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

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OBJECTIVE

To determine insulin dose adjustments required for coverage of high-fat, high-protein (HFHP) meals in type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

Ten adults with T1D received low-fat, low-protein (LFLP) and HFHP meals with identical carbohydrate content, covered with identical insulin doses. On subsequent occasions, subjects repeated the HFHP meal with an adaptive model-predictive insulin bolus until target postprandial glycemic control was achieved.

RESULTS

With the same insulin dose, the HFHP increased the glucose incremental area under the curve over twofold (13,320 ± 2,960 vs. 27,092 ± 1,709 mg/dL · min; *P* = 0.0013). To achieve target glucose control following the HFHP, 65% more insulin was required (range 17%–124%) with a 30%/70% split over 2.4 h.

CONCLUSIONS

This study demonstrates that insulin dose calculations need to consider meal composition in addition to carbohydrate content and provides the foundation for new insulin-dosing algorithms to cover meals of varying macronutrient composition.

Studies have demonstrated that dietary fat and protein cause postprandial hyperglycemia in patients with type 1 diabetes (T1D) (1), but definitive experimental data to guide clinical practice recommendations on how to adjust prandial insulin doses for higher fat and higher protein meals are lacking.

The objective of the current study was to *1*) determine the incremental differences in postprandial glycemia following a high-fat, high-protein (HFHP) meal compared with a low-fat, low-protein (LFLP) meal with identical carbohydrate content and *2*) determine how insulin doses should be adjusted to cover the HFHP meal.

RESEARCH DESIGN AND METHODS

Subjects

Ten adults with T1D using insulin pump and continuous glucose monitoring, aged 18–75 years, with T1D for >3 years, using an insulin pump for >6 months, and with

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an HbA_{1c} <8.5% (69 mmol/mol) were studied. The study was approved by the Joslin Institutional Review Board.

Study Protocol

Prior to the study all pump settings were optimized. One day prior to admission subjects inserted a new continuous glucose monitoring sensor, insulin infusion catheter, and reservoir filled with Lispro insulin (Lilly, Indianapolis, IN). After a 10-h fast, subjects were admitted to the Joslin Clinical Research Center. On admission, an intravenous catheter for blood sampling was inserted and the pump changed to an Animas OneTouch Ping (West Chester, PA). If the glucose concentration was outside the target range (80–130 mg/dL), a correction insulin dose or glucose tablets was administered as necessary and the test was delayed for 2.5 h.

On the first two admissions subjects consumed LFLP and HFHP meals in random order, with an identical insulin bolus calculated using their carbohydrate-to-insulin ratio (CIR) (delivered as a 50%/50% combination bolus over 2 h). On subsequent visits, subjects repeated the HFHP meal with an insulin dose estimated using a model predictive bolus (MPB) algorithm (details reported in the Supplementary Data). Visits were repeated up to four times until the following glucose criteria were achieved:

1. ≤10 mg/dL decrease from baseline (BL) during the first 2 h
2. Peak postprandial glucose ≤BL plus 80 mg/dL
3. 2-h postprandial glucose ≤BL plus 40 mg/dL
4. 6-h postprandial glucose within 20 mg/dL of BL
5. No hypoglycemia requiring treatment

Glucose concentrations were assessed using an YSI 2300 glucose analyzer (YSI, Yellow Springs, OH) from venous blood samples taken −30, −20, and 0 min prior to the meal and every 30 min thereafter for 6 h.

Diet

The meals consisted of a pizza base with marinara sauce (LFLP) or the same pizza base and sauce with added cheese (HFHP). Meals were prepared the morning of the session. The two meals were matched for carbohydrate (50 g), but varied in calories, fat, and protein: LFLP had 273 calories, 4 g of fat, and 9 g of protein and HFHP had 764 calories, 44 g of fat, and 36 g of protein. The pizza base had a glycemic index (GI) of 52 (J. Brand-Miller and K.J.B., unpublished data). Additional nutrition information is reported in Supplementary Table 1.

Adaptive MPB Algorithm

The MPB algorithm was applied in two steps. First, a metabolic model comprising an insulin pharmacokinetic/pharmacodynamic submodel (2), the Bergman minimal model (3,4), and a meal absorption model (5) was identified using a nonlinear generalized reduced gradient algorithm available in Microsoft Excel (Office 2013). Second, an optimal insulin DOSE (U), SPLIT (% given as bolus), and DURATION were obtained by minimizing the model-predicted glucose area below target from 0 to 120 min and area above target from 120 to 360 min following the meal. DOSE was constrained to be ≤1.75 times the previous maximum DOSE; if the constrained DOSE did not achieve the desired glucose criteria, the procedure was repeated. Further details on the model are provided in studies characterizing the effect of dietary fat on insulin requirements (6) and intraday changes in metabolism (7,8).

Statistical Analysis

Outcome data are reported as mean ± SE. Changes in insulin DOSE and glucose incremental area under the curve (iAUC) were assessed by repeated-measures ANOVA with correction for multiple comparisons (Dunnett procedure with the LFLP meal as control). Patient demographics are reported as mean ± SD. Statistical testing was done using GraphPad Prism, version 6.04.

RESULTS

Patient Characteristics

Ten patients (nine male, one female) were studied. Mean ± SD age was 60.4 ± 11.3 years, BMI was 25.8 ± 3.5 kg/m^2, HbA_{1c} was 7.1 ± 0.8% (54 ± 7 mmol/mol), and total daily insulin dose was 35.5 ± 14.8 U/day (range 17–65 U/day).

LFLP Meal Versus HFHP Meal

Fasting blood glucose concentrations on the two study days were similar (127 ± 8 mg/dL vs. 129 ± 5 mg/dL, $P = 0.702$). Despite using the same insulin dose, the glucose iAUC in the HFHP meal was more than double that of LFLP meal (27,092 ± 1,709 vs. 13,320 ± 2,960 mg/dL · min; $P = 0.0013$), with significant differences observed from 180 min onwards and >100 mg/dL differences in glucose concentrations at 6 h (Fig. 1).

Optimized Insulin Dose

In 7 of the 10 subjects, the model-optimized meal profile achieved our stopping criteria in one attempt. In 2 subjects the initial MPB was too high and in 1 subject the initial dose was too low, necessitating additional 2–3 visits. MPB decreased the glucose iAUC (27,092 ± 1,709 mg/dL · min to 11,712 ± 3,172 mg/dL · min; $P = 0.0013$) and the incremental change in blood glucose concentration (73 ± 4 mg/dL to 24 ± 11 mg/dL; $P = 0.001$). Additional

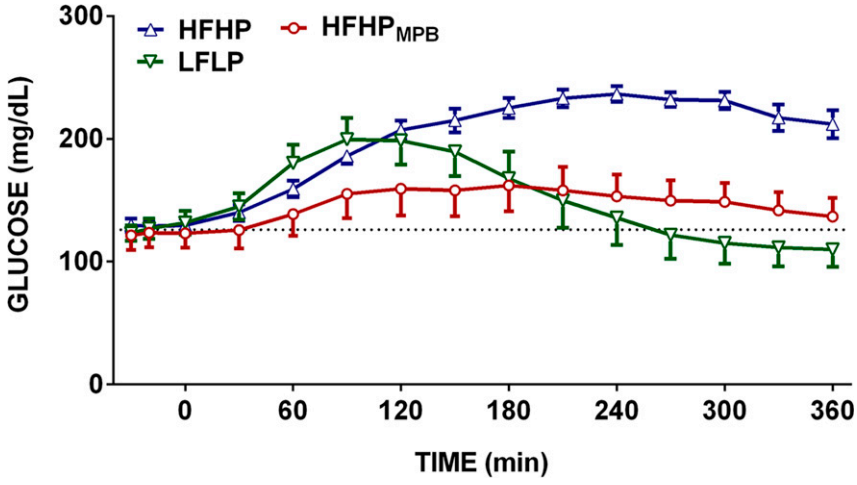

Figure 1—Postprandial plasma glucose response following LFLP and HFHP meals with identical carbohydrate content and insulin dose and an HFHP meal with optimal MPB ($HFHP_{MPB}$).

details are provided in Supplementary Table 2. The optimized dose was 65% ± 10% higher than that calculated from the patient's carbohydrate-to-insulin ratio but with considerable interindividual variability (17%–124%; 8 of the 10 subjects requiring 75% or more insulin). The optimal bolus delivery pattern was a dual-wave bolus, with a 30%/70% split, on average, over 2.4 h and optimal delivery patterns ranging from 10%/90% to 50%/50% split, with the extended bolus lasting from 2 to 3 h. No relationship was observed between the increased dose and total daily insulin dose ($P = 0.1224$).

CONCLUSIONS

To achieve target postprandial glucose control following the addition of 40 g of dietary fat and 27 g of protein to 50 g of carbohydrate, the insulin dose needed to be increased by 65% ± 10% and delivered as a combination bolus with a 30%/70% split over 2.4 h. The late postprandial hyperglycemia following the HFHP meal observed in this study is consistent with other reports (1), as is our conclusion that a combination bolus is better able to control a high-fat meal (9–11). However, our pizza base had a low GI, and HFHP meals consisting of higher GI carbohydrates may require more insulin up front, as a larger proportion of the glucose load will be absorbed in the earlier postprandial period (1).

There were substantial interindividual differences in the insulin dose required to optimize blood glucose levels, confirming the findings in our previous research using a closed-loop system (12). In this study, insulin doses varied from +17% to +124% of the CIR-derived dose, a sevenfold difference in incremental dose required. These differences in fat sensitivity highlight the need for individualized clinical advice regarding insulin adjustments for fat and protein. Applying the study findings and the observation that 20% of the subjects needed only a modest increase in dose, we recommend that for HFHP meals (>40 g fat, >25 g protein) patients should consider increasing the insulin dose calculated based from their CIR by 25%–30% and using a combination bolus with 30%–50% given initially and the remainder over 2–2.5 h. If the review of glucose profiles shows late (>3 h) hyperglycemia, then for subsequent similar meals the insulin delivered in the extended period should be increased. For patients on injection therapy the combination bolus can be mimicked by a preprandial injection of regular rapid-acting analog insulin or a preprandial injection of an analog insulin followed by an additional injection 60–90 min later.

To our knowledge, this is the first study to use a model-predictive control method to optimize an open-loop meal bolus, but similar methods have been used in artificial pancreas systems (13). Open-loop nonmodel-based insulin dosing algorithms accounting for fat and protein have been proposed. Of these, Pańkowska et al. (14) proposed the use of a fat-protein unit, but the method does not make allowances for interindividual differences in the effects of dietary fat and protein and was associated with a high rate of hypoglycemia (~1 in every 3 subjects) (15,16). A second method using the Food Insulin Index was shown to improve postprandial glycemic control over 3 h (17,18) but was also associated with trend toward hypoglycemia.

Our study has a number of limitations. We only studied adult subjects and these subjects were predominantly male. Further, we increased both protein and fat, making it difficult differentiate the individual effects. There is evidence to suggest that fat and protein have an additive effect on postprandial glycemia (19), and therefore our findings may be an overestimation if dietary fat or protein were added in isolation. Further research is needed to validate results for protein and fat in isolation. In addition, it is not known whether there is a threshold for the effect of dietary fat and/or protein on insulin requirements, i.e., is there a minimum amount of fat or protein in a meal before insulin doses need to be adjusted? Furthermore, it is not known whether there is a linear dose-response relationship between these macronutrients and the optimal insulin dose, i.e., if the fat and protein amount was halved, should the insulin dose also be halved? Again, further research is needed. Finally, the MPB approach used in this study requires pump basal rates to be appropriately configured.

This study *1*) demonstrates that to optimize postprandial glucose control some mealtime insulin doses may need to be based on the meal composition rather than carbohydrate content only and *2*) provides the foundation for the development of new insulin-dosing algorithms to cover HFHP meals.

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Author Contributions. K.J.B. contributed to the study design, implemented the study protocol including dose calculations, collected and interpreted the data, wrote the first draft of the manuscript and contributed to subsequent revisions, and contributed to intellectual content. E.T. oversaw the implementation of the study protocol, interpreted the data, critically reviewed the drafts of the manuscript, and contributed to intellectual content. G.M.S. conceived and designed use of the MPB, oversaw the implementation of the MPB, interpreted the data, contributed to the writing of the first draft of the manuscript and subsequent revisions, and contributed to intellectual content. H.A.W. conceived and designed the study, oversaw the study implementation and collection of data, interpreted the data, contributed to the writing of the first draft of the manuscript and wrote subsequent revisions, and contributed to intellectual content. H.A.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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