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ORIGINAL ARTICLE

Evaluation of a Novel Continuous Glucose Monitoring-Based Method for Mealtime Insulin Dosing—the *iBolus*—in Subjects with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion Therapy: A Randomized Controlled Trial

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Abstract

Objective: Prandial insulin dosing is an empirical practice associated frequently with poor reproducibility in postprandial glucose response. Based on continuous glucose monitoring (CGM), a method for prandial insulin administration (*iBolus*) is presented and evaluated for people with type 1 diabetes using CSII therapy.

Subjects and Methods: An individual patient's model for a 5-h postprandial period was obtained from 6-day ambulatory CGM and used for *iBolus* calculation in 12 patients with type 1 diabetes. In a double-blind, crossover study each patient underwent four meal tests with 40 g or 100 g of carbohydrates (CHOs), both on two occasions. For each meal, the *iBolus* or the traditional bolus (*tBolus*) was given before mealtime (t_0) in a randomized order. We measured the postprandial glycemic response as the area under the curve of plasma glucose (AUC-$PG_{0–5h}$) and variability as the individual coefficient of variation (CV) of AUC-$PG_{0–5h}$. The contribution of the insulin-to-CHO ratio, CHO, plasma glucose at t_0 (PG_{t0}), and insulin dose to AUC-$PG_{0–5h}$ and its CV was also investigated.

Results: AUC-$PG_{0–5h}$ was similar with either bolus for 40-g (*iBolus* vs. *tBolus*, 585.5 ± 127.5 vs. 689.2 ± 180.7 mg/dL·h) or 100-g (752.1 ± 237.7 vs. 760.0 ± 263.2 mg/dL·h) CHO meals. A multiple regression analysis revealed a significant model only for the *tBolus*, with PG_{t0} being the best predictor of AUC-$PG_{0–5h}$ explaining approximately 50% of the glycemic response. Observed variability was greater with the *iBolus* (CV, 16.7 ± 15.3% vs. 10.1 ± 12.5%) but independent of the factors studied.

Conclusions: A CGM-based algorithm for calculation of prandial insulin is feasible, although it does not reduce unpredictability of individual glycemic responses. Causes of variability need to be identified and analyzed for further optimization of postprandial glycemic control.

Introduction

Achieving near-normoglycemia has been established as the main objective for most patients with type 1 diabetes mellitus (T1DM).[1] However, insulin dosing still remains as an empirical process, and its success is highly dependent on the patients' and physicians' skills, either with multiple daily injections or with continuous subcutaneous insulin infusion (CSII), the current gold standard of insulin treatment.

Postprandial glucose control is a challenging issue in everyday diabetes care. Indeed, postprandial glucose excursions are the major contributors to plasma glucose (PG) variability in subjects with T1DM, and the poor reproducibility of postprandial glucose response is burdensome for patients and healthcare professionals.[2]

During the past 10–15 years, there has been an exponentially increasing use of technology in diabetes care with the expectation of making life easier for patients with diabetes. Some tools have been developed to facilitate the prandial bolus calculation, such as the "bolus advisors." More recently, the availability of continuous glucose monitoring (CGM) has opened new scenarios for implementation of more effective

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strategies of insulin treatment. This may be particularly relevant to CSII-treated patients for whom the information from the CGM may be used for fine-tuning of the insulin infusion ("sensor-augmented pump"). Results from clinical studies of preliminary models of sensor-augmented pump suggest that they may be effective in improving metabolic control, especially when included as part of structured educational programs aiming at patients' empowerment.[3,4]

The algorithms implemented into current bolus advisors (like the Accurate Insulin Management [AIM] system and its modifications)[5–7] are based on mean populational values estimated from nonrandom samples of CSII-treated patients. Individualization of the algorithms' parameters is largely empirical and is made by correcting mean populational values for weight and mean total daily insulin dose as an estimation of the personal mean insulin sensitivity. This results in an acceptable estimation of the mean insulin-to-carbohydrate (I:CHO) ratio (i.e., the prandial insulin need). However, in this algorithm the intra-individual glycemic variability due to variations in insulin sensitivity (between-day changes), estimation and/or absorption of carbohydrates (CHOs), and insulin absorption is not taken into account.

Currently, the availability of information from CGM may be used for characterization of an individualized postprandial prediction model and also for development of strategies to deal with the uncertainty of postmeal glycemic response. Recently, a nonheuristic CGM-based algorithm to deal with postprandial glycemic control, the *iBolus*,[8] has been tested in silico with positive results.[9] The algorithm is based on interval techniques (Set Inversion Via Interval Analysis [SIVIA]),[10] which allow for explicit consideration of intrapatient variability as interval quantities in model parameters. Calculation of a feasible set of insulin dose strategies (bolus plus increment/reduction of basal rate) to fulfill the given constraints on postprandial glycemia is then performed according to the patient's prediction model obtained from CGM.

The present study was planned to validate clinically the *iBolus* algorithm for prandial insulin dosing in comparison with a currently available traditional I:CHO ratio-based standard bolus (*tBolus*) in T1DM subjects using CSII.

Subjects and Methods

This was a randomized, prospective, single-center, double-blinded, two-way crossover study. Twelve subjects with T1DM under long-term intensive insulin treatment with CSII (nine women; 41.8 ± 7.3 years old; diabetes' duration, 20.2 ± 10.3 years; body mass index, 25.1 ± 2.8 kg/m^2; glycosylated hemoglobin [A1C], 8.0 ± 0.6%; basal insulin dose, 0.8 ± 0.3 U/h; I:CHO ratio, 1.3 ± 0.5 U/10 g of CHO [mean ± SD]) were studied in the hospital (inpatient study) following a period of ambulatory CGM. At the time of the study, all of the subjects were free at the screening of any significant microangiopathic complication or any signs or symptoms of autonomic neuropathy, as evaluated using a standard battery of cardiovascular tests.[11] The study was carried out according to the Declaration of Helsinki after written informed consent was obtained from all subjects and approved by the local institutional review board.

All volunteers were studied in the hospital on four different occasions in a random, computer-generated sequence. Each subject underwent a block of two 40-g CHO and a block of two 100-g CHO mixed-meal tests, each one at 1–2-week intervals, thus completing the four experiments in a mean of 6 weeks. The mixed meals had the same relative macronutrient composition (50% CHO, 35% fats, and 15% proteins). In both the 40-g CHO and 100-g CHO experiments, the patients received in a randomized order a *tBolus*, based on the individual I:CHO ratio (as suggested by the CSII built-in bolus calculator), or an *iBolus*, based on CGM and SIVIA. Both the involved investigators and patients were blinded regarding the bolus administration procedure during test meals. An independent unblinded investigator kept the randomization list and was in charge of administrating the prandial insulin the day of the in-hospital meal study.

Prior to each block of meal tests, subjects underwent at least two outpatient 6-day periods of CGM monitoring for the identification (the first 3 days) and validation (the last 3 days) of an individualized model to be used in the prediction of the 5-h postprandial period (0–5-h PP) (Fig. 1).[12] In order to account for intrapatient variability, a prediction model with interval parameters[9] was calculated from the previous identified model considering 20% uncertainty in insulin sensitivity and 10% in CHO estimation. The interval model was validated during the last 3 days of CGM, where the patients had a standardized meal daily (40-g, 60-g, or 100-g CHO content, the same composition of the inpatient study).[12] Finally, constraints on PG were posed, and the SIVIA algorithm led to a three-dimensional set of solutions that contained all the basal-bolus combinations for maintaining PG between 90 and 180 mg/dL for the given meal, according to the prediction model (Fig. 2).[8,9] The solution set may contain profiles either increasing (dual-wave bolus) or decreasing (temporal basal decrement bolus or superbolus,[9] as suggested by Walsh and Roberts[13]) postprandial basal rate as required to fulfill the constraints for the specific patient (Fig. 2). To test the robustness of the algorithm, on the days of the inpatient mixed-meal study, one of the most aggressive solutions of each set (the one containing the greatest bolus dose) was administered. However, it is worth noting that the maximum bolus dose from the set of solutions was independent of the *tBolus*.

On the days of the mixed-meal study, subjects were admitted to the Endocrine Clinical Research Center of the Clinic University Hospital of Valencia, Valencia, Spain, at 09:00 h. They were put in the sitting position, and two venous lines were prepared: one for arterialized venous blood sampling[14] and the other for insulin or glucose infusion, if required. Indeed, to ensure comparable metabolic conditions between studies, where appropriate, subjects received an intravenous infusion of regular human insulin following a feedback procedure to maintain PG close to 90 mg/dL until the beginning of the studies at 13:00 h (time 0 [t_0] of the study). Then, the test mixed-meal was consumed in 15–20 min. At the same time, insulin was administered following the randomization schedule, and PG was monitored for 5 h, until the end of study at 18:00h (time 300 min). In order to avoid hypoglycemia during time 0–300 min, a controlled glucose infusion was started if PG fell below 75 mg/dL, and the premeal glycemic levels were maintained (euglycemic clamp).

The area under the curve (AUC) of PG during the whole experiment (AUC-PG$_{0–5h}$) was calculated as a measure of the overall glucose-lowering efficacy of the mealtime insulin (*iBolus* or *tBolus*, in 40-g and 100-g CHO meals). In addition, the AUC of the glucose infusion rate (AUC-GIR$_{0–5h}$)

A Identification Protocol

Capillary pre-prandial glycaemia	Action
>150 mg/dL or 100-150 rising	Insulin Bolus infusion and 30 minutes later a 100g meal
< 100 mg/dL or 100-150 decreasing	40g meal and 2 hours later insulin bolus infusion

B Model validation considering intra-patient variability

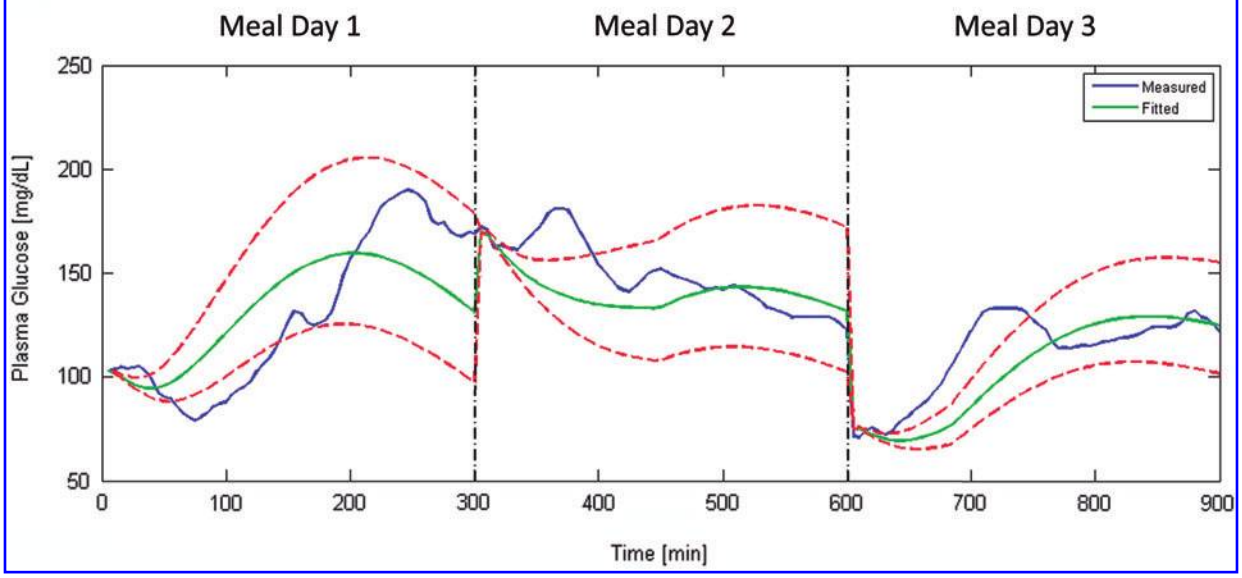

FIG. 1. **(A)** The identification protocol and **(B)** one of the two 3-day validation periods of Patient 2. **(A)** First, a mathematical model of the patient is derived from an ambulatory identification protocol with continuous glucose monitoring. Five-hour (300-min) lunch postprandial periods from 3 days were considered for identification following the protocol listed. Basically, identification is achieved through separation of meal from insulin dynamics by administering the bolus either 30 min before or 120 min after the meal. For safety reasons, this was done depending on the prevailing glucose concentrations (see Laguna et al.[12]). **(B)** Postprandial continuous glucose monitoring data from 3 additional days were used for model validation, where intrapatient variability was considered to be caused by day-to-day variations in insulin sensitivity and by the uncertainty in the estimation/absorption of carbohydrate of the meal. As a result, a model with interval parameters was derived characterizing intra-individual variability. This model predicts a range of postprandial glycemic excursions that the patient may exhibit (the area between the dashed lines). The fitted line represents the model prediction without considering uncertainty, whereas the measured line is the actual postprandial glucose profile from the continuous glucose monitoring. Color images available online at www.liebertonline.com/dia

represented a measure of the hypoglycemic exposure for each modality of insulin administration. Consequently, the lower the AUC-$PG_{0–5h}$ without risks of hypoglycemia, the greater the effectiveness of the prandial insulin administration to control the meal-related glucose excursion. The AUC of PG above the threshold of 140 mg/dL (AUC-$PG_{>140}$) was computed as an indicator of meal-induced hyperglycemic risk.

As a measure of the outpatient glycemic control, the AUC of the 0–5-h PP was calculated from the CGM data (interstitial glucose concentrations, AUC-$CGM_{0–5h}$) of the two 3-day validation periods.

Variability of the postprandial glycemic response of both the outpatient and the inpatient data was calculated as the coefficient of variation (CV) of the AUC-$CGM_{0–5h}$ and of the AUC-$PG_{0–5h}$. Glucose concentrations at t_0 (G_{t0} and in-hospital PG_{t0}), the mean prandial insulin dose (Insulin $dose_{0–5h}$), and their respective CVs (CV-G_{t0}, CV-PG_{t0}, and CV-Insulin $dose_{0–5h}$) were computed as well, as potentially related to variability of postprandial glucose.

A multiple linear regression analysis was performed to assess the parameters that best predicted the glycemic response. The model included those parameters usually considered for the optimization of insulin treatment (the I:CHO ratio, the amount of CHO, G_{t0}, or PG_{t0}) and a set of clinical variables (body mass index, diabetes' duration, and A1C), as independent variables. Although the Insulin $dose_{0–5h}$ cannot be considered independent from the other parameters, it was included in the model to account for potential nonlinearity of insulin pharmacodynamics (in relation to insulin dose) and for the effect of manual bolus administration and/or errors in the actual dose. In the inpatient study, only one 40-g CHO meal and one 100-g CHO meal were available for each type of treatment, and postprandial variability was determined as the CV of the 40-g AUC-$PG_{0–5h}$ and the 100-g CHO AUC-$PG_{0–5h}$ for either the *iBolus* or the *tBolus*. For this reason, mean values

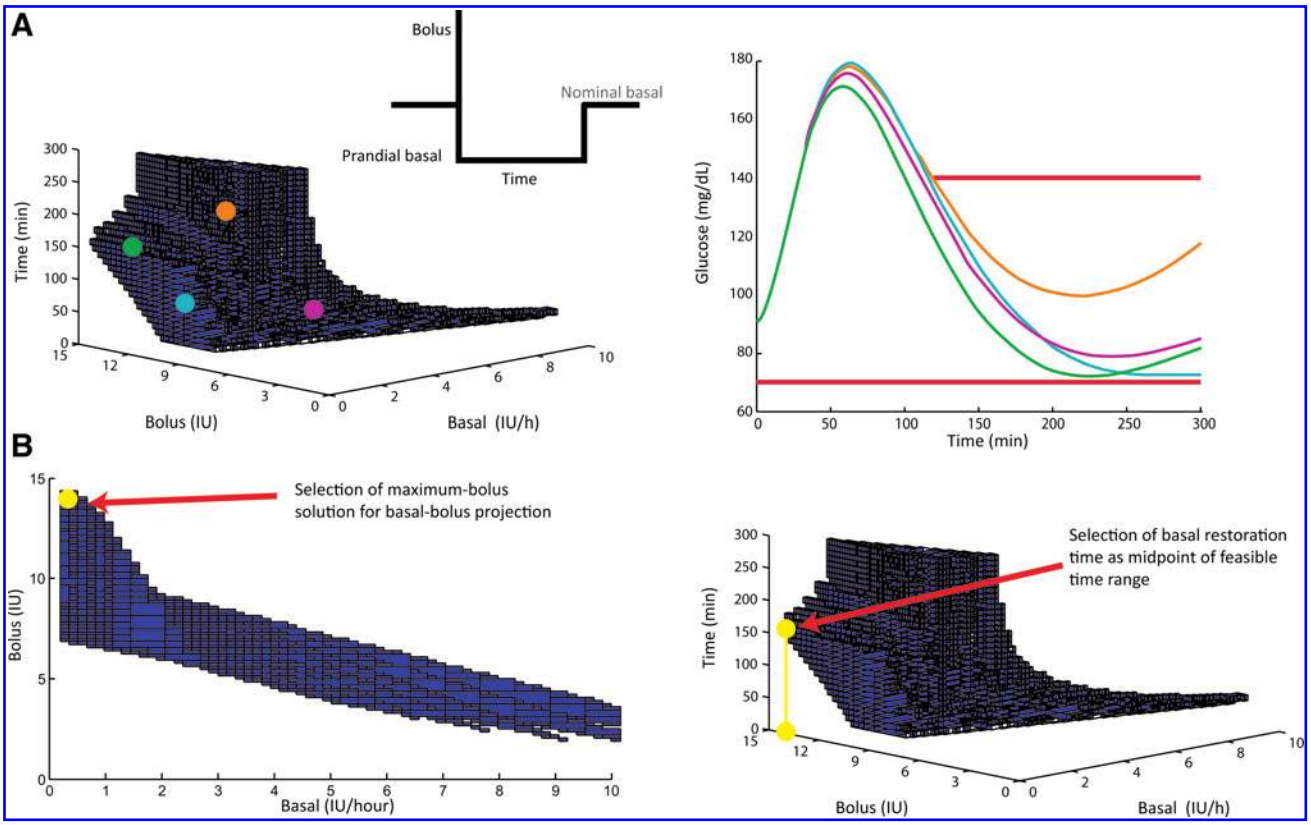

FIG. 2. **(A)** Based on the patient's interval model, a collection of feasible insulin infusion profiles leading to a good postprandial control (plasma glucose 90–180 mg/dL) was computed using a Set Inversion Via Interval Algorithm (SIVIA). Insulin infusion profiles were characterized by the amount of bolus, a prandial basal insulin rate, and a time of restoration of basal rate to its baseline. The feasible set was thus a three-dimensional group of solutions (*left panel*). Any infusion selected inside the set (grayscale circles of the set of solutions) will fulfill the imposed constraints (*right panel*) as shown by grayscale lines, which represents the predicted glycemic excursions following the selected solutions. **(B)** A solution with the highest possible bolus was selected to reach the lower possible postprandial peak. The basal-bolus combination with maximum bolus was selected from a two-dimensional projection of the feasible set, and then the midpoint of the feasible basal restoration time interval was selected. In this example, this selection resulted in a superbolus. However, the greatest bolus of the feasible set may be lower, and the lowest basal rate of the set may be greater than the usual patient's dose, resulting in solutions different from the superbolus. Color images available online at www.liebertonline.com/dia

were used, and the CHO factor was excluded from the analysis. The AUC-CGM$_{0–5h}$, AUC-PG$_{0–5h}$, and their respective CVs were the dependent variables.

The 6-day CGM period for model identification and validation was carried out with the Dexcom™ (San Diego, CA) Seven Plus®. During the in-hospital meal tests, PG was measured by means of a YSI 2300 STAT Plus (YSI Inc. Life Sciences, Yellow Springs, OH) every 5–15 min, depending on the prevailing blood glucose concentrations.

All data were subjected to repeated-measures analysis of variance with Huynh–Feldt adjustment for nonsphericity.[15] The analysis of variance model included the sequence of studies as a between-subjects factor, whereas test condition (*iBolus* vs. *tBolus*), CHO content of the meal (40-g and 100-g CHO conditions), and time (where appropriate) were the within-subjects factors. Subjects were entered in the model as random factors nested into the sequence. Post hoc comparisons with a nominal significance level of 0.05 (Newman–Keuls test) were carried out to pinpoint specific differences on significant interaction terms. The coefficient of determination R^2 was reported as a measure of the proportion of variability in the glycemic response that was accounted for by the statistical model. Data in the text were expressed as mean ± SD values, and those in the figures as mean ± SE values. Statistical analysis was performed using NCSS (Kaysville, UT) software (2007).

Results

The *iBolus* algorithm resulted in a clinically although not statistically significant approximately 30% greater mean insulin dose (bolus + 0–5-h PP basal) compared with the *tBolus*. The bolus dose accounted for the whole increment in the 40-g CHO meals (bolus + 164%; basal − 6%; median relative basal modification, −41%; interquartile range, −48%, +43%), whereas in the 100-g CHO meals both the basal insulin and the bolus insulin were equally increased (bolus + 129%; basal + 133%; median relative basal modification, +37%, interquartile range, −59%, +125%) (Table 1).

Despite different insulin doses, the *iBolus* and the *tBolus* resulted in a similar postprandial glycemic control. Indeed, the overall 0–5-h PP glycemic exposure (AUC-PG$_{0–5h}$), the hypoglycemic risk (AUC-GIR$_{0–5h}$), and the hyperglycemic

TABLE 1. INSULIN DOSE AND THE AREA UNDER THE CURVES OF PLASMA GLUCOSE, PLASMA GLUCOSE ABOVE 140 MG/DL, AND GLUCOSE INFUSION RATE OF THE 5-H POSTPRANDIAL PERIOD FOR THE *iBOLUS* AND THE *tBOLUS*

	40 g of CHO		*100 g of CHO*		*Difference for* iBolus − tBolus *[CI] for*		
Parameter	iBolus	tBolus	iBolus	tBolus	*40 g of CHO*	*100 g of CHO*	P *value*[a]
Insulin dose$_{0–5h}$[b]	9.9 ± 3.4	7.4 ± 2.1	18.0 ± 6.7	13.8 ± 4.3	2.6 [−0.7; 5.9]	4.1 [−0.06; 8.3]	0.32
Bolus dose	(7.1 ± 2.8)	(4.3 ± 1.5)	(13.9 ± 7.1)	(10.8 ± 3.8)			
AUC							
PG$_{0–5h}$	585.5 ± 127.5	689.2 ± 180.7	752.1 ± 237.7	760.0 ± 263.2	−103.6 [−233.3; 22.0]	−7.9 [−109.5; 93.7]	0.07
GIR$_{0–5h}$	150.1 ± 134.5	54.0 ± 87.4	88.9 ± 195.5	56.0 ± 121.1	96.1 [−78.5; 270.8]	32.9 [−141.7; 207.6]	0.45
PG$_{>140mg/dL}$	37.2 ± 63.5	77.5 ± 123.8	141.3 ± 182.8	144.6 ± 217.7	38.9 [−109.3; 31.3]	−2.6 [−72.9; 67.7]	0.29

Data are given for the 40-g carbohydrate (CHO) and the 100-g CHO meals and expressed as mean ± SD values. Difference between treatments is reported along with its confidence interval (CI).
[a]*P* value is from analysis of variance for repeated measures.
[b]Insulin dose is given in units.
AUC, area under the curve; GIR, glucose infusion rate (in mg/kg); PG, plasma glucose (in mg·h/dL).

risk (AUC-PG$_{>140}$) were not different with either method of prandial insulin calculation (Table 1). PG and the GIR time series showed an apparent trend for better glycemic control and a slightly greater risk of hypoglycemia with the *iBolus*, but only when the 40-g CHO meal was consumed (Fig. 3). However, this difference did not reach statistical significance.

Preprandial glucose concentrations were not different between studies, and CV-PG$_{t0}$ was small as a result of the insulin feedback procedure (mean intravenous insulin dose infused before the bolus administration 0.05 ± 0.06 and 0.04 ± 0.04 mU/kg/min for *iBolus* and *tBolus*, respectively; $P = 0.91$). However, the 0–5-h PP glycemic response varied in a wide range with both the *iBolus* (median CV, 14.7%; interquartile range, 4.5–27.9%) and the *tBolus* (median CV, 5.4%; interquartile range, 3.3–12.7%) (Table 2). Glucose variability was significantly greater with the *iBolus* (Table 2), likely because of the wider

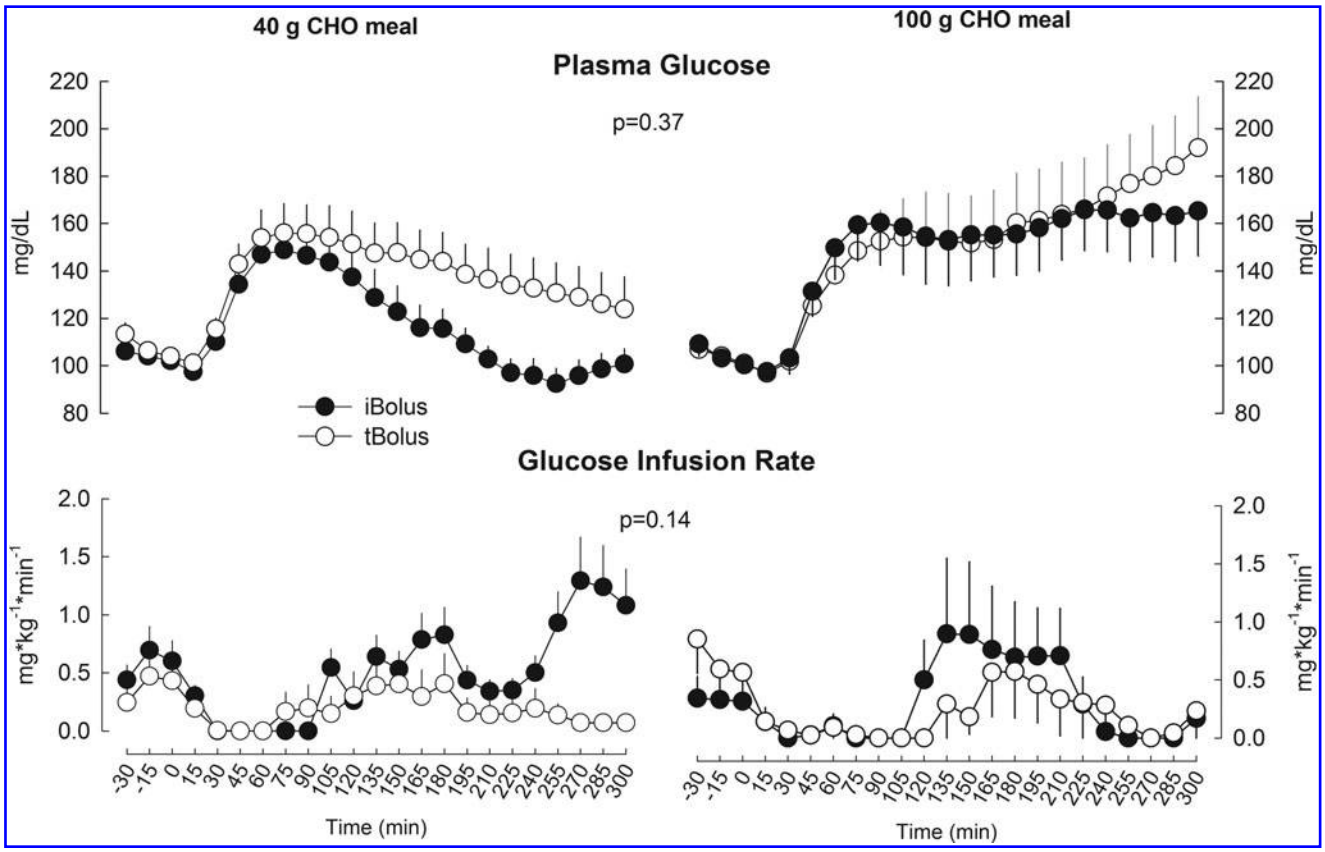

FIG. 3. **(Top panel)** Plasma glucose (in mg/dL) and **(bottom panel)** exogenous glucose infusion rate (mg/dL/min) for either the *iBolus* or the *tBolus*. For the sake of clarity the 40-g and 100-g carbohydrate (CHO) meals are presented separately. However, each patient underwent four studies following a two-way crossover design. Data are mean ± SE values. The *P* value is from analysis of variance for repeated measures.

Table 2. Intrasubject Variability of the Postprandial Glycemic Response Reported as the Intra-Individual Coefficient of Variation of the 5-H Postprandial Period

	CV		
	G_{t0}/PG_{t0} (mg/dL)[a]	Insulin dose (U)	$AUC_{0–5h}$ (mg/dL·h)[b]
Outpatient CGM			
Overall	32.3 ± 8.5% (128.7 ± 9.7)	28.7 ± 4.3% (10.7 ± 3.3)	29.6 ± 11.8% (769.5 ± 137.3)
40-g CHO	22.1 ± 11.8% (129.3 ± 33.2)	12.7 ± 14.8% (8.4 ± 3.2)[c]	21.0 ± 13.6% (754.1 ± 216.6)
60-g CHO	27.2 ± 9.2% (126.9 ± 33.0)	7.3 ± 6.3% (10.8 ± 2.8)[c]	22.1 ± 15.8% (732.1 ± 205.4)
100-g CHO	28.8 ± 15.9% (133.4 ± 35.9)	4.8 ± 4.1% (14.2 ± 4.7)[c]	21.7 ± 20.8% (823.2 ± 189.8)
P value[d]	0.45 (0.86)	0.73 (< 0.01)	0.98 (0.76)
Inpatient PG			
Overall	6.4 ± 2.5% (101.9 ± 4.1)	40.1 ± 11.6% (12.3 ± 3.6)	14.5 ± 10.5% (696.7 ± 175.3)
iBolus	6.7 ± 3.7% (101.2 ± 4.4)	39.5 ± 24.9% (13.9 ± 4.4)	16.7 ± 15.3% (668.8 ± 162.7)
tBolus	5.6 ± 5.0% (102.5 ± 5.5)	42.8 ± 3.3% (10.6 ± 3.2)	10.1 ± 12.5% (724.6 ± 198.7)
P value[d]	0.36 (0.43)	0.65 (0.007)	0.04 (0.07)

Data are mean ± SD percentage values. The mean ± SD absolute values are given in parentheses for glucose at t_0 (G_{t0} for outpatient and PG_{t0} for inpatient data), insulin dose, and area under the curve (AUC) of the 5-h postprandial period (0–5 h) for continuous glucose monitoring (CGM) and plasma glucose (PG) for completeness. For the inpatient study, data are from the 40-g and 100-g carbohydrate (CHO) meals (*iBolus* is compared with *tBolus* regardless of the CHO content of the meal).

[a]G_{t0} is interstitial glucose from outpatient CGM, PG_{t0} plasma glucose from inpatient PG.

[b]CGM glucose for outpatient CGM, PG for inpatient data.

[c]$P < 0.05$ for post hoc comparisons.

[d]*P* values are from analysis of variance for repeated measures.

CV, coefficient of variation.

range of insulin doses administered (Table 1). In the outpatient setting, 0–5-h PP intrasubject glucose variability was greater (median CV, 30.4%; interquartile range, 18.1–37.8%), as expected, because of less controlled conditions and the use of the less accurate CGM data instead of capillary glucose as the end point. It is interesting that glucose variability was associated with a high inconsistency in G_{t0} being independent of the CHO content of the meal (Table 2).

When the *tBolus* was considered, a multiple linear regression analysis revealed a significant model both in the outpatient and the inpatient setting (adjusted $R^2 = 0.51$ and 0.49, respectively). Preprandial glucose concentration was the variable that best predicted AUC-$CGM_{0–5h}$ and AUC-$PG_{0–5h}$, being positively correlated and explaining about 50% of glycemic response, whereas insulin dose, I:CHO, and CHO were poor predictors (Table 3). Diabetes' duration, A1C, and body mass index did not correlate to postprandial glycemic response and were removed from the analysis to avoid overfitting (Table 3). It is interesting that when data from the *iBolus* were analyzed, no significant correlation was observed between the considered independent variables and AUC-$PG_{0–5h}$.

Finally, variability did not appear to be explained by the variables considered, either with the *tBolus* or the *iBolus* (Table 3). Unexplained variability accounted for most of the

Table 3. Variation in Postprandial Glycemic Responses (and Their Respective Coefficients of Variation) Analyzed Through Multiple Regressions

	Outpatient CGM				Inpatient PG							
					AUC-$PG_{0–5h}$				CV AUC-$PG_{0–5h}$			
	AUC-$CGM_{0–5h}$		CV AUC-$CGM_{0–5h}$		iBolus		tBolus		iBolus		tBolus	
	R^2 (R^2 *adjusted*)	P *value*	R^2 (R^2 *adjusted*)	P *value*	R^2 (R^2 *adjusted*)	P *value*	R^2 (R^2 *adjusted*)	P *value*	R^2 (R^2 *adjusted*)	P *value*	R^2 (R^2 *adjusted*)	P *value*
Full model	0.57 (0.51)	< 0.0001	0.04 (0.000)	0.88	0.11 (0.00)	0.81	0.63 (0.49)	0.038	0.14 (0.00)	0.73	0.17 (0.00)	0.66
G_{t0} or PG_{t0}	0.50	< 0.0001	0.008	0.63	0.06	0.47	0.55	0.009	0.005	0.83	0.13	0.29
I:CHO ratio	0.03	0.17	0.006	0.68	0.04	0.99	0.09	0.20	0.03	0.60	0.03	0.60
CHO	0.0005	0.85	0.01	0.52	NA		NA		NA		NA	
Insulin dose	0.004	0.59	0.02	0.40	0.02	0.69	0.07	0.25	0.006	0.81	0.02	0.65

Models were built considering the insulin-to-carbohydrate (I:CHO) ratio, preprandial glycemia (glucose at t_0 [G_{t0}] in the outpatient continuous glucose monitoring [CGM] and plasma glucose [PG] at t_0 [PG_{t0}] in the inpatient study), prandial insulin dose, and the amount of carbohydrate (CHO) (the latter was excluded from the analysis of the inpatient data [see text for details]) as independent variables. The postprandial glycemic responses (area under the curve [AUC] $CGM_{0–5h}$ for the outpatient and $PG_{0–5h}$ for the inpatient study) and their respective coefficients of variation (CVs) were the dependent variables. The coefficient of determination R^2 is reported along with its *P* value (by analysis of variance).

NA, not applicable.

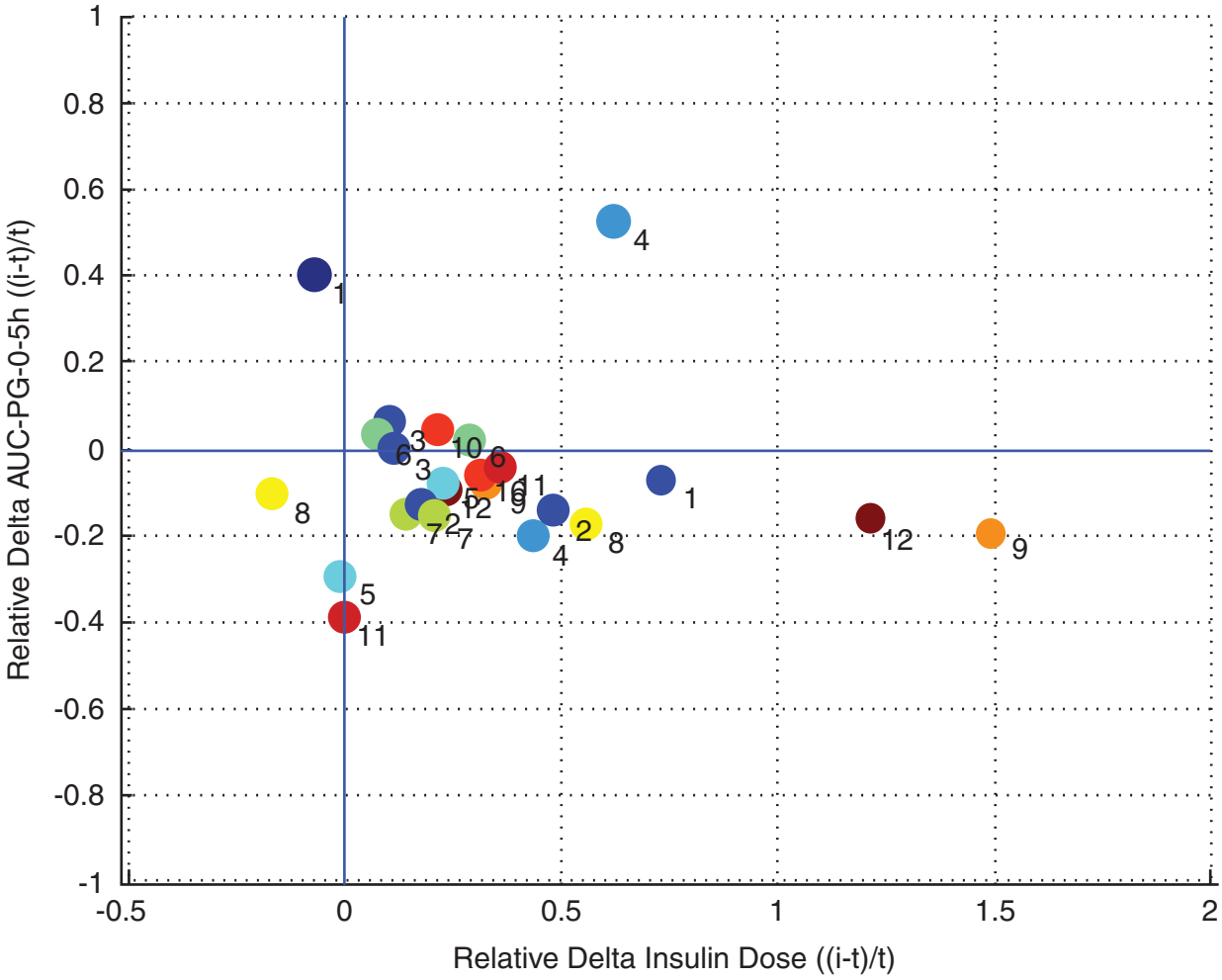

FIG. 4. Intra-individual relative changes in postprandial glucose response to different insulin doses while maintaining the same meal. Relative change (Delta) in insulin doses for both the 40-g and the 100-g carbohydrate meals ([*iBolus* – *tBolus*]/*tBolus*) are represented as the *x* variable. The relative Delta area under the curve of plasma glucose for the 5-h postprandial period (AUC-$PG_{0–5h}$) ([AUC_*iBolus* – AUC_*tBolus*]/AUC_*tBolus*) is the *y* variable. The "feasible" quadrants should be the upper left and the lower right: the lesser the insulin dose administered, the greater the postprandial glucose response; the greater the insulin dose administered, the lower the glucose response. However, we can see how giving more insulin to the same subject in some cases resulted in paradoxically higher plasma glucose (Subjects 3, 4, 6, and 10), whereas a lower (Subject 8) or the same (Subjects 5 and 11) insulin dose was associated with lower plasma glucose. This highlights the role of intra-individual glucose variability on postprandial glucose control in subjects with type 1 diabetes. Color images available online at www.liebertonline.com/dia

observed variability of the glycemic response. Indeed, a plot of the Δ Insulin dose versus the Δ AUC-$PG_{0–5h}$ (Δ as *iBolus* minus *tBolus*) revealed a poor correlation with a sometimes unexpected direct relationship between the two variables (Fig. 4): the Pearson correlation coefficient was 0.09 ($R^2 = 0.008$, $P = 0.68$), and the slope (the estimated change in Δ AUC-$PG_{0–5h}$ per unit change in Δ Insulin $dose_{0–5h}$) was 3.15 with a 95% confidence interval that included the 0 value [−12.6; 18.9].

Discussion

In this proof-of-concept study in CSII-treated patients with T1DM, a CGM-based strategy for prandial insulin calculation was tested and compared with the traditional prandial bolus procedure. Results seem to indicate that (1) CGM may be used to obtain an individual model of postprandial glycemic response,[12] (2) this model can be used for prandial insulin dosing, and (3) CGM-based insulin delivery results in a postprandial glycemic control similar to that achieved by standard bolus calculators. These results are encouraging and open the way to larger clinical studies aimed at validating less user-dependent strategies for prandial insulin dosing. However, several aspects of this study and its limitations deserve detailed discussion.

First of all, model identification was performed using models from the literature,[16–18] which were obtained through the analysis of a limited amount of data from small clinical studies.[16,19] In addition, not only the quality of the CHO but also the proteins and fats content of the meal can significantly affect glycemic postprandial response.[20–22] Consequently, available models are presumably specific to the meal used in the experiment and may not apply to meals of different composition, limiting prediction capabilities of the individual model derived from CGM. This may explain the differences

between the in silico[9] and the present clinical validation of the *iBolus*. Indeed, in the former the *iBolus* postprandial basal insulin rate was consistently reduced compared with the *tBolus*, to compensate for the greater bolus dose (temporal basal decrement bolus or superbolus). However, this was not the case in this study where, because of the heterogeneity of the real patients, the *iBolus* resembled either the superbolus or the dual-wave bolus according to the prediction model for each patient and meal. Nevertheless, the *iBolus* algorithm has at least two advantages: (1) it can consider uncertainty in the models' parameters. This means that individual variations in insulin sensitivity, meal absorption, or errors in the estimation of the amount of ingested CHO (among other factors) can be considered (or at least partially compensated) in insulin dosing. (2) It provides not a single but a set of solutions that, according to the model, are designed to maintain the patient in a prespecified glycemic range.[8,9] These features may be relevant in clinical practice because, if the individual models were good, they would allow for a more robust and safer insulin administration.[23]

Despite the limitations of the available models used to calculate the *iBolus*, the achieved glycemic control was at least similar to that obtained with the *tBolus*. Currently, the traditional bolus calculation is based on a multiple linear regression model where individual insulin requirements (the dependent variable) are based on a few parameters as the I:CHO ratio, the amount of the CHO of the meal, the correction factor/preprandial glycemia, and, when bolus advisors are used, also the insulin onboard.[6,7] Linearity and reproducibility of the postprandial glycemic response are assumed in this procedure as the amount of CHO and/or the preprandial glycemia increase the insulin dose rises linearly, whereas it is reduced proportionally to the insulin onboard. If this model were valid, the calculated insulin dose would result in similar postprandial glycemic response independent of the ingested CHO and preprandial glucose. Our results indicate that the assumption of linearity is only true regarding the amount of CHO of the meal. In fact, the *tBolus* postprandial glycemic control was independent of the CHO of the meal under both outpatient and inpatient conditions (Tables 1 and 3).

On the other hand, higher preprandial glucose appeared to be predictive of higher postprandial glucose, and preprandial glycemia explained about 50% of the observed variability (Table 3, outpatient and *tBolus* inpatient studies). One possible explanation of our finding could be the nonlinearity of the correction factor along the whole clinical range of insulin dose and PG. However, correction insulin dose is usually small and seldom greater than 10–15% of the total daily dose. Therefore, nonlinearity of insulin action per se hardly explains the effect of preprandial glucose. Additionally, this effect persisted also in the inpatient study despite the fact that very similar preprandial PG concentrations were ensured through insulin feedback (Table 3, *tBolus* column). A more suitable explanation is that the different preprandial glucose level is representative of different internal states of the patient, likely due to different degrees of insulinization or insulin sensitivity not being effectively compensated by the correction factor. In contrast, when the *iBolus* was administered the correlation between preprandial glucose and postprandial glycemia disappeared. This might be due to the greater complexity of the models used for the individualization of the treatment, with the *iBolus* providing better compensation for those variables represented by preprandial glucose. Nevertheless, neither glycemic control nor glycemic variability benefited from this feature of the *iBolus*, likely because of the poor reproducibility of postprandial glucose response originated by factors not represented in the model (nonmodeled dynamics).

The issue of glycemic variability deserves special attention. Variability is usually attributed to poor reproducibility of insulin absorption,[24] day-to-day variations of insulin sensitivity, inaccurate estimation of the CHO content of the meal, different meal composition,[20–22] and mistakes in insulin administration. Our data from outpatient CGM showed that mean variability of day-to-day intra-individual postprandial glycemic response was greater than 100% (CV near to 30%) despite theoretically standardized conditions. Part of the outpatient glycemic variability may be explained by modest differences in the glycemic index of the meals consumed at home (median glycemic index, 48; range, 42–60),[21,22] slightly different preprandial glycemia, and inaccurate glucose estimations from the CGM devices.

However, in the inpatient study all those factors were controlled before administration of either the *iBolus* or the *tBolus*, and, under these conditions, clinically significant differences in the insulin dose using different strategies (30% greater with the *iBolus* compared with the *tBolus* [see Tables 1 and 2]) achieved similar glycemic control (measured as plasma, not interstitial, postprandial glucose concentrations). In this regard, a recent study by Pańkowska et al.[25] investigated the effect of considering proteins and fats on postprandial glucose. Results demonstrated lower postprandial glucose with greater insulin dose but with higher variability (from their data a blood glucose SD of 45–90 mg/dL can be figured out). However, preprandial blood glucose was greater in the group receiving less insulin, making it difficult to perform a fair comparison with our study. Moreover, Pańkowska et al.[25] adopted a parallel design, preventing calculation of the intra-individual glucose response variability induced by different insulin doses. In contrast, in the present study the glycemic response to the same meal was not different despite the greater *iBolus* insulin dose. At the individual level, we observed nonsense responses, with the greater insulin dose resulting in higher postprandial glucose as well as the lower insulin dose achieving lower glycemic values. This must be regarded as "unexplained" variability, which makes it very difficult to control postprandial glucose response, whatever the model used for insulin dosing: the classical multiple regression model currently implemented in clinical practice, or new proposals.

In conclusion, theoretical feasibility of CGM-based insulin administration has been demonstrated in CSII-treated patients with T1DM. However, high intrasubject variability accounts for the greatest part of unpredictability of postprandial glycemic control and remains a barrier for the implementation of more effective insulin treatments. Differences in glucose responses to the same meal may be partially explained by differences in the preprandial metabolic status of the subject, as represented by premeal glucose concentrations. However, the major part of variability still remains unexplained, and its determinants should be investigated and integrated into new strategies for safer and more efficient insulin administration. Our method of insulin dosing based on the SIVIA algorithm, which allows for consideration of uncertainty in the

postprandial glucose response, is a forward step in prandial insulin calculation. When determinants of variability are known, they could be easily incorporated in the algorithm as interval parameters aiming at more robust insulin dosing according to the individual patient model. However, obtaining individualized models of postprandial glucose response is still too complex and must be simplified before CGM-based bolus advisors are introduced for large-scale validation studies.

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Author Disclosure Statement

No competing financial interests exist. P.R. contributed to the study concept and design, wrote the study protocol, performed meal tests, researched and analyzed the data, and wrote and edited the manuscript. F.J.A-B. contributed to the study concept and design and reviewed the study protocol and the manuscript. A.L. and A.R. researched and analyzed the data and reviewed the manuscript. J.F.A. supervised the protocol development and the research, contributed to the discussion, and reviewed the manuscript. J.V. contributed to the study concept and design and reviewed the study protocol and the manuscript. J.B. contributed to the study concept and design, supervised the protocol development and the research, analyzed the data, contributed to the discussion, and wrote and reviewed the manuscript. All authors are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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