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Assessment of optimal insulin administration timing for standard carbohydrates-rich meals using continuous glucose monitoring in children with type 1 diabetes: A cross-over randomized study

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ABSTRACT

Aims/Introduction: The present study was an assessment of postprandial glucose concentration after carbohydrates-rich meals using continuous glucose monitoring in 30 children with type 1 diabetes treated using continuous subcutaneous insulin infusion with a rapid-acting insulin analog.

Materials and Methods: Over a period of 3 days, participants administered simple boluses with different delay times between insulin administration and the beginning of carbohydrates-rich meal consumption (meal no. 1 containing 197 kcal, no. 2 containing 247 kcal and meal no. 3 containing 323 kcal; containing practically no protein and fat). In the present cross-over randomized study, we analyzed the average glucose concentration profiles in 5-min intervals, mean glucose at insulin administration, mean glucose after 120 and 180 min, mean and peak glucose, glucose peak time, areas under the glucose and glucose increase curves, and time period lengths with glucose <50, 70 mg/dL, and >140 and 200 mg/dL.

Results: For test meals at 20-min versus 0-min delay time, the study exposed a longer median time period to reach peak glucose (95 vs 65 min, $P = 0.01$) after meals. A tendency to the lowest peak and mean glucose, and the longest time with glucose within a normal range was observed in patients who administered bolus insulin 20 min before a meal.

Conclusions: For carbohydrates-rich meals, administration of a proper dose of a rapid-acting insulin analog is crucial. The influence of rapid-acting insulin analog administration timing seems to be of minor importance in comparison with correct insulin dose adjustment; however, a tendency to achieve more balanced glucose profiles was found in a group who administered insulin 20 min before a meal.

INTRODUCTION

Continuous subcutaneous insulin infusion is becoming a common diabetes mellitus therapy model, especially for children. Insulin pump diabetes mellitus therapy, by using different types of boluses, potentially enables insulin dosage resulting in close to physiological postprandial glucose control. However, it has still not been determined what is the best way of using rapid-acting insulin analogs administration to cover carbohydrates-rich meals. There are several studies about this topic[1–11], but the observations presented are often contradictory and do not lead to clear conclusions. In addition, among the multiple studies assessing glucose profiles, only several fingertip glucose measurements were used. Today, continuous glucose monitoring

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(CGM) systems are available, permitting more precise evaluation of the dynamics of glucose changes. These devices allow a strict registration of both postprandial and daily glucose concentration profiles.

The aim of the present study was to assess the optimal insulin administration timing for standard carbohydrates-rich meals using CGM in children with type 1 diabetes treated using continuous subcutaneous insulin infusion.

METHODS

Participants

The present study was carried out in 2009–2010 in the regional Diabetes Outpatients Clinic of Upper Silesia Child Health Center in Katowice, Poland. Patients fulfilling the inclusion and exclusion criteria presented in Table 1 were invited.

Considering the study protocol, the cooperation of patients and their parents was crucial. Often patients did not agree to participate, with their decision motivated by inconvenient and long-lasting monitoring, diet restrictions, and the necessity of the next visit after the monitoring period.

The study group consisted of 30 children with type 1 diabetes mellitus, treated with continuous subcutaneous insulin infusion (rapid-acting insulin analog), after a remission period, aged 4–17 years (9 boys, 21 girls; Table 2).

Participants were well metabolically controlled. The median glycated hemoglobin values were 6.5% (48 mmol/mol) for girls and 6.3% (45 mmol/mol) for boys, and for 78% of girls and 86% of boys the median glycated hemoglobin value was <7% (53 mmol/mol). The children were no longer in the remission period – the mean diabetes duration time was 5.48 ± 3.01 years for girls and 3.7 ± 2.61 years for boys. The average daily insulin requirement was 0.79 ± 0.17 U/kg/day for girls and 0.8 ± 0.23 U/kg/day for boys. The participants' physical characteristics corresponded to the physical characteristics of the participants' healthy peers: the standard deviation scores for body mass, height, and body mass index for both girls and boys were approximately 100. Participants were treated with rapid-acting insulin analogs Lispro (Humalog®; Eli Lilly and Company, Indianapolis, IN, USA) or Aspart (NovoRapid®; Novo Nordisk A/S, Bagsvaerd, Denmark). No particular analysis depending on insulin used was carried out.

Table 1 | Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Acceptance by patients and their parents	Lack of cooperation of the patient
Insulin pump therapy for at least 3 months	Coexistent conditions (celiac disease and other absorption disorders, thyroid gland and other endocrine disorders)
Daily insulin requirement >0.5 U/kg/24 h	
Diabetes mellitus lasting >1 year	Acute infections, vomiting, diarrhea
Four main meals nourishment regimen	Intensive physical exercise during CGM
Good metabolic control, HbA_{1c} <7.5% (58 mmol/mol)	
Rapid-acting insulin analog therapy	

CGM, continuous glucose monitoring; HbA_{1c}, glycated hemoglobin.

Methods of Research

Study Protocol

The study was designed in a cross-over model with randomization without a control group. Each of the groups analyzed consisted of the same participants.

In patients selected for the study, basal insulin flows and meal insulin doses were adjusted during their hospital stay preceding the exact measurements. Then, CGM using CGMS® (19 patients; Medtronic, Minneapolis, MN, USA) or REAL-Time® (11 patients; Medtronic) began.

The participants consumed test meals composed by a dietician. During the three following mornings, they ate breakfasts rich in simple carbohydrates, in which the energy derived from carbohydrates to energy derived from fat and protein ratio was approximately 2:1. One protein and fat exchange unit was defined as 100 kcal derived from protein or fat (Table 3).

For test meals rich in carbohydrates, the same insulin doses in simple boluses were administered, with different delay times between bolus administration and the moment of meal consumption beginning: (i) insulin administered at the moment of meal beginning (0'); (ii) insulin administered 10 min before the meal (10'); and (iii) insulin administered 20 min before the meal (20'). The order of the method of insulin administration was chosen randomly.

Participants were asked not to consume any meals during the analysis time, for at least 3 h. They were also asked to stop monitoring and take glucose in case of hypoglycemia <70 mg/dL, or take a corrected insulin dose in case of hyperglycemia >200 mg/dL. Patients and their parents did not report any side-effects of the study.

CGM Systems Used

Continuous glucose measurement was carried out with two different devices: Medtronic CGMS® or Medtronic REAL-Time®. The REAL-Time® system was used for patients treated with an integrated Medtronic Paradigm® 722 insulin pump. In patients treated with different pumps (Medtronic Paradigm® 712, 715 or Accu-Chek Spirit®), monitoring was carried out with a CGMS® device.

The CGMS® system consists of a portable monitor connected with a wire to an enzymatic electrode placed in subcutaneous tissue. Enzymatic glucose breakdown generates a current, which is measured, and mean values are stored every 5 min. The system requires entering the fingertip blood

Table 2 | Study group characteristics

Parameter	Girls	Boys	*P*
n	21	9	
Age (years)	13.86 ± 2.77 (12.6–15.12)	12.07 ± 3.10 (9.68–14.46)	NS
Body mass (kg)	49.57 ± 13.12 (43.6–55.54)	44 ± 16.22 (41.53–46.47)	NS
Body mass SDS	105.33 ± 16.03 (98.03–112.63)	101.92 ± 18.90 (97.4–106.44)	NS
Height (cm)	161 [148.5–170]	152.5 [134.75–171.5]	NS
Height SDS	100.86 ± 4.26 (98.92–102.8)	100.73 ± 4.13 (97.56–103.9)	NS
BMI (kg/m^2)	19.4 ± 2.91 (18.08–20.72)	18.23 ± 2.69 (16.16–20.3)	NS
BMI SDS	102.63 ± 11.00 (97.63–107.63)	100.75 ± 12.37 (91.24–110.26)	NS
Diabetes duration (years)	5.48 ± 3.01 (4.11–6.85)	3.7 ± 2.61 (1.69–5.71)	NS
HbA_{1c}, % (mmol/mol)	6.5 (48) [6.125 (43); 6.8 (51)]	6.3 (45) [5.65 (38); 6.9 (52)]	NS
Insulin requirement (U/24 h)	40 (27–50)	26 (18–60)	NS
Insulin requirement (U/kg/24 h)	0.79 ± 0.17 (0.71–0.87)	0.8 ± 0.23 (0.63–0.97)	NS
Percentage of participants with HbA_{1c} <7%, 53 mmol/mol (%)	86%	78%	NS

Data presented as the mean ± standard deviation (95% confidence interval)/median [quartiles 25–75%]. HbA_{1c}, glycated hemoglobin; NS, not significant; SDS, standard deviation score.

Table 3 | Meals composition and caloric value

No.	2% fat milk, g (kcal)	Cereal flakes, g (kcal)	Total caloric value (kcal)	No. carbohydrate exchange units (kcal)	No. protein and fat exchange units (kcal)
1	200 (102)	26 (95)	197	3 (~120)	0.7 (~70)
2	200 (102)	40 (145)	247	4 (~160)	0.8 (~80)
3	300 (153)	47 (170)	323	5 (~200)	1 (~100)

glucose level at least twice daily (calibration). After monitoring is finished, dedicated PC software is used for calculation of subcutaneous tissue glucose concentrations[12]. The REAL-Time® system is a modernized version of the CGMS® system. It uses the same electrodes and also requires calibrations, but allows a real-time glucose concentration presentation on an LCD display.

CGS systems reliability and precision was confirmed in multiple studies regarding CGMS®[13,14], RealTime®[15] and other available systems[14,16]. To obtain the best postprandial glucose profiles reliability, according to the manufacturer's recommendations, the analyzed profiles were closed between two calibrations: first at the insulin administration time and the other after 4–5 h for carbohydrates-rich meals, and after 10–11 h for fat and protein rich meals. In a previous study, a delay in changes in glucose concentration of subcutaneous tissue in comparison with blood of approximately 6.7 ± 5.1 min was described[17].

Calibration values were measured with personal fingertip glucose meters, mostly with Accu-Chek Go® and Optium Xido®. No further analysis was carried out.

The study was accepted by the bioethical committee of Medical University of Silesia, Katowice, Poland, and it conforms to the provisions of the Declaration of Helsinki.

Statistical Analysis

The time periods of CGM recording from insulin administration to 3 h after meal beginning divided in 5-min intervals were analyzed.

Recordings were divided according to the method of insulin administration into groups as described before.

Mean glucose profiles G_x (where x represents a 1 min since the moment the meal began) were calculated in 5-min intervals during the time periods analyzed (36, 38 and 40 measurement points in groups 0', 10' and 20').

The mean glucose concentrations at the time of insulin administration and when monitoring began (G_{start}) were calculated (for groups 0', 10' and 20' respectively $G_{start} = G_0$, $G_{start} = G_{-10}$, $G_{start} = G_{-20}$). Participants started to eat at G_0.

For every group, the subgroups examined were defined based on the glucose concentration value at the time of glucose administration, 120 min after the meal began (G_{120}) and at the time the monitoring ended. For time G_{start} and glucose at the end of monitoring, the following subgroups were created: hypoglycemia (<70 mg/dL), normoglycemia (70–110 mg/dL) and hyperglycemia (>110 mg/dL). For glucose G_{120}, the following subgroups were created: hypoglycemia (<70 mg/dL), normoglycemia (70–140 mg/dL) and hyperglycemia (>140 mg/dL).

The mean glucose rise profiles R_x according to formula: $R_x = G_x - G_{start}$ were calculated, where R_x represents an increase of glucose concentration in minute x after the meal begins, G_x represents glucose concentration in minute x after the meal begins and G_{start} represents glucose concentration at the time of insulin administration.

The peak glucose values (G_{max}), ratios of peak glucose to glucose 120 min after meal beginning (G_{max}/G_{120}), time from meal beginning after which peak glucose appeared (T_{max}), mean glucose during analyzed time period (G_m), mean glucose rise during analyzed time period (R_m), glucose standard deviation during analyzed time period (G_{SD}), area under the glucose curve (A_G), area under the glucose rise curve (A_R), time of hypoglycemia <50 and 70 mg/dL ($T_{<50}$ and $T_{<70}$), respectively, and time of hyperglycemia >140 and 200 mg/dL ($T_{>140}$ and $T_{>200}$), respectively, were found. For every participant, differences between the areas under the glucose curves for every group's pair (Δ_{AG}), between the areas under the glucose rise curves for every group's pair (Δ_{AR}) and their mean values were calculated. For example, $\Delta_{AG\ (0'–10')}$ represents for a single patient a difference between the area under the glucose curve after glucose administration at the time a meal began, and the area under the glucose curve after glucose administration 10 min before a meal beginning time. Accumulative column tracings presenting the time ratio spent in different glucose ranges in studied groups were prepared: <50, 50–70, 70–140, 140–200 and >200 mg/dL, respectively ($\%T_{<50}$, $\%T_{50–70}$, $\%T_{70\text{-}140}$, $\%T_{140\text{-}200}$, $\%T_{>200}$). All registered meals were divided depending on the CGS system used (CGMS® vs REAL-Time®). Comparison analysis of all measured parameters in both groups was carried out. Features distribution was determined using the Shapiro–Wilk test. For every parameter, a comparison of mean values between studied groups using one-way variance analysis with the Holm–Sidak test or Kruskal–Wallis one-way variance analysis on ranks with the Dunn test was carried out, depending on features distribution. Analysis results were considered significant when the *P*-value was <0.05.

Normal Glucose Ranges

In the present study, normal glucose values according to World Health Organization and International Diabetes Federation definition[18] were used. Glucose concentrations at the beginning and at the end of the monitoring period were considered fasting, thus normal glucose was between 70 and 110 mg/dL. For all meals, the normal glucose values after 120 min from the beginning of the meal were between 70 and 140 mg/dL.

RESULTS

Comparison of Values Obtained with Two Different CGM Systems

The differences between the mean values obtained with both systems were significant for three out of 60 analyzed parameters. CGMS® recordings showed longer lasting periods of hypoglycemia <70 mg/dL, and higher ratios of glucose levels <50 mg/dL and in the range of 50–70 mg/dL (Table 4).

These findings were probably caused by the use of different algorithms for glucose calculation, and suggest lower sensitivity to hypoglycemia in the case of the RealTime® system, but both devices are considered reliable[13,15]. The differences between systems do not have an influence on the differences between the mean values of the parameters in the study groups, because of the cross-over study model. Every group consisted of recordings of the same patients, so the distribution of the monitoring systems was identical for every compared pair of groups.

Analysis of Meal Size and Insulin Doses

The participants could choose one of three sizes of carbohydrates-rich meals, containing practically no protein and fat (Table 3). In total, 87 postprandial glucose profiles were analyzed. Meal no. 3, containing 323 kcal, was chosen most frequently – 52 times. Meals no. 1 (197 kcal) and no. 2 (247 kcal) were chosen nine and 26 times, respectively. The mean insulin dose administered was 7.96 ± 3.75 U (95% confidence interval 7.88–8.04). The mean insulin per carbohydrates exchange unit ratio was 1.77 ± 0.74 U (95% confidence interval 1.61–1.93).

Glucose Profiles Analysis

One recording was excluded from analysis from groups 0', 10' and 20' because of poor technical condition. Time of peak glucose concentration (T_{max}) was considered to be the time period from beginning the meal to the moment when the highest glucose level appeared during the analyzed time period. In some cases, a continuous glucose rise or drop during the whole analyzed period was observed with no local maximum. Arbitrarily, in such cases all the recordings were considered, where peak registered glucose was found during the first or last 10 min of the period analyzed. These cases were excluded from further T_{max} analysis (7, 5 and 6 cases in groups 0', 10' and 20', respectively).

Despite good metabolic control, the patients' motivation, and the will of the patients and their parents to cooperate, the median glucose concentrations at the start of monitoring, before the first daily meal, in two out of three groups examined slightly exceeded the normal ranges (in groups 0', 10' and 20',

Table 4 | Differences between parameters measured with different continuous glucose monitoring systems

Parameter	CGMS®	REAL-Time®	*P*
n	19	11	
$T_{<70}$ (min)	30 (0–75)	0 (0–5)	0.016
$\%T_{<50}$ (%)	0 (0–0.016)	0 (0–0)	0.040
$\%T_{50–70}$ (%)	0.082 (0–0.238)	0 (0–0.004)	0.008

Data presented as median (quartiles 25–75%). $\%T_{<50}$, time ratio spent in <50 mg/dL; $\%T_{50–70}$, time ratio spent in <50 and 70 mg/dL; $T_{<70}$, time of hypoglycemia <70 mg/dL.

respectively, 115, 118 and 106 mg/dL); and in two groups (0' and 10'), hyperglycemia was found in over half of the participants. Hypoglycemia in this period was quite rare in groups 0', 10' and 20', respectively; 2, 3 and no participants were affected (6.9, 10.3 and 0% of children examined, respectively; Table 5). The differences were not significant.

The median glucose 2 h after commencing a meal was on the border of normal values, and the mean glucose rise varied from 11.93 ± 47.85 in group 0' to 21.17 ± 52.44 in group 10'. Ratios of participants with normal glucose concentrations varied from 31% in group 10' to 58.6% in group 20'. Several participants sustained mild hypoglycemia <70 mg/dL (2, 5 and 3 cases in groups 0', 10' and 20', respectively). All of these were mild, registered only in CGM recording and did not require glucose tablets. Often hypoglycemia occurred during only one monitoring day. The differences were not significant (Table 6).

The mean glucose after 120 min was within a normal range, and the ratios of participants in whom glucose concentrations were normal were close to these from the beginning of monitoring.

Every day, participants were administered equal insulin doses, so glucose concentration decreases were probably not caused by overdosing.

Glucose concentrations after 180 min were comparable to initial glucose concentrations, and usually <10 mg/dL in group 20' to 23 mg/dL in group 0'. Only one group (20') showed glucose concentrations within the normal range for the majority of participants. Hypoglycemia at the end of the monitoring period was most frequent in group 0' (11 participants, 37.9%), and was rarest in group 20' (5 participants, 17.3%). Hyperglycemia after 180 min was most frequent in group 10' (13 participants, 44.8%). The differences were not significant (Table 7).

There were no significant differences in profiles of postprandial glucose concentration and postprandial glucose rise in any of the points analyzed (Figures 1,2).

Peak glucose concentrations occurred after 65 min in group 0', after 70 min in group 10' and after 95 min in group 20'. The difference between groups 0' and 20' was significant. Despite a lack of significance, a tendency to lower the peak and mean glucose in group 20' was observed with a small rate of hypoglycemia after 120 min, and the smallest rate after 180 min. Peak glucose concentrations were higher in comparison with glucose after 120 min, from 19% in group 20' to 41% in group 0'. The shortest time of hyperglycemia >140 mg/dL was found in group 20' (45 min in group 20' vs 90 min in group 0'). Hypoglycemia was incidental. The median time of hypoglycemia <70 mg/dL was 5 min in groups 0' and 10', and 0 min in group 20'. Hypoglycemia <50 mg/dL did not occur in any of the groups. The highest value of glucose standard variation was observed in group 20', which might suggest the highest variability and least stable glucose profile in this group. Besides the time to peak glucose concentration, other differences were not significant (Tables 8,9).

Table 5 | Glucose concentrations before meal

Parameter	Group			*P*
	0′	10′	20′	
n	29	29	29	
Initial glucose (mg/dL)	115 [88–150]	118 [104–132]	106 [92–137]	NS
Hypoglycemia <70 mg/dL (*n*)	2 (6.9%)	3 (10.3%)	0 (0%)	NS
Normoglycemia 70–110 mg/dL (*n*)	12 (41.4%)	8 (27.6%)	16 (55.2%)	NS
Hyperglycemia >110 mg/dL (*n*)	15 (51.7%)	18 (62.1%)	13 (44.8%)	NS

Data presented as *n* (percentage of whole group), median [quartiles 25–75%]. NS, not significant.

Table 6 | Postprandial glucose concentration after 120 min

Parameter	Group			*P*
	0′	10′	20′	
n	29	29	29	
G_{120} (mg/dL)	132.10 ± 44.81 [8.32]	139.31 ± 63.26 [11.75]	133.97 ± 64.72 [12.02]	NS
$G_{120} - G_{start} = R_{120}$ (mg/dL)	11.93 ± 47.85 [8.89]	21.17 ± 52.44 [9.74]	20.31 ± 65.36 [12.14]	NS
Hypoglycemia <70 mg/dL (*n*)	2 (6.9%)	5 (17.3%)	3 (10.4%)	NS
Normoglycemia 70–140 mg/dL (*n*)	15 (51.7%)	9 (31%)	17 (58.6%)	NS
Hyperglycemia >140 mg/dL (*n*)	12 (41.4%)	15 (51.7%)	9 (31%)	NS

Data presented as *n*, mean ± standard deviation [standard error of the mean]. G_{120}, glucose concentration 120 min after the meal began; G_{start}, glucose when monitoring began; NS, not significant; R_{120}, glucose rise after 120 min.

Table 7 | Comparison of initial minute postprandial glucose concentrations and after 180 min

Parameter	Group			*P*
	0′	10′	20′	
n	29	29	29	
G_{180} (mg/dL)	74 [61–110]	106 [66–140]	98 [71–120]	NS
$G_{180} - G_{start} = R_{180}$ (mg/dL)	−23 [−71–0]	−16 [−39–13]	−10 [−38–14]	NS
$\frac{G_{180}}{G_{start}}$ (%)	74.53 [49.44–99.23]	85.46 [64.01–109.74]	90.74 [66.35–115.6]	NS
Hypoglycemia <70 mg/dL (*n*)	11 (37.9%)	9 (31%)	5 (17.3%)	NS
Normoglycemia 70–110 mg/dL (*n*)	10 (34.5%)	7 (24.2%)	15 (51.7%)	NS
Hyperglycemia >110 mg/dL (*n*)	8 (27.6%)	13 (44.8%)	9 (31%)	NS

Date presented as the median [quartiles 25–75%]. G_{180}, glucose concentration 180 min after the meal began; G_{start}, glucose when monitoring began; NS, not significant; R_{180}, glucose rise after 180 min.

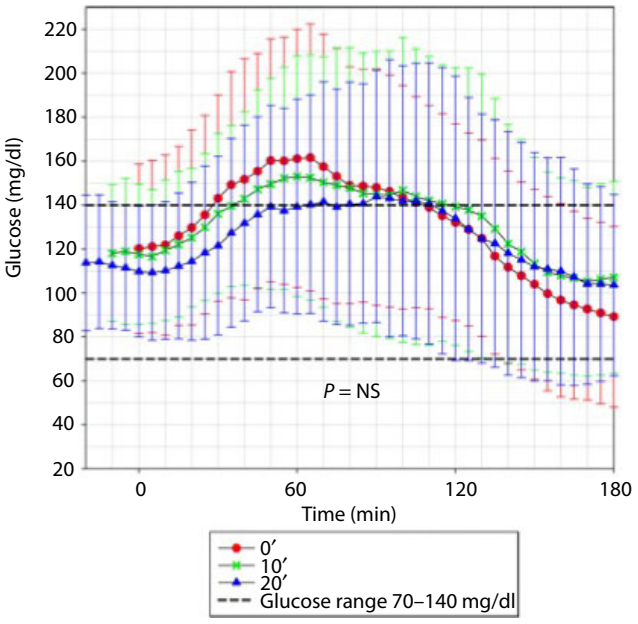

Figure 1 | Profile of mean postprandial glucose concentrations (dots, mean values; whiskers, standard deviation).

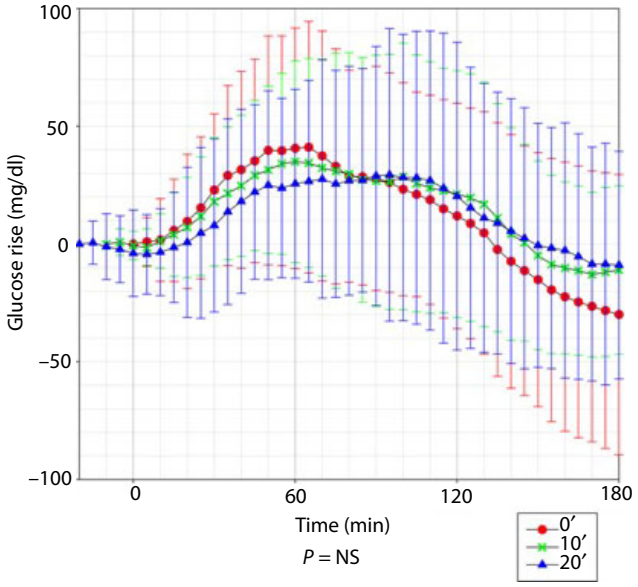

Figure 2 | Profile of mean postprandial glucose concentration rises (dots, mean values; whiskers, standard deviation).

During monitoring, short time duration ratios of hypoglycemia <50 mg/dL (from 2.7% in group 10', to 3.1% in group 0'), glucose concentration in the range of 50–70 mg/dL (from 6.7% in group 20', to 10% in group 10') and hyperglycemia >200 mg/dL (from 8.6% in group 20', to 11.8% in group 10') were found. During monitoring, time glucose concentrations were most frequently within the normal range (44.2%, 48.2% and 57.1% in groups 0', 10' and 20', respectively), and less frequently within the hyperglycemic range of 140–200 mg/dL (32.6%, 27.2% and 24.8% in groups 0', 10' and 20', respectively). The differences were not significant, but the shortest periods of hypoglycemia and hyperglycemia were observed in group 20', and time spent within the normal glucose range was the longest (Table 10).

DISCUSSION

Compared with the multitude of studies investigating the influence of high-protein and high-fat meals, there are fewer studies available regarding the selection of the best time delay between insulin administration and the beginning of carbohydrates-rich meal consumption[1–11,19,20]. Conclusions are incoherent and do not clearly show the best timing. The authors of some studies recommend insulin administration directly before a meal[4,5] or 15–30 min earlier[1–3,7,8], which results in decreased excursion rates[1–3,7–9] and longer glucose concentration time lasting within the normal range[1]. In two studies with larger participant groups (76 and 47 participants, respectively), no visible advantage of insulin administration before a meal was found[5,6]. The authors emphasized that, particularly in small children where it is often difficult to anticipate a size

Table 8 | Glucose concentration profiles description parameters

Parameter	Group			*P*
	0′ (1)	10′ (2)	20′ (3)	
G_{max} ($\frac{mg}{dL}$)	185.52 ± 48.52 [9.01]	176.03 ± 56.78 [10.54]	170.9 ± 56.72 [10.53]	NS
T_{max} ($\frac{mg}{dL}$)	65 [45–75]	70 [40–120]	95 [80–110]	1 vs 3 0.01 1 vs 2 NS 2 vs 3 NS
G_{max}/G_{120}	1.41 [1.24–1.57]	1.23 [1.04–1.62]	1.19 [1.06–1.84]	NS
G_m ($\frac{mg}{dL}$)	131.78 ± 37.69 [7.0]	131.69 ± 43.89 [8.15]	124.84 ± 40.49 [7.52]	NS
R_m ($\frac{mg}{dL}$)	11.6 ± 34.5 [6.41]	13.55 ± 30.27 [5.62]	11.19 ± 36.82 [6.84]	NS
G_{SD} ($\frac{mg}{dL}$)	35.04 ± 13.9 [2.58]	27.86 ± 13.07 [2.43]	28.17 ± 12.46 [2.31]	NS
A_G (5 × min × $\frac{mg}{dL}$)	4,791.24 ± 1,336.04 [248.1]	5,136 ± 1,711.87 [317.89]	5,055.62 ± 1,632.04 [303.06]	NS
A_R (5 × min × $\frac{mg}{dL}$)	411.76 ± 1,264.49 [234.81]	528.62 ± 1,180.7 [219.25]	450.03 ± 1,507.63 [279.96]	NS
$T_{<50}$ (min)	0 [0–0]	0 [0–0]	0 [0–0]	NS
$T_{<70}$ (min)	5 [0–30]	5 [0–40]	0 [0–20]	NS
$T_{>140}$ (min)	90 [30–115]	60 [0–140]	45 [0–110]	NS
$T_{>200}$ (min)	0 [0–30]	0 [0–40]	0 [0–5]	NS

Data presented as the mean ± standard deviation [standard error of the mean] or median [quartiles 25–75%]. G_{max}/G_{120}, ratio of peak glucose to glucose 120 min after the meal began; NS, not significant; $T_{<50}$, time of hypoglycemia <50 mg/dL; $T_{<70}$, time of hypoglycemia <70 mg/dL; $T_{<140}$, time of hypoglycemia <140 mg/dL; $T_{<200}$, time of hypoglycemia <200 mg/dL.

Table 9 | Mean differences between the area under glucose curves in pairs of groups for single participants, and between the area under glucose rise curves in pairs of groups for single participants

Parameter	Group			*P*
	0′–10′	0′–20′	10′–20′	
Δ_{AG} (5 × min × $\frac{mg}{dL}$)	−345.36 ± 1,633.28	−360.57 ± 1,749.51	38.59 ± 1,657.95	NS
Δ_{AR} (5 × min × $\frac{mg}{dL}$)	−35 [−1,018; 852]	12 [−1,001; 1,063]	385 [−257; 770]	NS

The mean ± standard deviation or median [quartiles 25–75%]. Δ_{AG}, the differences between the areas under the glucose curves for every group's pair; Δ_{AR}, the differences between the areas under the glucose rise curves for every group's pair.

Table 10 | Percentage of monitoring time spent within different glucose concentration ranges

Group	Glucose range (mg/dL)				
	<50	50–70	70–140	140–200	>200
0′	3.1%	9.1%	44.2%	32.6%	11.0%
10′	2.7%	10.0%	48.2%	27.2%	11.8%
20′	2.8%	6.7%	57.1%	24.8%	8.6%

of a meal a child will be willing to consume, insulin administration after a meal might be safer, because the risk of overdosing resulting in severe hypoglycemia is lower[6]. Another study investigating bolus strategies for low-glycemic index meals concluded that insulin administration 15 min before a meal brings better postprandial glucose control than insulin administration 15 min after a meal[21]. The authors of a study regarding type 1 diabetes obese adults did not find any significant advantages of insulin analog administration 5 min before or just before a meal, in comparison with postprandial dose[11]. In another study of obese type 2 diabetes adult patients, the authors showed that insulin analog administration before meals lowers postprandial hypoglycemia risk, but is also connected to a bigger body mass increase[10]. Even though the present study highlighted the benefits of injecting insulin before meal, Tamborlane *et al.*[22] found that most of the patients who were taking insulin bolus before meals were older, often unemployed with lower household income and engaged in less physical activity compared with those dosing bolus with or after meals. In half of the studies reviewed, study groups were small (at most 20 participants)[1,3,4,7], and in all the studies, postprandial glucose profiles were assessed with several point fingertip glucose measurements.

The mean glucose at 120 min in all groups stayed within the normal range, and ratios of participants in whom glucose stayed within the normal range were similar to those from the beginning of monitoring. In several participants, cases of asymptomatic hypoglycemia <70 mg/dL were registered in CGM recording.

Participants were asked not to take carry out intensive physical exercise during the monitoring period. Because registered mild hypoglycemia cases were asymptomatic and participants did not make detailed notes regarding physical activity, and other events, which might influence glucose concentration, hypoglycemia causes were not identified.

There were no significant differences in mean glucose rises at 120 min (Table 6), as shown in Table 7, and glucose median values after 180 min were close to the initial glucose median values at the end of monitoring in comparison with glucose at the start of monitoring, which was 10–23 mg/dL lower (depending on group), and from 74.53% to 90.74% of its value (depending on group). It shows an appropriate insulin dose selection for tested meals. The comparisons carried out showed a significantly shorter time to peak glucose in group 0' in comparison with group 20' (65 and 95 min, respectively). The peak glucose value in group 0' was 185.52 ± 48.52 mg/dL, and was higher in comparison with peak glucose in group 20', which was 170.9 ± 56.72 mg/dL, but the difference was not significant (Table 8). It is worth emphasizing that peak postprandial glucose in healthy individuals is much lower, and varies from 118.2 ± 13.4 mg/dL after lunch to 132.3 ± 16.7 mg/dL after breakfast[23]. Other parameters did not vary between the groups analyzed. In all groups, the time to peak glucose was <120 min, and was higher than glucose in the 120 min (Table 8). Taking into consideration particular features of glucose measurement in subcutaneous tissue that results in a delay in glucose changes in comparison with capillary blood[17], it is probable that peak glucose found in fingertip measurements would appear earlier by 6–7 min.

The lack of differences in hypoglycemia duration time suggests that insulin administration before a meal does not increase the risk of hypoglycemia, according to what was presented in studies published previously[1,2]. In the present study, contrary to the observations made in other studies[3,4,7,8], there were no clear visible advantages of a longer delay time between insulin administration and beginning of meal consumption. In particular, there was no significant decrease of hyperglycemia duration time, area under the glucose curve, mean glucose and glucose concentration variability (measured as glucose standard deviation). However, it should be emphasized that in group 20', a clear tendency was observed to the lowest peak and mean glucose, and the longest time with glucose within the normal range.

As shown in Table 9, the mean differences between areas under the glucose and glucose rise curves for single participants also did not significantly vary depending on timing. Similar observations were presented before by Schober and Urban[5,6].

Besides a single parameter (time to peak glucose), postprandial glucose profiles after carbohydrates-rich meals were not significantly influenced by the timing of insulin administration. The present results suggest that even though timing might have an influence on postprandial glucose, the delay time between insulin administration and meal consumption is not critical, and the administered insulin dose seems to be the most important parameter. However, beneficial tendencies observed in group 20' might encourage patients to administer insulin >12 min before carbohydrates-rich meal consumption.

In conclusion, the administration of a proper dose of a rapid-acting insulin analog is crucial for carbohydrates-rich meals. Also, the influence of the timing of rapid-acting insulin analog administration seems to be of minor importance in comparison with correct insulin dose adjustment. However, a tendency to achieve better balanced glucose profiles was found in a group who administered insulin 20 min before a meal.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Luijf YM, van Bon AC, Hoekstra JB, *et al.* Premeal injection of rapid- acting insulin reduces postprandial glycemic excursions in type 1 diabetes. *Diabetes Care* 2010; 33: 2152–2155.
2. Scaramuzza AE, Iafusco D, Santoro L, *et al.* Timing of bolus in children with type 1 diabetes using continuous subcutaneous insulin infusion (TiBoDi Study). *Diabetes Technol Ther* 2010; 12: 149–152.
3. Gredal C, Rosenfalck A, Dejgaard A, *et al.* Optimal dose and timing of insulin aspart to mimic first phase insulin response in patients with recently onset type 2 diabetes. *Diabetes Res Clin Pract* 2008; 80: 293–298.
4. Jungmann E. [Intensified insulin therapy of type 2 diabetes mellitus: pre- or postprandial injection of aspart insulin]). *Dtsch Med Wochenschr* 2005; 130: 1254–1257.
5. Danne T, Aman J, Schober E, *et al.* A comparison of postprandial and preprandial administration of insulin aspart in children and adolescents with type 1 diabetes. *Diabetes Care* 2003; 26: 2359–2364.
6. Florys B, Peczyńska J, Urban M. Ocena skuteczności humalogu stosowanego przed i po posiłku u młodzieży z cukrzycą typu 1. *Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw* 2001; 7: 37–44.
7. Rassam AG, Zeise TM, Burge MR, *et al.* Optimal administration of lispro insulin in hyperglycemic type 1 diabetes. *Diabetes Care* 1999; 22: 133–136.
8. Cobry E, McFann K, Messer L, *et al.* Timing of meal insulin boluses to achieve optimal postprandial glycemic control in patients with type 1 diabetes. *Diabetes Technol Ther* 2010; 12: 173–177.
9. Schernthaner G, Wein W, Shnawa N, *et al.* Preprandial vs. postprandial insulin lispro-a comparative crossover trial in patients with type 1 diabetes. *Diabet Med* 2004; 21: 279–284.

10. Ratner R, Wynne A, Nakhle S, *et al*. Influence of preprandial vs. postprandial insulin glulisine on weight and glycaemic control in patients initiating basal-bolus regimen for type 2 diabetes: a multicenter, randomized, parallel, open-label study (nct00135096). *Diabetes Obes Metab* 2011; 13: 1142–1148.
11. Jovanovic L, Giammattei J, Acquistapace M, *et al*. Efficacy comparison between preprandial and postprandial insulin aspart administration with dose adjustment for unpredictable meal size. *Clin Ther* 2004; 26: 1492–1497.
12. CGMS System Gold – How it works? Available from: http://www.medtronic-diabetes-me.com/Features-CGMS-System-Gold.html Accessed November 24, 2011.
13. The Diabetes Research in Children Network DirecNet Study Group. The accuracy of the CGMS in children with type 1 diabetes: results of the diabetes research in children network (DirecNet) accuracy study. *Diabetes Technol Ther* 2003; 5: 781–789.
14. Clarke WL, Anderson S, Farhy L, *et al*. Evaluating the clinical accuracy of two continuous glucose sensors using continuous glucose-error grid analysis. *Diabetes Care* 2005; 28: 2412–2417.
15. Mastrototaro J, Shin J, Marcus A, *et al*. The accuracy and efficacy of real-time continuous glucose monitoring sensor in patients with type 1 diabetes. *Diabetes Technol Ther* 2008; 10: 385–390.
16. Kovatchev B, Anderson S, Heinemann L, *et al*. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care* 2008; 31: 1160–1164.
17. Boyne MS, Silver DM, Kaplan J, *et al*. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes* 2003; 52: 2790–2794.
18. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Available from: http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/index.html Accessed November 24, 2011.
19. Neu A, Behret F, Braun R, *et al*. Higher glucose concentrations following protein- and fat-rich meals – the Tuebingen Grill Study: a pilot study in adolescents with type 1 diabetes. *Pediatr Diabetes* 2015; 16: 587–591.
20. Ralph Z, Guido F, Lutz H. Boluses in insulin therapy: a commentary. *J Diabetes Sci Technol* 2017; II: 165–171.
21. Bell KJ, Smart CE, Steil GM, *et al*. Impact of fat, protein and glycemic index of postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. *Diabetes Care* 2015; 38: 1008–1015.
22. Tamborlane WV, Pfeiffer KM, Brod M, *et al*. Understanding bolus insulin dose timing: the characteristics and experiences of people with diabetes who take bolus insulin. *Curr Med Res Opin* 2017; 33: 639–645.
23. Freckmann G, Hagenlocher S, Baumstark A, *et al*. Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals. *J Diabetes Sci Technol* 2007; 1: 695–703.