BRIEF REPORT

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Effect of nutrition on postprandial glucose control in hospitalized patients with type 2 diabetes receiving fully automated closed-loop insulin therapy

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Abstract

Fully automated closed-loop insulin delivery may offer a novel way to manage diabetes in hospital. However, postprandial glycaemic control remains challenging. We aimed to assess the effect of nutritional intake on postprandial glucose control in hospitalized patients with type 2 diabetes receiving fully closed-loop insulin therapy. The effects of different meal types and macronutrient composition on sensor glucose time-in-target (TIT, 3.9-10.0 mmol/L) and mean sensor glucose were assessed with hierarchical linear models using a Bayesian estimation approach. TIT was lower and the mean sensor glucose slightly higher, after breakfast compared with lunch and dinner, whereas the insulin dose was higher. Across meals, when carbohydrates were replaced by fat, or to a lesser extent by protein, postprandial glucose control improved. For breakfast, a 3.9% improvement in TIT was observed when 10% of the energy from carbohydrates was replaced by fat. Improvements were slightly lower during lunch and dinner (3.2% and 3.4%) or when carbohydrates were replaced by protein (2.2 and 2.7%, respectively). We suggest that reducing carbohydrate at the expense of fat or protein, could further improve glucose control during fully closed-loop insulin therapy in hospital.

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* Nicolas Banholzer and David Herzig contributed equally to the manuscript

1 | INTRODUCTION

The prevalence of diabetes among hospitalized patients is growing worldwide, calling for effective, resource-efficient and safe glucose management strategies.[1] Closed-loop insulin therapy, which is an emerging diabetes treatment modality that autonomously modulates insulin pump therapy based on sensor glucose values, was recently shown to achieve better glycaemic control than conventional management in hospitalized patients with type 2 diabetes.[2,3] Yet, reducing glucose excursions after meals using automated subcutaneous insulin delivery remains a challenge. While nutritional intake is known to have an important effect on postprandial glucose control,[4] the impact of specific meal characteristics during fully automated closed-loop insulin delivery is largely unexplored. Thus, the objective of this work was to assess the effect of nutritional intake on postprandial glucose control in patients with type 2 diabetes receiving fully closed-loop insulin therapy while in hospital.

2 | METHODS

2.1 | Study design and participants

This was an exploratory analysis using a subset of data from a two-centre randomized controlled clinical trial assessing the efficacy of closed-loop insulin delivery versus usual care in glucose control in hospitalized patients with type 2 diabetes.[2] The analysis included data from 39 closed-loop participants at a single centre whose nutritional intake was recorded during the study. The protocol was approved by the local ethics committee. All study-related procedures were performed in accordance with the local ethics standards and with the Declaration of Helsinki. All participants gave written informed consent before study enrolment.

2.2 | Study procedures

Participants received fully automated closed-loop insulin delivery for a maximum of 15 days or until hospital discharge. The closed-loop system utilized a predictive control algorithm (version 0.3.70) that modulated the subcutaneous insulin infusion using an insulin pump (Dana Diabecare R; Sooil, Seoul, South Korea) every 10-12 min based on sensor glucose measurements (Freestyle Navigator II; Abbott Diabetes Care, Alameda, CA). The system did not require meal announcement or pre-meal boluses. Participants received regular meals according to local hospital practice. Breakfast was served between 07:30 and 08:30, lunch between 11:30 and 12:30, and dinner between 17:30 and 18:30.
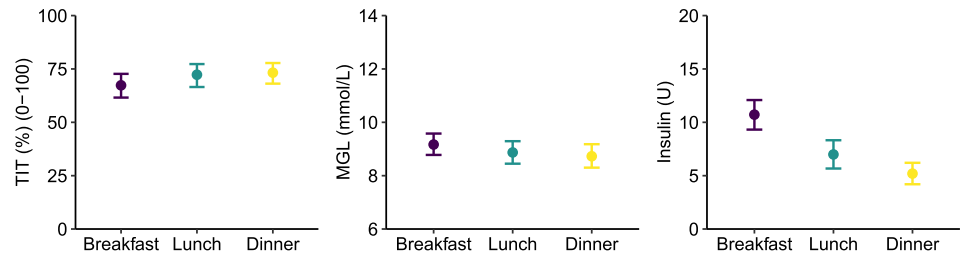
2.3 | Data collection and pre-processing

Nutritional intake (meal type, energy and macronutrient content) was assessed by a member of the research team using food records and nutritional information from the hospital menu planning system and food database. Continuous glucose monitoring and insulin delivery data were obtained from downloads of study devices. The postprandial period was defined as 3 h after serving the meal. If participants had a snack within the postprandial period, the period was discarded. Only records containing at least two postprandial data sets for each meal type and participant were eligible. Days with incomplete meal information were discarded for the calculation of daily energy and macronutrient intake. Postprandial glucose control was quantified by the proportion of time with sensor glucose between 3.9 and 10.0 mmol/L [time-in-target (TIT)] and mean sensor glucose level (MGL). Postprandial insulin dose was calculated based on the insulin dose delivered over the 3-h period. Missing sensor glucose values in the postprandial period were imputed using linear interpolation.

2.4 | Statistical analysis

The bibliographic reference to the programming language Stan, to the interface rstan and to the package brms is provided in Appendix S1. This study is based on the retrospective analysis of a clinical trial and no sample size calculation was performed. Nutritional intake was summarized using descriptive statistics. The effects of meal type and composition on postprandial glucose control were assessed with hierarchical linear models accounting for participant-specific effects. A Bayesian estimation approach is described in detail in Appendix S1. Separate models were implemented for the different glucose metrics. To assess the difference in postprandial glucose control between breakfast, lunch and dinner, the metric of interest was included as the dependent variable and meal-specific effects for breakfast, lunch and dinner as the independent variable. TIT was modelled with a beta distribution using a logit-link function, MGL was modelled with a normal distribution using an identity-link function, and insulin was modelled with a normal distribution on the log scale using an identity-link function. To assess the effects of macronutrient composition on glucose control, meal type, meal energy content and proportion of energy from fat and protein were included in a isocaloric substitution model whose coefficients indicate changes in outcomes by replacement of carbohydrate (as percentage of energy content) by fat or protein. Insulin on board and glucose levels at mealtime were included as adjustments. Insulin on board was calculated as described in Toffanin et al.[5] with an insulin peak time of 89 min[6] and a duration of action of 5 h. For the latter, the infused insulin dose per minute was considered a discrete bolus. In the results, we report the posterior mean and the

FIGURE 1 Postprandial glucose control: marginal effects (posterior mean and 95% credible interval) of different meals on time-in-target (TIT), mean sensor glucose (MGL), and amount of infused insulin (insulin) in the postprandial period

95% credible interval (CrI) based on the 2.5% and 97.5% quantile of the posterior distribution.

3 | RESULTS

3.1 | Nutritional intake

In total, 822 meals from 39 participants (for characteristics see Table S1 in Appendix S1) were analysed: 272 for breakfast, 284 for lunch and 266 for dinner. In total, five meals and postprandial data were excluded from the analysis from participants that contributed less than two observation per meal type. Total daily energy intake was 1445 ± 594 kcal, from which 43 ± 12% (155 ± 66 g) was carbohydrates, 40 ± 10% (65 ± 31 g) fat and 17 ± 6% (61 ± 26 g) protein. Carbohydrate content was 62 ± 25 g for breakfast, 52 ± 22 g for lunch and 61 ± 31 g for dinner. Further meal characteristics are reported in Appendix S1.

3.2 | Glucose control and insulin doses

TIT was 67.5 ± 30.7%, 74.7 ± 35.0% and 75.4 ± 31.6% following breakfast, lunch and dinner, respectively. MGL was 9.1 ± 1.9 mmol/L following breakfast, 8.8 ± 2.1 mmol/L following lunch, and 8.6 ± 1.9 mmol/L following dinner. Insulin doses were 10.4 ± 7.5, 6.6 ± 6.0 and 5.0 ± 4.1 U, respectively. Further metrics of glucose controls are reported in Appendix S1.

3.3 | Effect of meal type on postprandial glucose control

Model-derived TIT was on average slightly lower after breakfast [67.5%, 95% CrI (62.0%; 72.6%)] than after lunch [72.4%, 95% CrI (66.9%; 77.2%)] and dinner [73.3%, 95% CrI (68.1%; 78.7%)]. Similarly, MGL was on average slightly higher following breakfast [9.2 mmol/L, 95% CrI (8.8 mmol/L; 9.6 mmol/L)] than following lunch [8.9 mmol/L, 95% CrI (8.5 mmol/L; 9.3 mmol/L)] and dinner [8.7 mmol/L, 95% CrI (8.3 mmol/L; 9.2 mmol/L)]. Amount of insulin infused was higher following breakfast [10.7 U, 95% CrI (9.4 U; 12.1 U)] than following lunch [7.0 U, 95% CrI (5.7 U; 8.3 U)] or dinner [5.2 U, 95% CrI (4.2 U; 6.2 U)]. Estimated postprandial glucose control and insulin amount following meal type are shown in Figure 1.

3.4 | Isocaloric substitution analysis: effect of meal macronutrient composition on postprandial glucose control

Across all meals, energy intake was inversely associated with TIT [−0.23, 95% CrI (−0.35; −0.11)]. Regarding meal macronutrient composition, TIT increased when energy from carbohydrates was replaced by fat [2.08, 95% CrI (1.22; 2.96)] and slightly increased when replaced by protein [1.36, 95% CrI (−0.10; 2.79)].

The estimated associations between energy intake and TIT translate into an average increase in TIT of 3.9% for an average breakfast, 3.4% for an average lunch and 3.3% for an average dinner, if 10% of energy from carbohydrates is replaced by fat (with all other variables at their mean). For 10% isocaloric substitution of carbohydrates by proteins, increases in TIT are smaller, with an increase of 2.6% for breakfast, 2.3% for lunch and 2.2% for dinner. Detailed numbers and 95% CrI are reported in Appendix S1.

Analogously, there was a positive association between meal energy intake and MGL [0.29, 95% CrI (0.15, 0.43)]. MGL decreased when energy from carbohydrates was replaced by fat [−2.63, 95% CrI (−3.47; −1.80)] and slightly decreased when replaced by protein [−1.64, 95% CrI (−3.02; −0.27)].

Insulin requirements were positively associated with energy intake [0.09, 95% CrI (0.04, 0.15)] and were lower when energy from carbohydrates was replaced by fat [−0.96, 95% CrI (−1.43; −0.47)] and slightly lower when replaced by protein [−0.67, 95% CrI (−1.60; 0.25)].

4 | DISCUSSION

The present study assessed the effects of meal type and macronutrient composition on postprandial glucose control in hospitalized patients with type 2 diabetes receiving fully closed-loop insulin therapy. We observed worse postprandial glucose control following breakfast compared with lunch and dinner and higher insulin dose delivered. Across meal types, macronutrient composition had a relevant effect on postprandial glucose control. The isocaloric substitution analysis revealed an improvement in postprandial control and a reduction in insulin requirements if energy from

carbohydrate is replaced by fat, or to a lesser extent by protein (Figure 2).

To our knowledge, this is the first study evaluating the effects of meal type and macronutrient composition on glucose control during fully closed-loop insulin delivery. The inferior postprandial glucose control and higher insulin doses after breakfast compared with lunch and dinner suggest that breakfast poses greater challenges to automated systems. A similar pattern with higher excursions after breakfast compared with lunch was observed in previous work exploring fully closed-loop insulin delivery in adults with type 2 diabetes in a controlled research setting.[7] Concordantly, the postprandial rise in glucose in response to identical meals was more pronounced in the morning compared with later in the day in insulin-naïve individuals with type 2 diabetes.[8] The underlying mechanisms remain speculative and possible explanations may include the lack of residual insulin from a preceding meal[9] and higher endogenous glucose production[10] in the morning.

The glycaemic benefits of isocaloric substitution of carbohydrates with fat and protein could be simply the consequence of the corresponding reduction in carbohydrates as the major contributor to postprandial glucose excursions.[11] Nonetheless, carbohydrate-independent effects might be considered. Fat intake slows gastric emptying, thereby delaying and attenuating postprandial glycaemic excursions.[12] Protein intake similarly delays gastric emptying and may additionally stimulate endogenous insulin secretion in individuals with type 2 diabetes because of the insulinotropic effect of certain amino acids.[13]

To date, no other studies exploring fully automated closed-loop systems have evaluated the effect of meal macronutrient composition on postprandial glucose control. However, Gingras et al. evaluated the
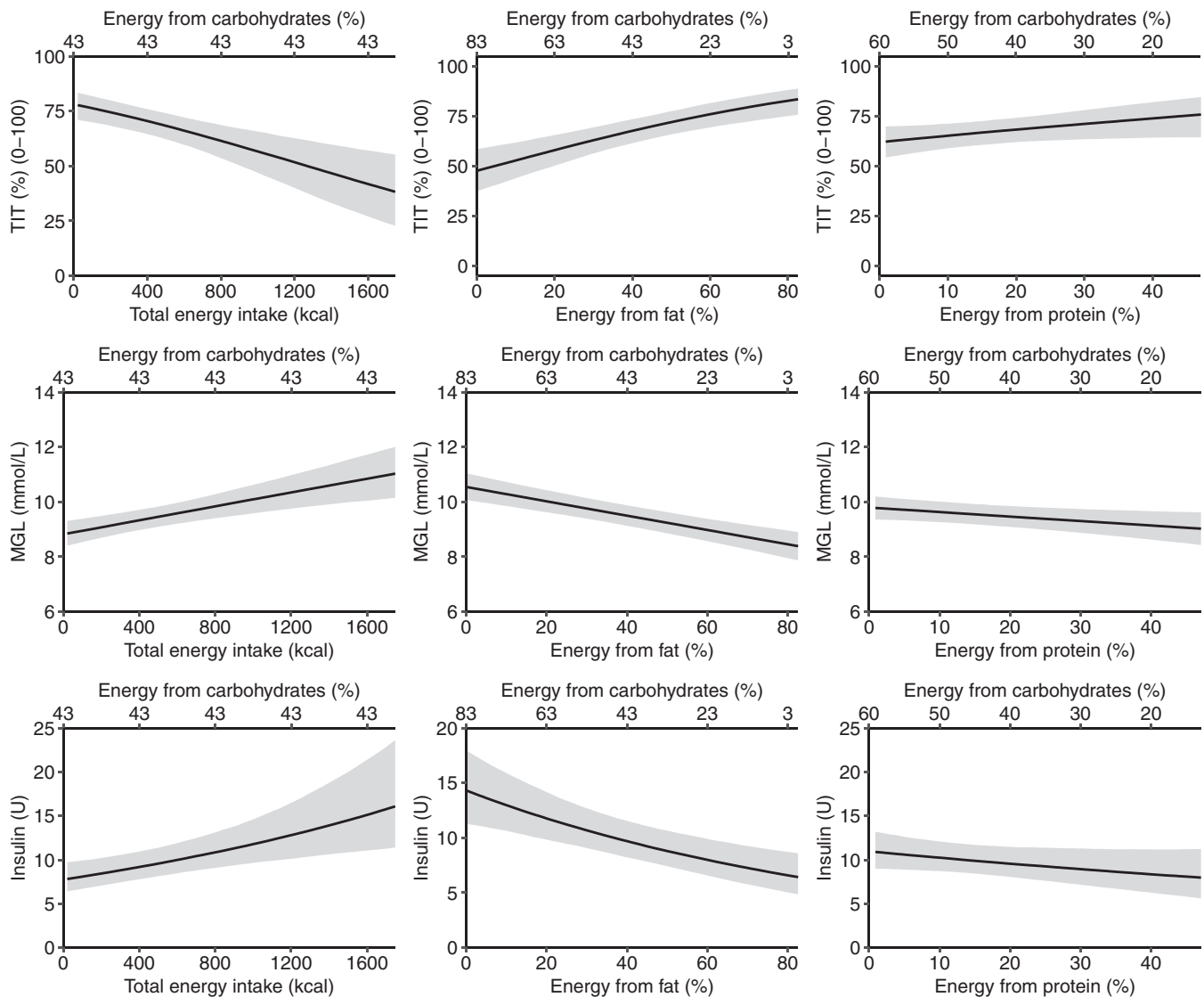
FIGURE 2 Postprandial glucose control by macronutrient content. Figure shows marginal effects (posterior mean and 95% credible interval) for total energy intake, energy from fat and energy from protein (% of total) on time-in-target (TIT), mean sensor glucose (MGL), and amount of infused insulin (insulin) in the postprandial period

effect of varying amounts of fat and protein in meals of equivalent carbohydrate content and with a fixed insulin dose during hybrid closed-loop insulin delivery in type 1 diabetes.[14] Adding fat and protein to a fixed amount of carbohydrate delayed the glycaemic peak by 40 min and postprandial insulin requirements were 39% higher without impacting overall postprandial glucose control.[15]

The strength of our study includes investigation of the relatively unexplored area of the role of nutrient intake in fully automated closed-loop performance, which could have practical relevance.

Nevertheless, we do acknowledge several limitations. Nutritional intake was assessed using food diaries, possibly resulting in underreporting of total daily nutritional intake. However, the effects of meal type and macronutrient composition were assessed based on captured meals and should not be affected by potentially missed meals. Timing of the postprandial period was defined by the time of food serving, while exact time of meal intake remained uncertain. However, small variations in timings of intake should only exhibit fewer effects on assessed metrics over a 3-h postprandial period. Still, a 3-h period may not be sufficient to capture late meal effects, particularly in the context of meals with high-fat and/or high-protein content. Analysis was limited to the effect of macronutrient quantity without considering qualitative aspects (e.g. types of carbohydrates, fibre content), which may further influence the glycaemic impact of food. Finally, we acknowledge the limitation inherent to an exploratory study.

In conclusion, this study offers insights into the role of nutrition in postprandial glucose control during fully automated closed-loop therapy in type 2 diabetes. Our findings suggest that reducing carbohydrate at the expense of fat and protein improves postprandial performance of a fully closed-loop system. This simple, safe and effective dietary strategy may further augment the benefits of fully automated closed-loop glucose control for the management of type 2 diabetes in hospital. Interventional studies are warranted to provide more specific guidance on meal macronutrient composition of specific meal types.

CONFLICT OF INTEREST
RH received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk; license fees from B. Braun and Medtronic; served as a consultant to B. Braun, patents and patent applications related to closed-loop; director at CamDiab. All other authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS
LB screened and enrolled participants and conducted the study visits. LB, DH, NB, MA and SF designed the retrospective analysis. NB analysed the data and produced the display items. DH, MA, CTN, LB and SF contributed to the data analysis. LB and RH designed the original study. RH designed the control algorithm. DH, MA, NA and LB interpreted the results and wrote the manuscript. All authors critically reviewed the manuscript and will ensure that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved. LB is the guarantor of this work and takes main responsibility for the integrity and accuracy of the data.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14187.

DATA AVAILABILITY STATEMENT
The datasets and scripts generated and/or analyzed during this work are available from the corresponding author on reasonable request

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.