ORIGINAL ARTICLE

DOI: 10.4274/jcrpe.galenos.2022.2022-8-10

J Clin Res Pediatr Endocrinol 2023;15(2):138-144

Novel Modified Algorithm for High Fat/High Energy Density Meal in Type 1 Diabetes: Less Hypoglycemia

Yasemin Atik Altınok, Günay Demir, Hafize Çetin, Samim Özen, Şükran Darcan, Damla Gökşen

Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, İzmir, Turkey

What is already known on this topic?

Optimal postprandial glycemia depends on matching insulin to the carbohydrate, protein, and fat contents of meal, after a high fat/high energy density meal in individuals with type 1 diabetes.

What this study adds?

Additional insulin dose (64%) for high fat/high energy density meal increased time in normoglycemia without hypoglycemia.

Abstract

Objective: This aim of this study was to investigate the effect of additional insulin dosing for high fat/high energy density mixed meal over 12 hours.

Methods: In this single-center, non-blinded, randomized, cross-over study, a high fat/high energy density test meal was used to study the impact on glycemic response of either carbohydrate counting (CC) on the first day and the Pańkowska algorithm (PA) on the second test day. The two methods were compared in 20 adolescents with type 1 diabetes (T1D), aged 9-18 years, using insulin pump therapy and continuous glucose monitoring on postprandial early (0-120 min), late (120-720 min), and total (0-720 min) glycemic response.

Results: There was no difference between groups in the duration of normoglycemia in the early period. Postprandially, 50% of patients developed hypoglycemia using the PA at a median of 6.3 (5.6-7.9) hours and the PA was subsequently modified for the remaining ten patients. Area under the curve (AUC) for the early period decreased non-significantly in the CC group, indicating less normoglycemia. No significant difference was found in the AUC of the PA (no hypoglycemia n = 4) and modified PA groups (no hypoglycemia n = 6) over the whole period (0-12 hours). AUC for level 2 hyperglycemia was statistically greater in the PA-no hypoglycemia patients compared to modified PA-no hypoglycemia patients.

Conclusion: There were inter-individual differences in glycemic response to high fat/high energy density meals. An individualized approach to insulin dosing by evaluating food diary and postprandial glucose monitoring appears to be optimal for children and adolescents with T1D.

Keywords: High fat, glycemic variability, insulin pump therapy, type 1 diabetes mellitus

Introduction

The primary goal of diabetes management is to achieve normal or near-normal blood glucose levels. Food and nutrition interventions that reduce postprandial blood glucose excursions are important in this regard since dietary carbohydrate is the major determinant of postprandial glucose levels (1). Thus, carbohydrate counting (CC) is conventionally recommended for preprandial insulin dose calculation for individuals with type 1 diabetes mellitus (T1D) on intensive insulin therapy and insulin infusion pump therapy. Although carbohydrate is the predominant macronutrient affecting postprandial blood glucose excursions, recent research has shown that dietary fat

Address for Correspondence: Yasemin Atik Altınok MD, Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, İzmir, Turkey
Phone: +90 232 390 12 30 **E-mail:** yaseminatik@yahoo.com.tr **ORCID:** orcid.org/0000-0001-5851-1012

Conflict of interest: None declared
Received: 05.09.2022
Accepted: 12.12.2022

and protein can also significantly impact the postprandial glycemic profile (2,3,4,5,6,7,8,9).

When consumed separately, both protein and fat may cause an increase in postprandial glycemia, depending on the quantity (6,10,11). However, most meals contain both fat and protein and when a meal containing high levels of both fat and protein is consumed, the combined impact is additive and causes significantly higher glucose excursions. Closed-loop studies have suggested that for high-fat meals the insulin dose needs to be increased by 42% and for high fat/high protein mixed meals by 39% (6,12). However, it should be noted that the increased insulin requirement after high-fat meal consumption can show great differences between individuals. These findings suggest that a change in insulin dose is warranted and, in most patients, additional insulin may be required but there is no international consensus about the preprandial insulin dose estimation for high fat/high protein mixed meals. The American Diabetes Association acknowledges that for people with diabetes who are prescribed a flexible insulin therapy program, education on how to use CC and on dosing for fat and protein content should be used to determine mealtime insulin dosing (13). The International Society for Paediatric and Adolescent Diabetes (ISPAD) has noted that the optimal insulin bolus dose and delivery for meals high in fat and protein are undefined with randomized controlled trials required (14).

A novel insulin dosing algorithm has been proposed which takes account of the glycemic impact of fat/protein when calculating mealtime insulin dose. Pańkowska et al. (15) developed an algorithm for calculating the preprandial insulin dose based on all macronutrients (carbohydrate, fat, and protein) of the meal and described a "fat/protein unit (FPU)" as 100 kcal from fat and/or protein.

The aim of the present study was to compare the impact of additional dosing with extended insulin bolus, as described by the Pańkowska algorithm (PA) versus CC on postprandial glucose excursions for high fat/high energy density mixed meal on postprandial glucose excursions for the first 12 hours after the meal in adolescents with T1D using insulin pump therapy (IPT) and a continuous glucose monitoring system (CGMS).

Methods

A single-center, non-blinded, randomized, cross-over study was performed between July 2017-April 2018.

Participants

Twenty adolescents with T1D were recruited. The inclusion criteria were: T1D for at least one year and treatment with IPT for at least six months; body mass index (BMI) z-score of >-1 <2; and total daily insulin use of ≥0.5 U/kg to avoid inclusion of participants in the remission phase of diabetes. Exclusion criteria were: concomitant dietary restrictions (eg, Celiac disease or food allergy); cystic fibrosis; concurrent conditions that can be associated with delayed gastric emptying or altered digestion; and the use of any medication that is known to modify glycemia, such as glucocorticoids or oral antidiabetic drugs.

Study Design

Participants attended the clinic a week before for the insertion of Guardian™ Connect (Medtronic MiniMed, Inc., Northridge, California) CGMS. In the seven days leading up to the study, participants or their caregivers were contacted daily by the pediatric endocrinologist to review the CGMS blood glucose levels of participants, and the food and activity diary. CGMS readings were used to adjust basal rates, insulin carbohydrate ratio (ICR), and sensitivity factors so that normoglycemia was achieved within the week prior to the study.

On study days, participants were admitted to the hospital, and meals were served at 6.30 pm. The meal was a high fat/high energy density test meal containing 80 g carbohydrate (34%), 70 g fat (66%), and 35 g protein (14%). The total energy of the meal was 4563 kJ (1090 kcal).

The detailed composition and ingredients of the test meal are given in Supplementary Table 1. Participants should have no glucose fluctuations in the two hours before study entry as measured by CGMS, no correction boluses for at least four hours before test meal consumption, and fasting glycemia in the range 70-180 mg/dL on both study days.

On the first study day participants calculated the insulin dose for the test meal by CC. On the second study day, the insulin dose was calculated using the PA algorithm or modified PA algorithm. The cross-over design allowed the

Table 1. Characteristics of the study subjects

	Participants (n = 20) Median (min-max)
Female/male (n)	11/9
Age (years)	14.42 (9-21)
BMI z-score	0.13 (-1.17-1.9)
Diabetes duration (years)	7 (2.08-17.83)
HbA1c (%)	7.3 (5.7-10.4)
HbA1c (mmol/mol)	56 (39-90)
Insulin (IU/kg/day)	0.8 (0.55-0.97)
Basal insulin to total daily insulin (%)	42 (33-64)

BMI: body mass index, HbA1c: hemoglobin A1c, min-max: minimum-maximum

comparison of each patient eating the same meal twice but using the two different counting methods to calculate an appropriate insulin dose. Consumption of the test meal was completed in 20 minutes under supervision by a caregiver and a research team dietician. The flow diagram of the study is presented in Figure 1.

Algorithm for Calculating and Delivering Preprandial Bolus Insulin

Initially, two insulin algorithms were used to calculate preprandial insulin dose: CC and PA. However, during the study half of the patients using the published PA experienced hypoglycemic events and so the PA was modified for the remaining patients.

For CC each participant's individualized ICR was expressed as insulin per one carbohydrate unit (CU = 10 g carbohydrate) and this was used to calculate individual preprandial insulin doses, which were delivered in a standard bolus.

For PA, the insulin dose was calculated according to the carbohydrate content (1 CU = 10 g carbohydrate) but also took into account the fat and protein content (1 FPU = 100 kcal from fat and protein) of the test meal. The participant's individualized ICR was calculated, expressed as insulin per 1 CU and 1 FPU with the same insulin ratio used for 1 CU or 1 FPU. The total insulin dose was delivered for CU in a standard bolus and FPU in an extended bolus. According to Pańkowska et al. (15), the extended bolus should be given for eight hours for a meal containing ≥4 FPU. As the test meal had 7.7 FPUs, the extended bolus was delivered over eight hours.

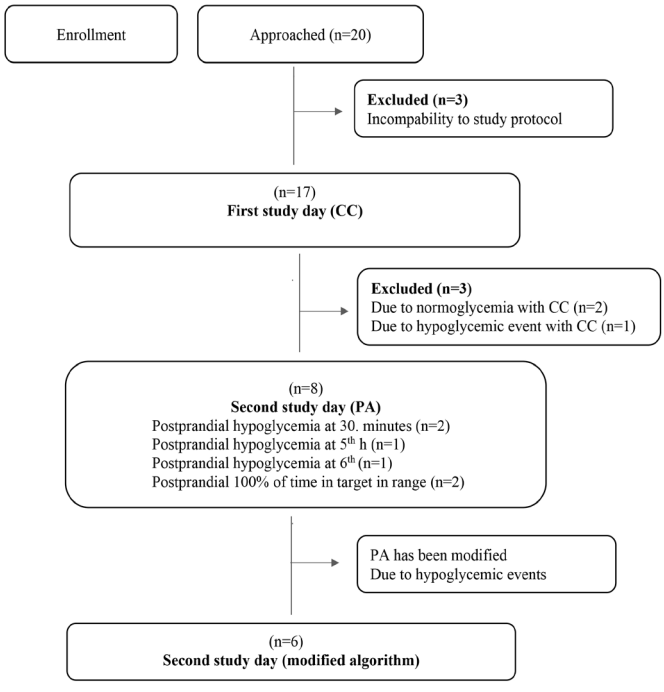

Figure 1. Flow diagram

CC: carbohydrate counting, PA: Pańkowska algorithm

The PA was subsequently modified as follows. The PA participant's individualized ICR was calculated, expressed as insulin per 1 CU and 1 FPU. However, 1 FPU was now equated to 150 kcal from fat and protein (the same insulin ratio was used for 1 CU or 1 FPU). The test meal was now calculated to contain five FPUs, and so still required the extended bolus to be delivered over eight hours (15).

During the study period, no additional meals, snacks, or other food and no physical activity were allowed and no correction boluses were administered.

Measurement of Glycemia

Postprandial glycemia was measured by CGMS during the subsequent twelve hours. Postprandial glucose excursions were evaluated by reference to the International Consensus on Use of Continuous Glucose Monitoring, as described by Danne et al. (16) level 1 hypoglycemia glucose value of 70-54 mg/dL (3.9-3.0 mmol/L) with or without symptoms, level 2 hypoglycemia glucose level of < 54 mg/dL (< 3.0 mmol/L) with our without symptoms; level 1 hyperglycemia glucose value of > 180 mg/dL (10 mmol/L) and glucose ≤250 mg/dL (13.9 mmol/L) and level 2 hyperglycemia glucose level of > 250 mg/dL (13.9 mmol/L). If hypoglycemia occurred during the study period, participants consumed 0.3 g/kg carbohydrate (white sugar). The data of the participants experiencing hypoglycemic events with the PA were not included in the twelve-hour data analysis of the study.

Primary and Secondary Outcomes

The primary outcomes were glucose area under the curve (AUC) and % of time in range (TIR) according to CC, PA, and modified PA algorithms. The secondary outcomes were the number of hypoglycemic events over the study period which were verified by capillary blood glucose measurements.

Statement of Ethics

The study protocol was reviewed and approved by the Ege University Medical Faculty Ethics Committee, approval number: 16-12.1/44 and the Ministry of Health of Turkey (date: 22.07.2016). This trial was registered at www.clinicaltrials.gov as NCT05152121.

Statistical Analysis

SAS® software (SAS system for Windows, version 9.3; SAS Institute, Cary, NC, USA) was used for statistical analysis. Significance was assumed with a p value of < 0.05. AUC calculation was performed according to the Trapezoidal

rule. The Wilcoxon Rank Sums test and Wilcoxon Signed Rank test were used to compare between and within-group differences in terms of AUC. The minimum sample size for p = 0.01 and 1-p = 0.99 was calculated as 18, with an error of 4% (d = 0.04) at the 95% ($\alpha = 0.05$) confidence interval limits for 0.80 power.

Results

Characteristics of the Participants

Twenty adolescents participated in the study. Their ages ranged from 9-18 years and the sex mix was 11 male (55%) and nine female (45%). One was excluded due to incompatibility during the preparation of the study, and two refused the consumption of the test meal on the second study day. Seventeen of the participants completed the CC protocol, while eight of them used the standard PA, and six of them used the modified algorithm on the second study day (Figure 1). The study session was not completed due to one hypoglycemic event and two episodes of normoglycemia after the test meal on CC as there may be a risk of hypoglycemia when additional doses are given for fat and protein on the second study day.

Demographic data of study participants are given in Table 1. Participants median (range) age was 14.4 (9-18) years, BMI z-score was 0.13 (-1.17-1.9), duration of diabetes was 7 (2-17.8) years, HbA1c was 56 (39-90) mmol/L [equivalent to 7.3% (5.7-10.4%)], total insulin requirement was 0.8 (0.55-0.97) IU/kg and basal insulin ratio was 42% (33-64). The level of HbA1c was not a criterion for inclusion in the study, because the doses of insulin were adjusted for seven days before the study. The median basal insulin dose was 0.34 IU/kg (0.24-0.47).

First Study Day

After consumption of test meal calculating insulin dose by CC (n = 17), one patient was hypoglycemic postprandially at the second hour and two patients remained normoglycemic for 12 hours. This resulted in these three patients being excluded from the second part of the study since the additional dose of insulin calculated for fat and protein can cause hypoglycemia. For the first postprandial 12 hours CC patients were in TIR in 26.4% and experienced level 1 and level 2 hyperglycemia for 28.5% and 17.4%, respectively.

Second Study Day

On the second day of the study, 4/8 participants using the standard PA algorithm developed hypoglycemia at a median (range) time of 6.25 (5.58-7.91) hours. The PA algorithm was then modified as previously described. In the six participants using the modified PA, hypoglycemia did not develop in the ensuing 12 hours.

There were no significant differences between HbA1c, BMI z-score, insulin dose/kg, and diabetes duration between participants who used PA and the modified algorithm. There was no difference in the time spent in normoglycemia in the first two hours after meal consumption in the three groups; median AUC for PA = 119.99; modified PA = 91.64, and CC = 69.75). The AUC for the initial two hours was decreased non-significantly in the CC group indicating less normoglycemia (data not shown).

There was no significant difference between the different methods of insulin dose calculation during the first 5.58 hours postprandial when the first hypoglycemic event developed with unmodified PA. Although it was not statistically significant, the AUC decreased in level 1 and level 2 hyperglycemia with the modified algorithm (Table 2).

There was no significant difference in the AUC of the participants who completed the PA algorithm with no hypoglycemic event (n = 4) when compared to participants who used the modified algorithm (n = 6) over the postprandial 12 hours. Although not statistically significant, the median AUC in level 2 hyperglycemia decreased with the modified algorithm (Table 3).

Although median time spent in normoglycemia was decreased with the modified PA compared to unmodified PA, level 2 hyperglycemia was decreased in the modified algorithm for the postprandial period 2-12 hours (Table 4).

Table 2. Postprandial AUC for 5.58th hour (time first hypoglycemic event detected)

AUC	PA hypoglycemia (-) Median (min-max) n = 4	PA hypoglycemia (+) Median (min-max) n = 4	Modified algorithm Median (min-max) n = 6
< 3 mmol/L (< 54 mg/dL)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
3-3.8 mmol/L (54-69 mg/dL)	0.0 (0.0-0.0)	0.0 (0.0-11.1)	0.0 (0.0-5.6)
3.9-10 mmol/L (70-180 mg/dL)	201.9 (23.5-293.5)	290.9 (237.7-340.7)	186.8 (79.1-285.5)
10.1-13.9 mmol/L (181-250 mg/dL)	39.6 (0.0-96.3)	7.5 (0.0-11.9)	24.9 (0.0-89.5)
> 13.9 mmol/L (> 250 mg/dL)	22.5 (0.0-69.7)	0.0 (0.0-0.0)	0.0 (0.0-200.2)

AUC: area under the curve (mg/dL x min), PA: Pańkowska algorithm, min-max: minimum-maximum

Table 3. Postprandial glucose AUC with PA and modified algorithm for 0-12 hours

AUC	PA with no hypoglycemia Median (min-max) n = 4	Modified algorithm Median (min-max) n = 6	p*
< 3 mmol/L (< 54 mg/dL)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000
3-3.8 mmol/L (54-69 mg/dL)	0.0 (0.0-7.471)	0.0 (0.0-24.468)	0.667
3.9-10 mmol/L (70-180 mg/dL)	277.950 (202.579-589.268)	218.856 (15.735-461.048)	0.476
10.1-13.9 mmol/L (181-250 mg/dL)	27.446 (0.0-94.126)	84.090 (0.0-295.821)	0.609
> 13.9 mmol/L (> 250 mg/dL)	23.037(0.0-66.296)	0.0 (0.0-259.687)	0.005

*Wilcoxon signed-rank test.
AUC: area under the curve (mg/dL x min), PA: Pańkowska algorithm, min-max: minimum-maximum

Table 4. AUC for PA and modified algorithm total time for 2-12 hours

Total time	PA with no hypoglycemia Median (min-max) n = 4	Modified algorithm Median (min-max) n = 6	p*
< 3 mmol/L (< 54 mg/dL)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000
3-3.8 mmol/L (54-69 mg/dL)	0.0 (0.0-11.0)	0.0 (0.0-24.0)	0.666
3.9-10 mmol/L (70-180 mg/dL)	90.0 (69.0-115.0)	80.0 (2.0-104.0)	0.476
10.1-13.9 mmol/L (181-250 mg/dL)	20.5 (0.0-28.0)	41.5 (0.0-116.0)	0.347
> 13.9 mmol/L (> 250 mg/dL)	12.5 (0.0-30.0)	0.0 (0.0-76.0)	0.500

*Wilcoxon signed-rank test.
AUC: area under the curve (mg/dL x min), PA: Pańkowska algorithm, min-max: minimum-maximum

Discussion

This is the first study to compare traditional mealtime insulin dose estimation (CC) with one novel (PA) and one new insulin-dosing algorithm (the modified PA) for high fat/high energy density meals for the postprandial 12-hour period. Our results showed an increased time in normoglycemia without hypoglycemia with the new algorithm but an increased incidence of hypoglycemia using the PA when compared with the traditional CC. The insulin dose calculated for PA and the modified algorithm was 94% and 64% higher, respectively, than the insulin dose for the CC method. This novel modified algorithm achieves better glycemic control with less hypoglycemia in children and adolescents with T1D with a longer duration of follow-up than the PA.

Using PA, 50% of the patients were hypoglycemic at a median postprandial time of 6.25 hours. This finding was similar to previous studies which have compared CC and the unmodified PA for high-fat meals and high protein meals (4,17,18,19,20). In contrast, Pańkowska et al. (4) reported no difference in hypoglycemia between PA and CC but postprandial glucose monitoring was only performed for two hours. In our study, when the insulin dose was calculated with PA, hypoglycemia occurred around six hours postprandially. However, no hypoglycemic event occurred in patients using the modified algorithm for the whole 12 hours monitoring period and AUC was lower than for CC. Similar to our modified algorithm experience, Smith et al. (19) found that an additional 60% of the meal insulin dose significantly reduces the glycemic excursion up to postprandial five hours without increasing the incidence of hypoglycemia. AUC for normoglycemia, and level 1 and level 2 hyperglycemia was similar during the latter ten hours of monitoring (2-12 hours postprandial) with both the modified algorithm and PA, with the caveat that only patients without hypoglycemia were included. Compared to the PA, the median time spent in level 2 hyperglycemia decreased and the time spent in normoglycemia decreased with the modified algorithm (Table 4). Thus the PA resulted in more time spent in normoglycemia, but at the cost of an increased risk of hypoglycemia.

There is no consensus about the insulin dose required for high fat/high energy density meals. ISPAD guidelines recommend an increase of 15% to 20% of the bolus for high fat/high protein meals (14). A systematic review for high-fat meals (≥40 g of fat), recommended bolus dose increase up to 30-35% accompanied by using combo bolus with 50/50 split over 2-2.5 hours and review late postprandial glucose and adjust total insulin dose as indicated (21). Wolpert et al. (6) suggested a mean insulin dose increase of 42% for a high-fat meal (60 g fat) compared to a low-fat meal (10 g fat), with marked significant individual differences, with some

participants requiring more than twice as much insulin while others required no extra insulin. We showed non-significant lower AUC for normoglycemia than CC with the modified algorithm with an insulin dose increase of 64% for a high-fat meal (70 g fat), with no hypoglycemia for 12 hours. In the current study, a postprandial observation period of 12 hours was chosen. Wolpert et al. (6) demonstrated in their closed-loop study that after a 60 g high-fat meal, the impact of added fat continues for at least five hours. We, therefore, designed a longer observation period to assess the effect of insulin on meals with high fat/high energy density meals. Since participants consumed the test meal in the evening, we were able to follow for a full twelve hours.

Study Limitations

Our study has strengths and limitations. One of the strengths was that glycemic stability was evaluated daily for one week before the study and this also allowed the optimization of individual carbohydrate/insulin ratio and sensitivity factors for each participant. Another strength of the study was the extended postprandial monitoring using CGMS. The main limitation of this study was the small sample size, partly due to poor adherence to the study protocol in adolescent participants. However, the findings are of interest and may provide an improvement on the original PA so we believe that this warrants confirmation of the findings using larger group sizes, which should be adequately powered.

This study was also limited to participants using IPT to take advantage of more sensitive insulin dosing and the use of the dual-wave bolus option. Therefore, the study should also be performed in patients using multiple daily injections.

Conclusion

Although carbohydrates are the primary determinant of postprandial glucose levels, recent research has shown that insulin dosing based on carbohydrate quantity alone is inadequate for optimal glycemic control after a high fat/high energy density meal in individuals with T1D. The dose and delivery type of preprandial insulin may need adjustment, not only to carbohydrate quantity but also to the fat content of the meal to achieve stable postprandial normoglycemia. However, our study has shown marked inter-individual differences in response to the test meal. We, therefore, suggest that, due to these differences and the lack of large-scale prospective data, an individualized approach to insulin dosing for high fat/high energy density meals should be adopted currently. This can be done by evaluating food diaries and the use of postprandial glucose monitoring. This may represent the present best practice for children and adolescents with T1D.

Acknowledgment

The authors would like to sincerely thank all adolescents for participating in this study. We would also like to thank Mr. Jeremy Jones for his help in editing the English language used in this paper.

Ethics

Ethics Committee Approval: The study was approved by the Ege University of Local Ethics Committee (protocol number: 16-12.1/44, date: 20.12.2016).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Günay Demir, Hafize Çetin, Samim Özen, Concept: Yasemin Atik Altınok, Damla Gökşen, Design: Yasemin Atik Altınok, Damla Gökşen, Data Collection or Processing: Günay Demir, Hafize Çetin, Analysis or Interpretation: Yasemin Atik Altınok, Günay Demir, Literature Search: Yasemin Atik Altınok, Günay Demir, Writing: Yasemin Atik Altınok, Samim Özen, Şükran Darcan, Damla Gökşen.

Financial Disclosure: This work was supported by the; Ege University Scientific Research Projects Coordination (grant numbers: 18-TIP-008).

References

1. American Diabetes Association; Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 2008;31(Suppl 1):61-78.
2. Jones SM, Quarry JL, Caldwell-McMillan M, Mauger DT, Gabbay RA. Optimal insulin pump dosing and postprandial glycemia following a pizza meal using the continuous glucose monitoring system. Diabetes Technol Ther 2005;7:233-240.
3. Wolever TMS, Mullan YM. Sugars and fat have different effects on postprandial glucose responses in normal and type 1 diabetic subjects. Nutr Metab Cardiovasc Dis 2011;21:719-725.
4. Pańkowska E, Błazik M, Groele L. Does the Fat-Protein Meal Increase Postprandial Glucose Level in Type 1 Diabetes Patients on Insulin Pump: The Conclusion of a Randomized Study. Diabetes Technol Ther 2012;14:16-22. Epub 2011 Oct 20
5. Smart CE, Evans M, O'Connell SM, McElduff P, Lopez PE, Jones TW, Davis EA, King BR. 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. Epub 2013 Oct 29
6. Wolpert HA, Atakov-Castillo A, Smith SA, Steil GM. 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. Epub 2012 Nov 27

7. Paterson MA, Smart CEM, Lopez PE, Howley P, McElduff P, Attia J, Morbey C, King BR. 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. Epub 2017 Mar 19
8. 8 van der Hoogt M, van Dyk JC, Dolman RC, Pieters M. Protein and fat meal content increase insulin requirement in children with type 1 diabetes - Role of duration of diabetes. J Clin Transl Endocrinol 2017;10:15-21.
9. Neu A, Behret F, Braun R, Herrlich S, Liebrich F, Loesch-Binder M, Schneider A, Schweizer R. Higher glucose concentrations following protein- and fat-rich meals - the Tuebingen Grill Study: a pilot study in adolescents with type 1 diabetes. Pediatr Diabetes. Pediatr Diabetes 2015;16:587-591. Epub 2014 Oct 20
10. Paterson MA, Smart CE, Lopez PE, McElduff P, Attia J, Morbey C, King BR. 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. Epub 2015 Dec 6
11. Evans M, Smart CEM, Paramalingam N, Smith GJ, Jones TW, King BR, Davis EA. Dietary protein affects both the dose and pattern of insulin delivery required to achieve postprandial euglycaemia in Type 1 diabetes: a randomized trial. Diabet Med 2019;36:499-504. Epub 2019 Feb 20
12. Gingras V, Bonato L, Messier V, Roy-Fleming A, Smaoui MR, Ladouceur M, Rabasa-Lhoret R. Impact of macronutrient content of meals on postprandial glucose control in the context of closed-loop insulin delivery: A randomized cross-over study. Diabetes Obes Metab 2018;20:2695-2699. Epub 2018 Jul 18
13. American Diabetes Association Professional Practice Committee. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):60-82.
14. Smart CE, Annan F, Higgins LA, Jelleryd E, Lopez M, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: Nutritional management in children and adolescents with diabetes. Pediatr Diabetes 2018;19(Suppl 27):136-154.
15. Pańkowska E, Szypowska A, Lipka M, Szpotańska M, Błazik M, Groele L. Application of novel dual wave meal bolus and its impact on glycated hemoglobin A1c level in children with type 1 diabetes. Pediatr Diabetes 2009;10:298-303. Epub 2008 Oct 20
16. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA, Beck R, Bosi E, Buckingham B, Cobelli C, Dassau E, Doyle FJ, Heller S, Hovorka R, Jia W, Jones T, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Maahs D, Murphy HR, Nørgaard K, Parkin CG, Renard E, Saboo B, Scharf M, Tamborlane WV, Weinzimer SA, Phillip M. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 2017;40:1631-1640.
17. Lopez PE, Evans M, King BR, Jones TW, Bell K, McElduff P, Davis EA, Smart CE. A randomized comparison of three prandial insulin dosing algorithms for children and adolescents with Type 1 diabetes. Diabet Med 2018;35:1440-1447. Epub 2018 Jun 19
18. Kordonouri O, Hartmann R, Remus K, Bläsig 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. Epub 2012 Jul 6
19. Smith T, Fuery M, Knight B, Harris M, Howley P, King B, Smart C. In young people with Type 1 Diabetes using insulin pump therapy giving an additional sixty percent of the mealtime insulin dose improves postprandial glycemia following a high fat, high protein meal. 44th Annual Conference of ISPAD, P234. Available from: http://medialibrary.ispad.cyim.com/mediatheque/media.aspx?mediaId = 49532&channel = 9857
20. Piechowiak K, Dżygało K, Szypowska A. The additional dose of insulin for high-protein mixed meal provides better glycemic control in children with type 1 diabetes on insulin pumps: randomized cross-over study. Pediatr Diabetes 2017;18:861-868. Epub 2017 Jan 24
21. 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.

Click for Supplementary Table 1 access link: http://glns.co/kqb82