curve (AUC) (≥8 mmol/L), using the trapezoidal method; and, finally, duration of elevated post-prandial glucose – total time of elevated post-prandial glucose spent above 6 mmol/L.

The following participant characteristics were investigated as potential co-variates related to the outcome measures: gender; age; weight (measured on a precision health scale with participants wearing only light clothing and no shoes); height (using a wall-mounted stadiometer with the head in the Frankfort Horizontal Plane); duration of diabetes; HbA1c (Siemens DCA Vantage System from Siemens Medical Solutions, PA, USA); total daily insulin; active insulin time setting; carbohydrate-to-insulin ratio; insulin sensitivity factor; and meal energy, carbohydrate, fat and protein content.

Statistical analysis

The computer software package IBM® SPSS® Statistics version 23 (Statistical Package for Social Sciences, IBM, New York, USA) was used. Significance was set at $p < .05$. Normally distributed data is reported as mean ± standard deviation (SD) and non-parametric data as median (25th; 75th percentiles). The order of treatment effect was tested for using repeated measures analysis of variance (ANOVA). Since no order of treatment effect was observed for any of the outcome variables, the data of the two treatment periods was combined. Paired t-tests for normally distributed data, and the Wilcoxon Matched Pairs test for non-parametric data were used to compare the LFLP and HFHP meals. Repeated measures ANOVA was used to compare the blood glucose levels and insulin dosages over the 10 h period between the two meals and also to perform sensitivity analysis to test for the possible influence of the use of two different CGM transmitters. In order to determine the influence of inherent patient characteristics unrelated to the test meals on the outcome variables, univariate mixed models were performed and data reported as β (95% confidence intervals (CI)). Characteristics found to be significantly related to the outcome variables were tested for interaction with the test meals by creating interaction terms, using continuous variables, in separate mixed models. Bivariate models were used when adjusting for age or pubertal status, and for determining the combined effect of fat and protein.

Results

Of the 32 participants recruited, 22 successfully completed the study. Dropouts were the result of poor adhesion to the study protocol (n = 10). There was no difference in baseline characteristics between the participants who completed and those who did not complete the study (data not shown). Descriptive data for the 22 participants who completed the study is provided in Table 1. The mean age of the participants was 10.4 ± 4 years. Nine were female, and the median duration of diabetes was 3.5 (1.5; 8.0) years. Sixteen participants had a BMI/age z-score indicating normal weight (z = −1 to 1), five were at risk of becoming overweight (z = 1–2) and one was overweight (z = 2–3) (data not shown).

Insulin requirement and glucose response curve data for the two test meals are reported in Table 2 (sensor glucose and correction insulin) and Fig. 1 (blood glucose) and Fig. 2 (meal bolus and correction insulin). The HFHP meal required significantly more insulin than the LFLP meal, namely eight times more post-meal correction insulin (1.2 *vs.* 0.15 units), and 1.3 times (30%) more total meal insulin (3.48 *vs.* 2.7 units). The LFLP meal resulted in significantly more hypoglycaemic events compared to the HFHP meal (7 *vs.* 1). Although the HFHP meal did not cause a significantly higher peak sensor glucose value ($p = .14$), the time to reach peak sensor glucose value was borderline significantly longer ($p = .056$). However, the HFHP did result in a longer duration of elevated post-prandial glucose (364 *vs.* 185 min) and a significantly larger AUC (198 *vs.* 46.3). There was no difference in the time of first or largest correction insulin dose between the two meals. Sensitivity analysis for the use of two different CGM transmitters revealed that it did not have any effect on the outcome variables in response to the two test meals.

Table 1
Characteristics of the study population (n = 22).

Variable	Mean ± SD/median (25th; 75th percentile)
Participant characteristics	
Male n (%)	13 (59)
Age (years)	10.4 ± 4.00
Weight (kg)	39.0 ± 17.0
Height (m)	1.41 ± 0.25
Duration of diabetes (years)	3.5 (1.5; 8.0)
HbA1c (%)	8.23 ± 0.82
(mmol/mol)	66 ± 18
Total daily insulin (u/kg)	0.75 ± 0.18
Active insulin or insulin on board setting time (h)	3.32 ± 0.72
CHO ratio for study meal (g CHO/insulin unit)	8.34 (9.68; 22.0)
Insulin sensitivity factor for night (mmol/L glucose / insulin unit)	5.50 ± 3.57
Test meals characteristics	
Meal carbohydrates (g)	40.2 ± 9.08
Meal energy (kcal) HFHP	396 ± 91.0
Meal protein (g) HFHP	26.6 ± 6.72
Meal fat (g) HFHP	15.3 ± 4.03
Meal energy (kcal) LFLP	273 ± 63.2
Meal protein (g) LFLP	10.6 ± 3.37
Meal fat (g) LFLP	7.72 ± 2.25

SD – standard deviation; BMI – body mass index; HbA1c – glycosylated haemoglobin; CHO – carbohydrate; HFHP – high fat, high protein meal; LFLP – low fat, low protein meal.

Table 2
Insulin dosage and sensor glucose response curve comparisons between test meals.

Dependent variable	LFLP	HFHP	*P*
Total correction insulin (units)	0.15 (0; 0.53)	1.2 (0.48; 2.32)	<.0001
Total meal insulin (units)[a]	2.70 (1.68; 5.80)	3.48 (2.43; 7.81)	<.0001
Additional insulin required (%)[b]	11.3 ± 5.36	31.1 ± 16.3	<.0001
Time of 1st correction bolus (min post-meal)	352 ± 204	352 ± 170	.81
Time of largest correction bolus (min post-meal)	399 ± 192	420 ± 160	.7
Basal suspend duration (min)	86.1 ± 79.9	53.3 ± 53.9	.052
Duration of elevated post-prandial glucose (min)[d]	185 ± 124	364 ± 142	<.0001
Peak sensor glucose value post-meal (mmol/L)	9.22 ± 2.09	10.3 ± 2.77	.14
Time to peak sensor glucose value (min post-meal)	233 ± 204	342 ± 178	.056
Sensor glucose peak excursion[c]	3.42 ± 1.94	4.29 ± 2.77	.18
AUC (above 8 mmol/L)	46.3 (0; 211)	198 (11.7; 505)	.02
Occurrence of hypoglycaemic events n (%)	7 (32)	1 (0.05)	.02

[a] Food bolus and correction boluses.
[b] Correction bolus expressed as% of initial food bolus.
[c] (Difference between peak sensor glucose value and target of 6 mmol/L); AUC – area under the sensor glucose curve.
[d] Total time of elevated post-prandial glucose spent above 6 mmol/L. Data reported as mean ± SD or median (25th; 75th percentile) depending on normality.

The characteristics inherent to the study population but unrelated to the test meals that impacted the outcome variables were also investigated, and the significant relationships reported in Tables 1 and 2 of the Online Supplement. Additional adjustment for age and/or pubertal status did not significantly alter the results. Characteristics that showed significant association were tested for interaction with the test meals in subsequent analysis. Online Supplement Table 1 additionally shows that both protein and fat meal content influence total meal and correction insulin requirements. Total meal insulin increased by 0.12 units for every 1 g increase in protein. This relates to one unit additional correction insulin for every 8 g protein in a mixed meal already containing carbohydrates. For fat, total meal insulin increased by 0.24 units for every 1 g increase, translating to one unit additional correction insulin for every 4 g fat in a mixed meal already containing carbohydrates. This 2:1 ratio was confirmed in a bivariate model determining the effect of fat and protein combined and is in agreement with the observed effect on AUC, with 1 g fat also having double the effect 1 g of protein does (Online Supplement Table 2).

There was a significant interaction between the test meals and duration of diabetes in terms of peak sensor glucose values ($p = .014$). The difference in peak sensor glucose values between the two test meals was larger in individuals who have had diabetes for longer (Online Supplement, Fig. 1). Similarly, interactions were observed between the test meals and duration of diabetes ($p < .001$), total daily insulin use (u/kg) ($p = .003$) and HbA1c ($p = .003$) in terms of AUC. The difference in AUC between the two test meals was larger in individuals who have had diabetes for longer (Online Supplement Fig. 2), those with a higher total daily insulin use (Online Supplement Fig. 3) as well as individuals with higher HbA1c (Online Supplement Fig. 4). These differences remained after additional adjustment for age and/or pubertal status.

Discussion

Although there is emerging evidence that protein and fat influence the insulin requirement of children with type 1 diabetes [3,4,6,10], the recommended method of calculating prandial insulin is still based on meal carbohydrate content only. This is due to inconsistent findings in the literature and increased post-prandial hypoglycaemia in children when following methods to increase meal insulin based on fat and protein content [3,6]. This study emphasises the urgent need to revisit the calculation of insulin requirement as well as the manner in which it should be delivered when using insulin pump therapy in children with type 1 diabetes. Our data indicate that when comparing two meals with the same carbohydrate content but different fat and protein contents, the HFHP meal, representing a typical mixed-meal dinner and not a take-out meal as in most other studies, required on average eight times more post-meal correction insulin than the LFLP.

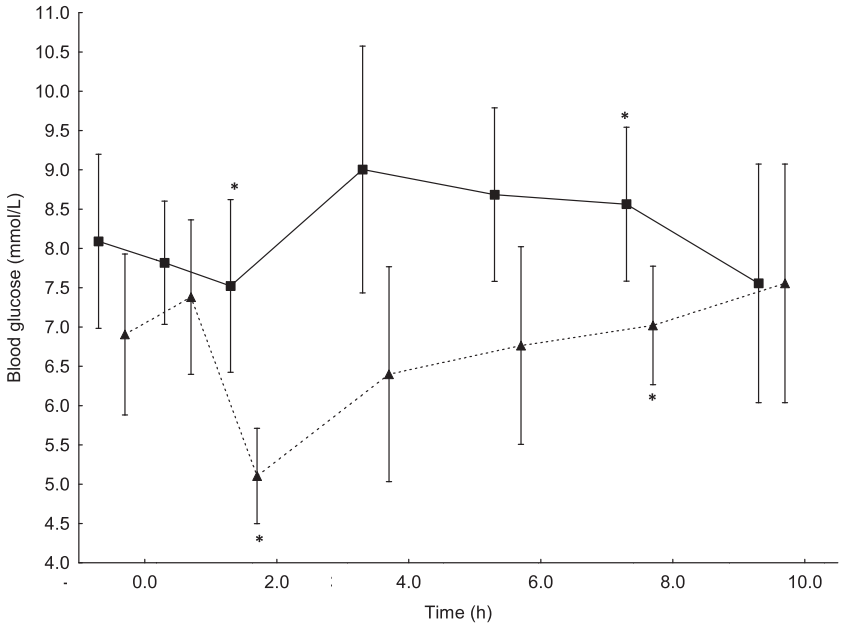

Fig. 1. Blood glucose levels before (Time 0 h) and after (Time 0.5–10 h) intervention ■ – High fat, high protein meal; ▲ – Low fat, low protein meal; mean and 95% CI * – significant difference between the two meals ($p < .05$) at the respective time points.

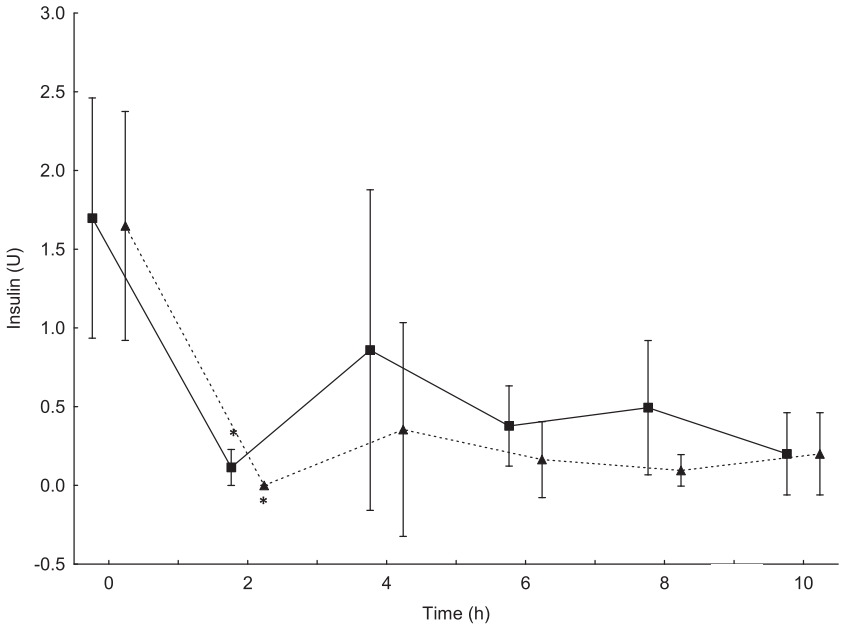

Fig. 2. Meal bolus (T 0 h) and correction insulin (T 2–10 h) ■ – High fat, high protein meal; ▲ – Low fat, low protein meal; mean and 95% CI * – significant difference between the two meals ($p < .05$).

This additional insulin was determined by allowing two-hourly post-prandial correction insulin boluses for 10 h post-meal, which is a major difference in study design compared to other studies in the field. The addition of protein and fat to the meal did not result in significantly higher absolute blood glucose levels, but it did result in a significantly larger AUC and longer time spent above target. In addition, the duration of diabetes and the total daily insulin use significantly influenced the post-prandial blood glucose response to the two meals, with individuals having diabetes for longer and those with a higher total daily insulin use showing the largest differences between the two meals.

The addition of fat and protein to a CHO-containing meal significantly extended the duration of post-prandial hyperglycaemia from up to three hours for the LFLP meal to up to 8.5 h for the HFHP meal. This is in agreement with Neu et al. [9] who found elevated blood glucose levels in adolescents for up to 12 h following a HFHP meal (without allowing post-meal correction insulin) and three hours for a standard meal. This may suggest that even for LFLP mixed meals, extended insulin delivery, to over three hours, can be considered, with individual ranges varying from one to five hours. For HFHP mixed meals, boluses may have to be set as long as six hours, with ranges from four to 8.5 h. However, advising a patient to spread an extended bolus from anything between three and 8.5 h is not very practical. It calls for the identification of factors (see below) contributing to this large inter-individual variation in order to accurately advise a patient on extended bolus duration and the amount of insulin required.

Eight hypoglycaemic events were recorded in this study: seven after the LFLP meal, five of which occurred during the first two post-prandial hours (data not shown). Similarly, in the study by Neu et al. [9], 60% of adolescents had hypoglycaemia after a standard meal with no hypoglycaemic events occurring after a HFHP meal. This emphasises the limitations of carbohydrate counting in children with type 1 diabetes and shows that in some instances it may overestimate the amount of insulin required. The fact that almost all of the hypoglycaemic events occurred in the LFLP meal supports findings from another study that has shown protein to be protective of hypoglycaemia [5]. Participants who experienced hypoglycaemia with their LFLP meal still required additional correction insulin for their HFHP meal, highlighting the fact that protein and fat meal content significantly increases insulin requirement. Our study showed an average increased insulin need of 31% for HFHP meals in children with a 2:1 ratio for fat and protein. A closed-loop study by Wolpert et al. [4], in adults, showed an average increase of 42% for high-fat meals compared with low-fat meals, also with marked inter-individual differences.

In an attempt to identify factors contributing to this large inter-individual variation in glycaemic response and consequent insulin requirements, we investigated participant characteristics such as age, pubertal status, gender, weight, body mass, glycaemic control, duration of diabetes, pre-meal blood glucose and markers of insulin sensitivity such as total daily insulin use. Our data showed that duration of diabetes and total daily insulin use influenced the insulin requirement and blood glucose response to the two meals, also after adjustment for the different ages of the study participants. Individuals with a longer duration of diabetes showed a larger difference in peak sensor glucose value between the two test meals. Similarly, individuals who have had diabetes for longer, those with higher total daily insulin use and higher HbA1c, demonstrated a larger difference in AUC between the two meals. The above suggests that this phenomenon might be explained in terms of insulin resistance that develops with longer duration of type 1 diabetes, which may in turn influence insulin requirement and glucose response to different meal compositions It is likely not a mere consequence of metabolic differences across the age range.

Insulin resistance is commonly associated with type 2 diabetes, but in recent years studies have shown it to be present in type 1 diabetes as well [10–12]. Insulin resistance in type 1 diabetes is not thought to be associated with current glycaemic control [10] or with BMI, fat percentage, plasma lipids, visceral fat or physical activity level [10]. Some of the main proposed mechanisms for insulin resistance in type 1 diabetes are inhibited insulin signalling, caused by chronic hyperglycaemia, an increase in plasma free fatty acids (FFA) and amino acids, as well as inflammatory processes [11]. Insulin resistance may further be attenuated by chronic iatrogenic hyperinsulinemia in people with type 1 diabetes [11], which could explain why longer duration of diabetes, and thus longer exposure to iatrogenic insulin, can cause insulin resistance, at

any age. There is also evidence that dietary fat and increased FFA can impair insulin sensitivity and elevate glucose production from the liver [13,14]. Excessive amino acid and lipid availability interfere with insulin signalling [11]; this interference can therefore explain a state of reduced insulin sensitivity after HFHP meals. In the event of HFHP mixed meals, there is additional substrate for gluconeogenesis, in the form of FFA and amino acids, which may explain why these types of meals have such an effect on the post-prandial glycaemic curve and which adds to the increase in total additional insulin requirement [11].

The large inter-individual variation in glycaemic response and concurrent insulin requirements observed begs the question whether one method of calculating insulin for meals containing different macronutrients can be used for all patients. The observed influence of duration of diabetes and the potential effects of insulin resistance may explain why current methods quantifying insulin requirement considering meal content and current blood glucose level only, such as CHO counting, may not be working adequately for all patients.

A limitation of this study is that it was performed with a rather small sample size due to the difficulty of recruiting and retaining patients in private care in addition to poor protocol adherence by the paediatric study population. The sample size was however in line with [5,15,16] or larger than [9,17,18] other studies published in this field. In addition, insulin resistance *per se* was not measured. As is done in practice, we used a lower sensitivity factor and higher insulin use per kilogram body weight as proxy markers for indicating insulin resistance. Furthermore, variables such as time of first and largest correction bolus were interpreted based on two-hourly blood glucose testing, due to the study protocol and not necessarily at the time when the highest post-prandial glycaemia occurred. Two-hourly finger prick testing and correction bolusing were chosen as for most patients the active insulin setting would not allow more frequent correction boluses. Lastly, this study did not distinguish between elevated post-prandial glucose due to food or to the effect of growth hormone and cortisol peaks in the early morning hours [14] (glycaemic patterns were followed until 04:00 in the morning). To our knowledge, this was the first study where post-prandial correction dosages were used to determine total meal insulin. Hence, our results should be confirmed in larger study populations before definite conclusions can be drawn.

Future studies should investigate if the time of day influences meal insulin requirements by testing the same meals at different times of the day. For HFHP mixed meals, the feasibility and practicality of the pre-meal addition of one unit insulin for every 4 g fat and one unit for every 8 g protein, in combination with the usual CHO ratio and CHO counting method, administered in prolonged bolus form, should be investigated. Acknowledging the large inter-individual differences in glycaemic response to meals; this method may also not be suitable for all children with type 1 diabetes but may address the need of specifically patients who have post-prandial hyperglycaemia following these type of meals. The contribution of duration of diabetes, and the concomitant development of insulin resistance, to insulin requirements should also be further elucidated as this study was not specifically designed to investigate this observation. In addition, future research should explore the use of extended boluses which can be spread over a mean of six hours, ranging from four hours to 8.5 h, for HFHP mixed dinner meals. As this duration is likely to be dependent on more factors, not investigated in this study, the identification of these additional factors should receive priority.

This study highlights the additional insulin needed for typical mixed meals in children with type 1 diabetes and shows that all macronutrients require insulin, with the addition of each 1 g of fat requiring double the amount of correction insulin compared to each 1 g of protein. For the first time, duration of diabetes (regardless of age) is shown to be strongly associated with post-prandial hyperglycaemia, likely due to the development of insulin resistance. CHO counting alone fails to prevent post-prandial hyperglycaemia, especially in HFHP mixed meals, and in future, bolus wizard set-ups might require more input than target ranges, carbohydrate ratios and sensitivity factors. Duration of diabetes, and fat and protein ratios may all form part of essential inputs to prevent post-prandial hyperglycaemia.

Authors' contributions

M. vd H. conceptualised and executed the study, performed the statistical analysis and wrote the paper. J. v D. conceptualised the study, oversaw medical aspects and treatment of participants, and critically reviewed the final manuscript. R. D. conceptualised the study and critically read the final manuscript. M. P. conceptualised the study, performed statistical analysis and co-wrote the manuscript.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jcte.2017.10.002.

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