Correlation Between Amount of Carbohydrate in Mixed Meals and Insulin Delivery by Artificial Pancreas in Seven IDDM Subjects

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The effects of mixed meals containing varying amounts of carbohydrate (CHO) on blood glucose levels and insulin delivery by an artificial pancreas were studied in seven insulin-dependent diabetes mellitus subjects. Each patient received, at random over 3 consecutive days, three mixed meals containing 60, 80, and 140 g complex CHOs. There was a high and linear correlation between total amount of insulin delivered to restore blood glucose values and amount of CHO consumed: 12.1 ± 1.3 to 31.2 ± 5.2 U insulin were needed for 116 ± 16 to 198 ± 24 min. However, neither the time lapse between the beginning of meal intake and blood glucose increase nor the peaking time for blood glucose variation were significantly different between meals. We suggest that some of the data obtained in this study might be useful in programming an open-loop insulin-infusion system. *Diabetes Care* 12:427–29, 1989

It has been shown that integrated plasma insulin levels in healthy subjects and prandial insulin requirements in insulin-dependent diabetes mellitus (IDDM) patients increase proportionally to meal carbohydrate (CHO) content (1–3). In a previous study on IDDM subjects controlled by an artificial pancreas, we found a high and almost linear correlation between the total amount of insulin delivered by the device and the amount of CHO consumed in the range of 20–60 g; these meals were light snacks or small lunches and were far below the maximum consumption range of the subjects (4).

In in vitro models, it has been shown that adult human pancreatic islets increase their insulin secretion linearly when incubated with media containing 4–20 mM glucose (5). In another study on perifused fetal rat pancreases, the dose-response curve of insulin secretion to glucose (range 2–56 mM) suggested a sigmoidal response (6). Therefore, we decided to investigate the problem of correlation between meal size and insulin needs under higher and up to maximum stimulation, compatible with clinical situations.

MATERIALS AND METHODS

Subjects. Seven IDDM subjects were studied: mean ± SE age 43 ± 3 yr, body mass index 24 ± 2 kg/m^2, duration of diabetes 18 ± 3 yr, and daily subcutaneous insulin needs 39 ± 5 U/day. All were C-peptide negative (after intravenous glucagon stimulation). All subjects were fully informed of the experimental purpose of the investigation. The protocol was approved by the hospital ethical committee.

Meals. Each patient was tested on 3 consecutive days, with three test meals containing 60, 80, and 140 g CHO administered in a random order. All meals consisted of the same foodstuffs, i.e., rice, white bread, butter, lean ground beef, cheese, and fruit. Water was permitted but was not recorded. Table 1 gives the calorie and nutrient content of the meals. Each meal was eaten at 1300 in ~20 min after a 5-h fast.

Closed-loop regulation procedure. The procedure of closed-loop blood glucose control, with the use of a device constructed in our department, has been described elsewhere (7). The glucose oxidase method with a glucose analyzer was used as glucose sensor (YSI, Yellow Springs, OH).

Calculation and statistical analysis. Statistical methodology used analysis of variance and standard linear regression curve calculation. Results are given as means ± SE.

RESULTS

Figure 1 shows mean blood glucose and insulin infusion rate variations observed after the three mixed meals containing 60, 80, and 140 g CHO. Table 2 shows the numerical values characterizing blood glucose and insulin rate variations. The time lapses observed between beginning of meal intake and development of a significant (>10%) blood glucose increase above basal value (also corresponding to the beginning of insulin infusion above basal rate) were between 23 and 27 min and were not significantly different. However, peak blood glucose values were significantly higher ($P < .01$) and correlated positively ($r = .56$, $P < .01$; y [of blood glucose in mM] = $0.59x$ CHO [g] + 144.6) when CHO content of the meal increased (peaking time not significantly different). These peak values were recorded 53–68 min after the start of the meal. Integrated blood glucose increments above basal value (areas under the curves) were significantly different between the three types of meals

TABLE 1
Meal composition

	Meal 1	Meal 2	Meal 3
Carbohydrate (g)	60 (51)	80 (50)	140 (49)
Protein (g)	25 (21)	36 (21)	46 (15)
Fat (g)	14 (28)	19 (29)	42 (36)
Energy (kcal)	466	635	1122

Numbers in parentheses are percentages.

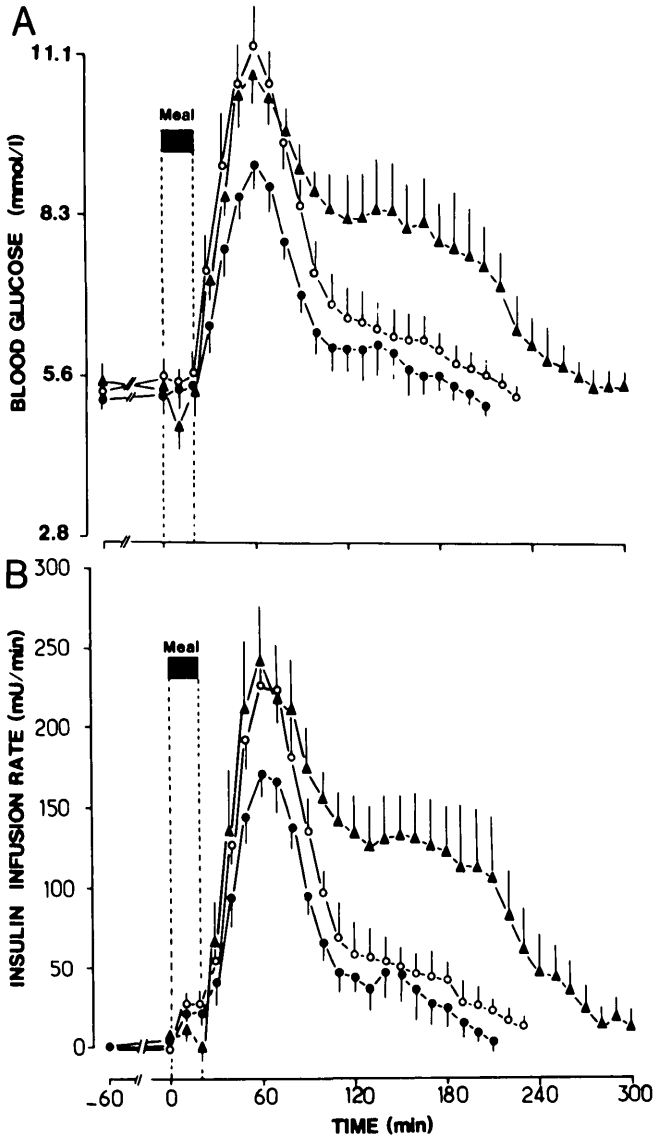

FIG. 1. *A*: mean blood glucose variations. *B*: mean insulin infusion rate variations delivered by artificial pancreas after 3 mixed meals containing 60 (●), 80 (○), and 140 (▲) g carbohydrate in 7 insulin-dependent diabetic patients. Values are means ± SE.

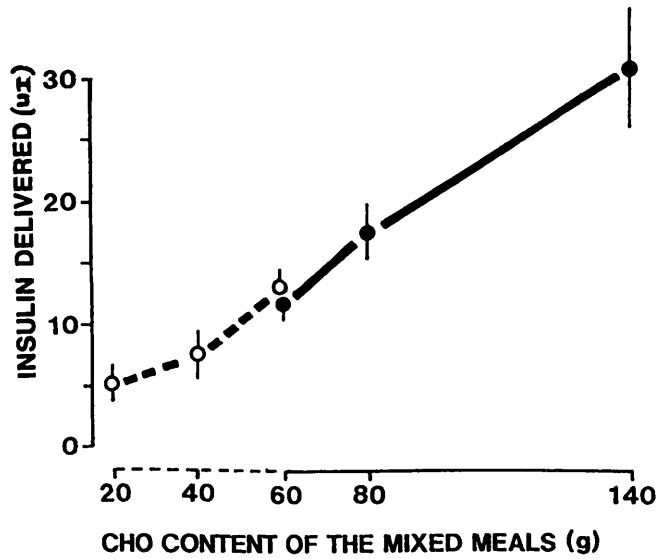

FIG. 2. Correlation between total amount of meal carbohydrate content and total amount of insulin needed to restore basal blood glucose values. Results observed in this study are indicated by (●) versus results from previous study (○) (4). Values are means ± SE.

($P < .01$) and linearly correlated to CHO intake ($r = .64$, $P < .01$; $y = 1.84x$ CHO + 75.0) (Fig. 2), whereas the greater the meal CHO content, the more blood glucose values increased and the longer blood glucose excursion above basal values was sustained (e.g., from ~2 h with 60-g CHO meal to >3 h with 140-g CHO meal; differences were significantly different, $P < .01$) (Table 2). The total amount of insulin needed to restore blood glucose levels to basal values was, respectively, 12.1 ± 1.3, 17.6 ± 2.2, and 31.2 ± 5.2 U for the 60-, 80-, and 140-g CHO meals with a linear correlation ($r = .70$, $P < .001$; y [of intravenous insulin] = 0.24x CHO − 1.9) (Fig. 2). No patient experienced a hypoglycemic attack beyond the period of data presentation (Fig. 1).

TABLE 2
Characteristics of blood glucose and insulin infusion-rate variations after intake of mixed meals containing 60, 80, and 140 g carbohydrate in seven IDDM subjects

	Carbohydrate (g)			
	60	80	140	*P*
Time lapse between beginning of meal intake and blood glucose increment (min)	26 ± 3	23 ± 3	27 ± 3	NS
Peak blood glucose values (mM)	9.5 ± 0.38	11.1 ± 0.66	12.0 ± 0.33	<.01
Peaking time for blood glucose variations (min)	53 ± 3	56 ± 2	68 ± 10	NS
Duration of blood glucose increment above starting value (min)	116 ± 16	150 ± 18	198 ± 24	<.01
Area under the curve for blood glucose variations (mM/min)	178 ± 18	232 ± 29	338 ± 42	<.01
Insulin needs for restoring basal value (U)	12.1 ± 1.3	17.6 ± 2.2	31.2 ± 5.2	<.001

Values are means ± SE.

DISCUSSION

In this study we tested the blood glucose response and insulin needs by an artificial pancreas with liberal CHO intake. The initial intake of 60 g was chosen to compare results with our previous study data (4); the upper dose of 140 g was considered as the most CHO-enriched meal a diabetic patient could reasonably eat, corresponding to an approximate daily intake of 400–450 g CHO/3500 cal. In fact, some patients in our study experienced some difficulties in finishing the 140-g CHO meal, which included 100 g of bread, 200 g of rice (cooked weight), a 150-g apple, and a 125-g apple compote sweetened with 20 g sucrose. Insulin needs after the 60-g CHO-enriched meal in our study were similar to those found 6 yr ago with a different apparatus programmed on different parameters, i.e., 12.1 ± 1.3 vs. 13.3 ± 1.5 U, respectively (Fig. 2; 4).

We were able to reproduce the results of our previous study because the same sources of starch were used on both occasions. If different sources of CHO were to be used, it can be assumed that different results would have been observed (8,9). Not only were insulin needs for the 60-g CHO-enriched meal very close, but the slopes of the two correlation curves were also grossly similar, allowing us to conclude that there is a linear correlation between meal CHO content and insulin needs from 40 to 140 g CHO (Fig. 2). From these results it appears that, at least at lunchtime, intravenous insulin needs are ~0.20–0.24 U/g CHO. These results are in accordance with those obtained by Mirouze et al. (10). In the same manner, Service et al. (1) have shown in normal subjects that as meal size increases, postprandial glycemia and insulin secretion increase proportionately. Similar results have been observed by the same group in IDDM subjects (3). The type of relationship observed in these clinical observations is in accordance with results observed in vitro because a linear correlation has also been observed at physiological glucose concentrations, with a plateau obtained only at high or extremely high glucose concentrations (5,6,11–13).

We conclude, that the linear correlation between meal CHO intake and insulin needs required to consume this meal remains valid even for CHO intake reaching the upper limit of what can be considered as tolerable in diabetic subjects. This type of result may help in programming open-loop systems by the intravenous route, the intraperitoneal route in which kinetics of resorption are close to those of the intravenous route, and the subcutaneous route (14–16).

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