Correlation Between the Nature and Amount of Carbohydrate in Meal Intake and Insulin Delivery by the Artificial Pancreas in 24 Insulin-dependent Diabetics

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SUMMARY

We have studied the effects of mixed meals and dextrose intake on blood glucose and insulin delivery by the artificial pancreas in 24 insulin-dependent diabetics. A group of 12 patients had 3 mixed meals containing at random 20, 40, and 60 g of complex carbohydrate along with protein and fat; another group of 12 diabetics, comparable in weight, age, and duration of diabetes, received at random 20, 40, and 60 g of dextrose.

Dextrose ingestion led to a higher initial blood glucose increase than did the mixed meal, but the duration of blood glucose increase lasted significantly longer after the mixed meal than after the dextrose load. The areas under the curves of hyperglycemia were not significantly different. There was a high (but not linear) correlation between the total amount of insulin delivered in order to restore initial blood glucose values and the amount of CHO consumed. There was no correlation with age, body weight, duration of diabetes, nor with the nature and order of administration of the CHO load; 5.1 ± 1.6 to 13.7 ± 2.1 units of insulin were needed for a period of 94 ± 11 to 132 ± 11 min. It is suggested that some of the data obtained in this study might be useful in the programming of an open-loop insulin infusion system. DIABETES *30*:101–105, February 1981.

The influence of orally ingested simple and complex carbohydrates with or without protein, fat, and dietary fibers on blood glucose, lipid, and hormone response has been extensively studied in normal and non-insulin-dependent diabetic subjects.[1–15] However, there are few studies in insulin-dependent diabetics.[16–20] This could be due to lack of reliable methodology for such patients. The artificial pancreas could help in solving this problem, as the response to a given meal can be precisely recorded and studied.

The aim of this work was to study the effects of usual mixed meals and oral dextrose loads on insulin delivery by the artificial pancreas in lean, insulin-dependent diabetics. The mixed meals, containing fixed amounts of complex carbohydrates, were made up of variable amounts of protein and fat. The meals were designed so as to fit the food habits of the patients in our country, and were similar to what they normally consume in the morning for breakfast or at noon for lunch. Dextrose was chosen as an indicator of the upper limits for insulin needs for a given amount of carbohydrate in a meal and also as representative of a type of food, i.e., refined sugars.

PATIENTS AND METHODS

Patients. Twenty-four long-term insulin-dependent diabetics, comparable in age, weight, height, duration of diabetes, and insulin dosage, and fully informed of the experimental nature of the investigation, were studied. Mean clinical data are given in Table 1.

Twelve patients were randomly assigned to the mixed meal protocol and the twelve others to the oral dextrose challenges.

Closed-loop regulation procedure. The last intermediate s.c. insulin was injected at least 16 h before starting the experiment. The artificial pancreas, built in our department as described elsewhere,[21,22] was connected to the patient between 7:00 a.m. and 7:30 a.m. Blood glucose values, initially high in every patient, were first brought down to normal values, between 3.7 and 5.5 mmol/L, and then maintained at this level for at least 1 h before starting the experiment. The parameters for programming the artificial pancreas[20,23,24] were the same in all patients and were not modified during

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TABLE 1
Clinical data for the 24 insulin-treated diabetic subjects

	Receiving mixed meals (N = 12)	Receiving dextrose meals (N = 12)	P
Age (yr)	34 ± 4	31 ± 5	NS
Duration of diabetes (yr)	7 ± 2	10 ± 2	NS
Weight (kg)	58 ± 2	58 ± 2	NS
Height (cm)	169 ± 2	165 ± 2	NS
Subcutaneous insulin dosage the day before the test (U/day)	49 ± 6	51 ± 5	NS

P = statistical significance and NS = not significant.
Values are means ± SEM.

the experiment. (MI = 300 mU/min, BI = 150 mg/dl, PI = 33, K1 = 100, and K2 = 10).

Meals. The dextrose challenges consisted in administering, on the same day to each patient of the assigned group, three oral loads in random order containing 20, 40, and 60 g of dextrose diluted in 300 ml of pure water and ingested in 10 min. The mixed meal protocol consisted in administering on the same day in random order three meals containing 20, 40, and 60 g of complex carbohydrates. These meals consisted of bread, butter, milk, one boiled egg, and coffee in the morning; bread, meat, a vegetable, and fruit for lunch; and bread, butter, and cheese for dinner, and were ingested in 15 min. The meals contained fixed amounts of carbohydrates but were not isocaloric; the fat and protein content varied depending upon the hour of day, in order to resemble a normal breakfast lunch or dinner. Table 2 gives the approximate carbohydrate, protein, and fat caloric content in these mixed meals. The first meal was eaten between 8:30 a.m. and 9:00 a.m., the second one at 1:00 p.m., and the last one at 6:00 p.m. Blood glucose levels ranging between 4.0 and 5.5 mmol/L were maintained between meals for at least 1 h. Patients sat on their beds or in armchairs throughout the experiment.

Calculations and statistical analysis. The random protocol was devised in such a manner that, in each group of 12 patients, 20 g of carbohydrate was taken by 4 patients for their first meal, by 4 other patients for their second meal, and by the last 4 patients for their third meal. The same rule was valid for 40- and 60-g CHO meals.

An excursion of 10% above the basal blood glucose (BG) value followed by sustained hyperglycemia was considered as the starting point for our calculation, and the ending point was considered to be the point at which the basal value was observed again.

The comparisons were made with a two-way analysis of variance taking into account the order of administration of the different CHO doses.

TABLE 2
Carbohydrate, protein, fat (in grams), and total calorie (in kcal) composition of the meals when taken as breakfast (first meal), at lunch (second meal), and dinner (third meal)

	20-g Carbohydrate meal	40-g CHO meal	60-g CHO meal
If taken as the FIRST meal			
Protein (g)	12	12	7
Fat (g)	6	6	15
Calories (kcal)	182	262	403
If taken as the SECOND meal			
Protein (g)	28	28	30
Fat (g)	16	30	15
Calories (kcal)	336	542	495
If taken as the THIRD meal			
Protein (g)	10	10	15
Fat (g)	18	21	15
Calories (kcal)	282	389	435

RESULTS

Blood glucose excursion above basal values. Figure 1 shows the mean blood glucose variations observed after the oral dextrose loads and after the mixed meals.

Table 3 gives the mean areas under the curves of blood glucose variation as an expression of the total excursion of blood glucose above basal values. Table 4 gives the mean values for duration of blood glucose increase above basal values (thus the duration of insulin infusion above basal rates). In terms of means, blood glucose increase was greater for a shorter period of time after dextrose loads than after mixed meals (Figure 1), but mean overall blood glucose increase, as assessed by measuring area under the curves of blood glucose variations (Table 3), was similar after dextrose and mixed meals. A positive dose-response effect was only observed for dextrose challenge ($P < 0.001$).

The mean duration of BG increases above basal values (Table 4 and Figure 1), corresponding to the total duration of high rate insulin infusion was significantly ($P < 0.01$) shorter after dextrose than after mixed meals. The influence of meal CHO content was significant between 40 and 60 g ($P < 0.05$).

The time delay between the beginning of meal intake and blood glucose increase, also corresponding to the begin-

FIGURE 1. Mean blood glucose variations observed after dextrose (N = 12, upper graph) and mixed meals (N = 12, lower graph) in insulin-dependent diabetics (N = 24) controlled by an artificial pancreas and receiving 20 g (triangle), 40 g (open circle) and 60 g (closed circle) of carbohydrate. Zero time is taken when first significant (10%) increase of blood glucose above basal value was observed. Values are mean ± SEM.

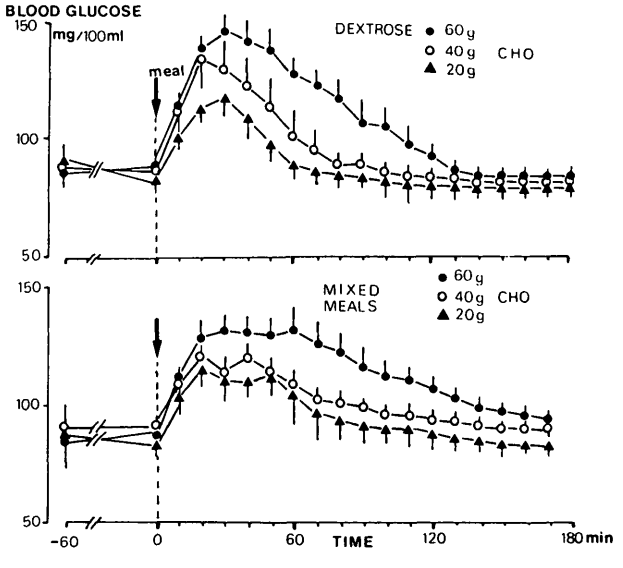


TABLE 3
Areas under the curves of blood glucose variations (arbitrary units, mean ± SEM)

Meal CHO content (g)	20	40	60	P
Nature of the meals				
Mixed meals	218 ± 73	201 ± 40	397 ± 70	NS
Dextrose loads	142 ± 19	216 ± 60	395 ± 38	*
P	NS	NS	NS	

P = statistical significance, NS = not significant, and * = P < 0.001.

TABLE 5
Time delay between the beginning of meal intake and blood glucose increase (corresponding to high-rate insulin delivery start, min ± SEM)

Meal CHO content (g)	20	40	60	P
Nature of the meals				
Mixed meals	19 ± 3	11 ± 2	12 ± 2	NS
Dextrose load	18 ± 2	17 ± 5	14 ± 2	NS
P	NS	NS	NS	

P = statistical significance, NS = not significant.

ning of high rate insulin infusion, was observed, in terms of means, between 11 and 19 min (Table 5). The absorption of a dextrose load did not seem to be quicker than for a mixed meal, the time delay between the beginning of meal ingestion and the first significant blood glucose increase was similar in both types of meals and also did not correlate with the meal CHO content.

Insulin delivery by the artificial pancreas. The insulin required to restore basal blood glucose values is shown in Figure 2 and Table 6. Blood glucose variations and, due to these variations, insulin delivery, was faster and greater after dextrose than after mixed meals. At 30 min 71 ± 7, 72 ± 5, and 45 ± 5% of the total amount of insulin needed were infused, respectively, after the 20-, 40-, and 60-g dextrose loads as compared with 50 ± 7, 61 ± 7, and 37 ± 6% after mixed meals.

The mean total amount of delivered insulin necessary to restore basal blood glucose values correlated highly with the amount of meal CHO content ($P < 0.01$), but was not different after dextrose and mixed meals (Table 6 and Figure 3). The correlation was not linear. The total amount of insulin delivered did not correlate with the order of meal administration nor with the amount of insulin injected subcutaneously nor with body weight in these lean patients.

DISCUSSION

Blood glucose variations of insulin-dependent diabetic subjects were studied after the ingestion of a variable amount of carbohydrate, either as complex carbohydrate in a mixed meal or as simple sugar (dextrose), and while controlled by the artificial pancreas. The amounts of insulin delivered by the device during these challenges were compared. The patients received the kind of food usually eaten at each particular time of day. The amounts of CHO, protein, fat, and dietary fiber composition were, thus, not the same in the morning, at noon, or in the evening.

TABLE 4
Duration of blood glucose increase above basal values and of insulin infusion above basal rates (min ± SEM)

Meal CHO content (g)	20	40	60	P
Nature of the meals				
Mixed meals	94 ± 11	95 ± 14	132 ± 11	*
Dextrose loads	67 ± 7	75 ± 6	109 ± 8	*
P	†	†	†	

P = statistical significance; * = P < 0.05 (comparison of 20 g and 40 g versus 60 g of meal CHO content), † = P < 0.01.

It should be noted that the overall blood glucose variations in these insulin-dependent patients, with the algorithms and mean parameters utilized in programming our artificial pancreas, remained withing the physiologic range as compared with blood glucose variations observed in nondiabetics after meals or after glucose tolerance tests.[6,7,17,19] In our study, as observed in normal subjects,[5,6] blood glucose increased to higher levels, but for a shorter period of time after the dextrose loads than after the mixed meals. Similarly, the overall kinetics of insulin secretion by the artificial pancreas was also comparable to those observed in peripheral veins in normal subjects[4–6,13,14] after a meal of dextrose.

We expected that, with the addition of fat, protein, and dietary fibers to the complex carbohydrate in the meals, blood glucose excursion would be less than after oral dextrose load, as observed in normal and in diabetic subjects.[25–27] We therefore expected a diminution of the insulin delivery by the artificial pancreas in the former situation. In fact, we observed that blood glucose excursion above basal value and insulin delivery by the artificial pancreas was delayed but not diminished on an overall basis. The presence of pro-

FIGURE 2. Mean insulin delivered every 10 min by the artificial pancreas after dextrose (N = 12, upper graph) and mixed meals (N = 12, lower graph) in the same patients (cf. Figure 1 for symbols).

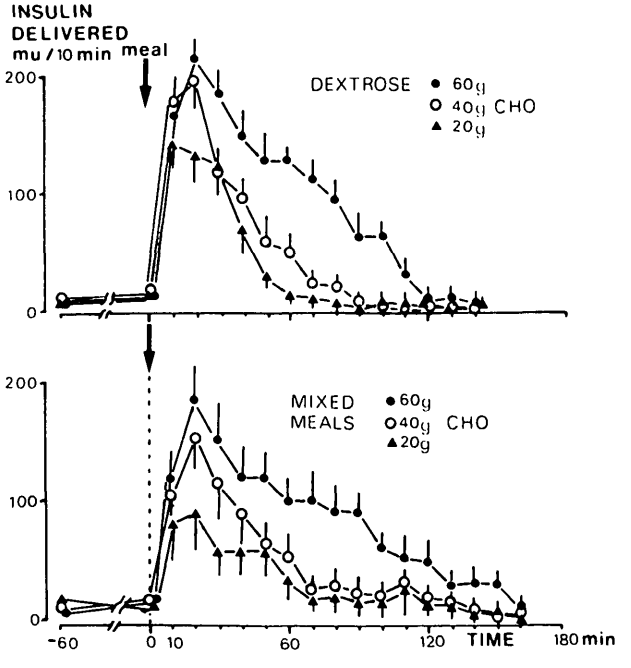


TABLE 6
Total amount of insulin delivered necessary to restore basal blood glucose values (in units, mean ± SEM)

Meal CHO content (g)	20	40	60	P
Nature of the meals				
Mixed meals	5.1 ± 1.6	7.6 ± 1.9	13.3 ± 1.5	*
Dextrose loads	5.6 ± 0.6	7.4 ± 1.5	13.7 ± 2.1	*
P	NS	NS	NS	

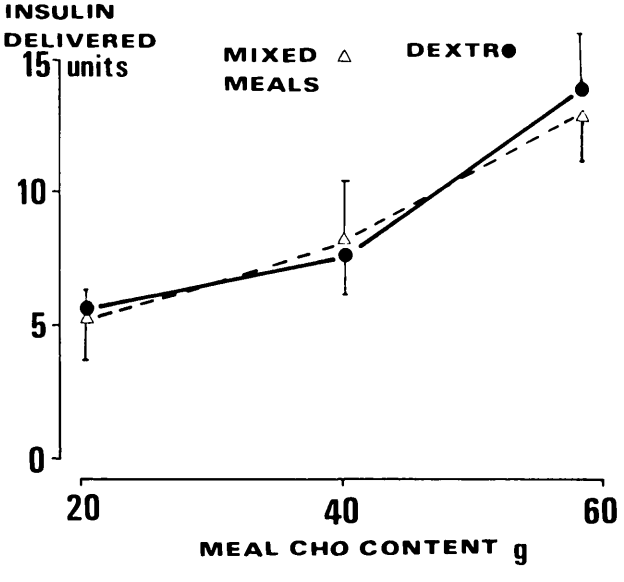
P = statistical significance, * = $P < 0.01$, NS = not significant.

tein, fat, and fibers mainly influence gastric emptying.[5,7,25] In our study the time delay before significant blood glucose increase after a meal was not shorter when the fat, protein, and fiber content was much higher, i.e., at lunch, than after breakfast or dinner. Surprisingly, no differences were observed for this parameter (time delay) either between mixed meal and dextrose loads, perhaps because of the relative hyperosmolarity of the dextrose solution ingested.

In our study the total amount of insulin infused by the artificial pancreas to restore basal blood glucose values did not differ, for a given amount of CHO, after a dextrose load and mixed meal even if insulin-infused kinetics differed. These results should be compared with the observation of Crapo, Olefsky, and Reaven[5,6] that mean areas under the curves of plasma insulin variations in normal subjects were comparable in response to dextrose, bread, and potatoes for an equivalent amount of CHO content.

Although it did not correlate with the nature of the carbohydrate ingested, the total amount of insulin needed for a meal correlated highly with the total CHO content of a meal, with a good subject-to-subject reproducibility; this correlation was not linear. Some previous studies have already reported a ratio between the total amount of insulin needed for a meal and the CHO content of the meal.[28,29] In the Mirouze study[29] this correlation was expressed as the number of units per g of CHO, and thus seemed to be linearly correlated to the amount of CHO absorbed. Irsigler and Kritz,[28] in long-term insulin infusion in 5 insulin-dependent diabetics, found a constant relationship in two patients between CHO intake and the amount of insulin required to achieve normoglycemia. Their results fit our study only for 40 g of carbohydrates, underestimating the needs for 20 and 60 g.

Figure 3. Correlation between the total amount of a meal carbohydrate content and the total amount of insulin needed to restore basal blood glucose values (insulin delivered) after dextrose (closed circle) and mixed meals (triangle). Values are mean ± SEM.



In both studies,[28,29] the authors noted that the ratio varied according to the time of day, more insulin being needed in the morning than later in the day. These observations seem to be in accordance with clinical observations of an increase in insulin needs in the morning[29,30]. Our study did not show any influence of the order of meal administration on insulin delivery by the artificial pancreas. As the first meal was given at 8:30 a.m. and the third one a 6:00 p.m., no circadian rhythm for apparent insulin requirements was noted.

This could be due to the design of our experiment, by which high blood glucose levels were first brought down to normal by the artificial pancreas with a large amount of insulin before beginning the first meal. Thus, in our study, the patients probably began with peripheral hyperinsulinism. This also could indicate that a circadian rhythm does not actually exist[31] or at least not in all patients[32]. It should also be stressed that, in normal subjects, carbohydrate tolerance diminishes during the day,[3,8,9,11,12,15] suggesting a diminished response to insulin during the day in normal and non-insulin-dependent diabetics,[10] rather than the claimed increased sensitivity in insulin dependent subjects.[29–31]

The lack of correlation between the total amount of insulin delivered by the artificial pancreas and patient body weight could be due to the fact that all patients were very lean; in the same way, the lack of correlation with duration of diabetes or previous s.c. insulin dosage might be due to the fact that all patients had very similar durations and requirements.

A number of parameters derived from this study might be useful in the programming of an open-loop insulin infusion system: (1) the total amount of insulin correlated highly, but not linearly, with the total amount of meal carbohydrate content but not with the nature (dextrose or complex carbohydrates in a mixed meal) or order of administration of these meals; (2) kinetics of insulin infusion, which seem to depend upon the type of carbohydrate (dextrose or complex CHO) and total CHO content of the meal; (3) the duration of insulin infusion rate after a meal: it can be assumed that reproducing such physiological profiles for insulin infusion in the open-loop system[35] could optimize the amount of insulin injected and, therefore, reduce peripheral hyperinsulinism more effectively than square wave insulin infusions;[36] and (4) the time delay between the beginning of meal intake and blood glucose increase, which also corresponds to the beginning of high rate insulin infusion, did not correlate with the nature or amount of CHO ingested. This is probably a parameter of great importance in programming insulin delivery systems for the i.v. and probably the s.c. and i.p. routes as well. As already suggested by Service,[31] reducing this time could probably improve BG control and/or diminish insulin delivery and, therefore, reduce peripheral hyperinsulinism.

Preliminary results from our laboratory[33,34] have shown that the data can be useful in the programming of an open-loop system and may subsequently be adapted to each individual, if necessary.

This approach might greatly improve blood glucose control, minimize peripheral hyperinsulinemia, and provide greater dietary freedom for diabetics, including the occasional ingestion of refined sugar from time to time.

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