Influence of Maturity-onset Diabetes on Splanchnic Glucose Balance After Oral Glucose Ingestion

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SUMMARY

To determine the extent to which altered splanchnic glucose balance contributes to postprandial hyperglycemia in diabetes, splanchnic glucose exchange was determined in seven maturity-onset diabetics and 10 healthy control subjects in the basal state and for three hours following oral ingestion of 100 gm. of glucose.

In the basal fasting state, arterial glucose levels in the diabetics (153±24 mg./100 ml.) were 75 to 80 mg./100 ml. higher than in controls while splanchnic glucose output was similar in the two groups (132 to 145 mg. per minute). Following glucose ingestion, arterial glucose concentration in the diabetics rose to peak levels (295±35 mg./100 ml.) that were 55 per cent higher than in controls and remained 100 to 125 mg./100 ml. above basal levels and 150 to 200 mg./100 ml. above control levels three hours after glucose. Splanchnic glucose output rose rapidly in the diabetics to values four times the basal rate at 15 to 30 minutes after glucose feeding and remained 60 per cent or more above basal levels throughout the three-hour period. In contrast, in the controls following a similar early rise, splanchnic glucose output returned to basal levels by 90 minutes. As a consequence, total splanchnic glucose output over three hours in the diabetics (53±4 gm.) was 33 per cent greater than in controls. In addition, the increment in splanchnic glucose output above basal levels in the diabetics (30±5 gm.) was 100 per cent greater than in controls and could account for 75 per cent of the augmented glucose accumulation in body fluids observed at three hours.

It is concluded that in maturity-onset diabetics (1) net splanchnic glucose output is increased after glucose ingestion, suggesting that a greater proportion of an oral glucose load enters the systemic circulation than in healthy controls; (2) failure of splanchnic glucose retention is the major factor responsible for postprandial hyperglycemia in maturity-onset diabetes. DIABETES *27*:121-26, February, 1978.

It is well established that the liver is a major site of insulin action in the regulation of glucose homeostasis.[1-3] In normal subjects small increments in insulin suppress hepatic glucose output without increasing peripheral glucose utilization.[4] In addition, following the ingestion of an oral glucose load, the major portion (60 per cent or more) is retained within the splanchnic bed while only 15 per cent is available for disposal by peripheral tissues along insulin-dependent pathways.[3] In the insulin-deficient diabetic, increased gluconeogenesis in the fasting state[5,6] and the failure of intravenous glucose to inhibit hepatic glucose output[5] have been demonstrated. The effect of insulin deficiency on the hepatic handling of ingested glucose has not, however, been examined in man. The present study was consequently undertaken to determine the influence of mild to moderate diabetes, as observed in the maturity-onset diabetic, on splanchnic glucose exchange following glucose ingestion. Specifically, these studies were designed to determine the extent to which failure of hepatic retention of ingested glucose contributes to postprandial hyperglycemia.

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METHODS

Two groups of subjects were studied. The diabetic group consisted of seven adult males between 40 and

55 years of age. The diagnosis of diabetes had been established by intravenous glucose tolerance testing,[7] which demonstrated an absolute glucose disappearance rate (K_t) of <0.9 per cent per minute. Fasting blood glucose concentrations ranged between 105 and 170 mg./100 ml. None of the subjects had a history of ketoacidosis or liver disease, and none had been treated with insulin or oral hypoglycemic agents. All were within 20 per cent of ideal body weight (based on Metropolitan Life Insurance Table, 1959). The control group consisted of 10 healthy adult male volunteers between 24 and 37 years of age. For at least three days prior to the study all of the subjects ingested a weight-maintaining diet containing 250 to 300 gm. of carbohydrate. The nature, purpose, and possible risks entailed in the study were carefully explained to all subjects prior to obtaining their voluntary consent to participate.

The studies were performed in the morning after an overnight (12-to-14-hour) fast. The procedure employed for hepatic venous and brachial arterial catheterization has been described previously.[3-5] After the catheters were in place, simultaneous arterial and hepatic venous blood samples were drawn repeatedly at 10-minute intervals during a 30-minute basal, control period. One hundred grams of glucose dissolved in 170 ml. of water were then ingested over two minutes. Blood samples were then obtained at 15-minute intervals for three hours after the ingestion of the glucose load.

The methods employed for the determination of hepatic blood flow and for measurement of glucose, alanine, lactate, pyruvate, and glycerol in whole blood and for the determination of immunoreactive insulin and glucagon in plasma have been described previously.[3-5,8,9]

The unpaired and paired *t* test and the analysis of variance were employed in the statistical analyses.[10] The total glucose output from the splanchnic bed during the three-hour period following glucose ingestion was calculated for each subject by determining the total area under the curve describing splanchnic glucose output. The increase in splanchnic glucose output above basal was calculated by determining the area of the portion(s) of the glucose output curve that exceeded the basal rate of splanchnic glucose output. Glucose accumulation in the glucose space was calculated as the product of the rise in arterial glucose concentration between 0 and 180 minutes and the glucose space, which was taken as 25 per cent of body weight.[7,11] Data in the text, tables, and figures are presented as the mean ± S.E. Data on the control group have been previously published.[3]

RESULTS

Arterial Concentrations and Splanchnic Exchange in the Basal State (Table 1)

Prior to glucose ingestion, arterial glucose levels were, as expected, higher in the diabetic group than in controls. Arterial insulin levels were also elevated (presumably reflecting the hyperglycemia), while glucagon levels were comparable in the two groups. Splanchnic glucose output in the basal state was also comparable in the diabetic and control groups.

TABLE 1

Arterial glucose, insulin, and glucagon concentrations and splanchnic glucose output in the basal state in diabetics and controls

	Arterial glucose mg./100ml.	Arterial insulin μU./ml.	Arterial glucagon pg./ml.	Splanchnic glucose output mg./min.
Diabetics	153±24	20±4	67±18	132±30
Controls	76±3	7±2	55±10	145±17
P*	<0.01	<0.01	N.S.	N.S.

*Significance of difference between diabetic and control groups.

In table 2, the basal arterial concentrations and splanchnic exchange of the gluconeogenic substrates alanine, lactate, pyruvate, and glycerol are shown. In the diabetic group arterial lactate and glycerol levels were increased 55 and 100 per cent, respectively. No differences were observed in splanchnic exchange of alanine, lactate, and pyruvate. In the case of glycerol, splanchnic uptake was increased 100 per cent in the

TABLE 2

Splanchnic exchange of gluconeogenic substrates in the basal state in diabetics and controls

		Alanine	Lactate	Pyruvate	Glycerol
Arterial concentration	Diabetics	216±20	690±60	55±3	66±5
μmoles/liter	Controls	231±21	440±30	49±4	33±3
P*		N.S.	<0.001	N.S.	<0.001
Splanchnic exchange	Diabetics	70±13	260±40	17±5	53±5
μmoles/min.	Controls	57±16	230±30	15±4	26±3
P*		N.S.	N.S.	N.S.	<0.01
Fractional extraction (%)	Diabetics	23±6	37±4	19±8	56±8
	Controls	22±5	44±6	25±9	69±6
P*		N.S.	N.S.	N.S.	N.S.

*Significance of difference between diabetic and control groups.

diabetics, reflecting the elevated arterial levels. Splanchnic fractional extraction of each of the gluconeogenic substrates was comparable in the diabetic and control groups.

Response to Glucose Ingestion

In figure 1 the effects of glucose ingestion on arterial glucose and glucagon are compared in the diabetics and controls. As expected, the diabetics demonstrated a greater rise in blood glucose, which remained 100 to 125 mg./100 ml. above basal levels and 150 to 200 mg./100 ml. above control levels three hours after glucose ingestion. Plasma glucagon concentrations fell by 30 per cent in both the diabetic and control groups.

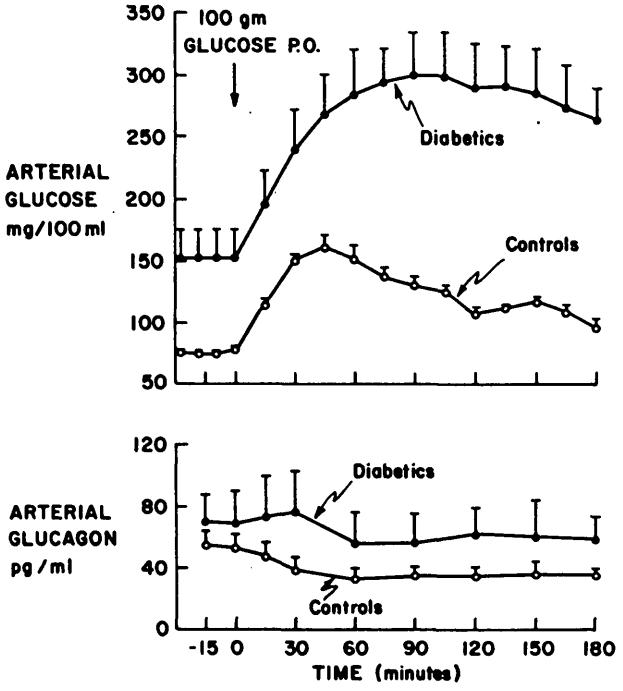

FIG. 1. Arterial blood glucose and arterial plasma glucagon in diabetic and normal control subjects before and after glucose ingestion. Mean values ± S.E.M. are shown. In both the normal controls and diabetics the glucagon values at 60 and 90 minutes were significantly below the basal (−15,0) concentrations ($p<0.05$, paired t test).

In figure 2, the plasma insulin levels after glucose ingestion are shown for the diabetic and control groups. Despite the hyperinsulinemia in the basal state in the diabetics, the absolute insulin levels were not significantly different in the two groups at 30 to 90 minutes. At 120 to 180 minutes, the insulin levels were, however, greater in the diabetic group. Inasmuch as hyperinsulinemia in maturity-onset diabetes may reflect hyperglycemia,[12] the two groups were compared with respect to the percentage increment in plasma insulin. As shown in figure 2, the percentage rise in insulin was 50 to 250 per cent greater in the controls than in the diabetics at 30 to 90 minutes.

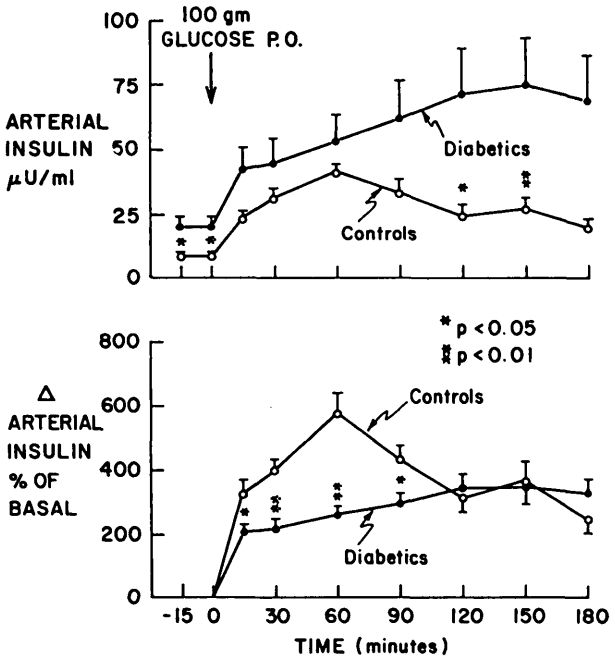

FIG. 2. Arterial plasma insulin levels in diabetic and control subjects before and after glucose ingestion. The absolute insulin concentrations (upper panel) and the changes in insulin (as per cent of basal) are shown (lower panel). P values refer to the significance of the differences between controls and diabetics.

In figure 3, the effects of glucose ingestion on splanchnic glucose output (SGO) in the diabetic and control groups are shown. In both groups there was a rapid increase in SGO to values two-to-fourfold the basal rate by 15 to 30 minutes. In the controls this rapid rise was followed by a decline to levels that were not significantly different from baseline ($p>0.1$) at 90 to 135 minutes. A second, transient increase occurred at 150 minutes in the controls. In contrast, in the diabetics SGO remained 60 per cent or more above basal levels ($p<0.05$ to 0.01) throughout the 180-minute observation period.

In table 3, the cumulative splanchnic glucose output during the three-hour period of observation following glucose ingestion is shown for each of the diabetic subjects and for the control group. Both the total glucose output and the increase in glucose output above basal levels are shown. The mean total SGO

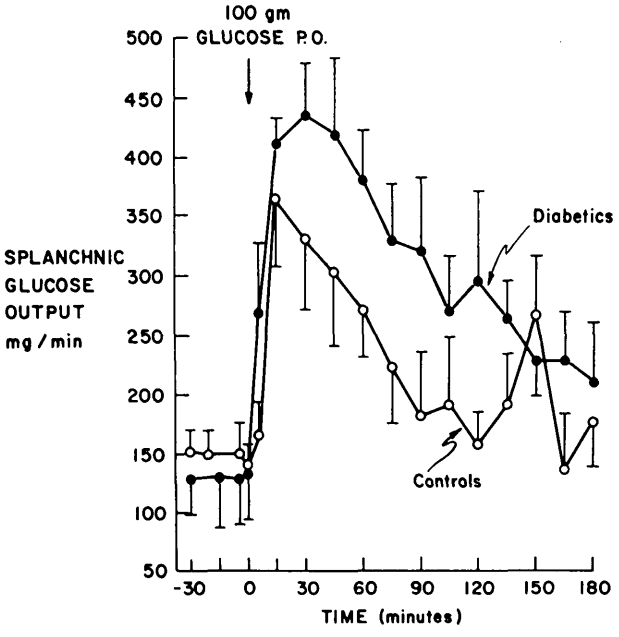

FIG. 3. Splanchnic glucose output in diabetic and control subjects before and after glucose ingestion. The values in the diabetic group after glucose ingestion (5 to 180 minutes) were significantly greater than in controls ($p<0.02$, analysis of variance). The area under the curve was also significantly greater in the diabetic group ($p<0.02$) (see table 3 for the individual values).

over three hours was 53±4 gm. in the diabetics, which was 33 per cent greater than in the controls ($p<0.02$). In addition, the mean increase in SGO above basal levels during the three-hour period was 30±4 gm. in the diabetics, which was 100 per cent greater than in controls ($p<0.02$). Table 3 also shows the extent of accumulation of glucose in the glucose space after three hours. Glucose accumulation in the glucose space in the diabetics was 23±5 gm. at three hours, which was seven-to-eightfold greater than in controls ($p<0.001$).

TABLE 3

Effect of 100-gm. glucose ingestion on splanchnic glucose output (SGO) and glucose accumulation in the glucose space in diabetic and normal subjects

	SGO after 100 gm. of glucose		Glucose accumulated in glucose space at 3 hr. (gm.)
	Total SGO gm./3 hr.	Increase in SGO above basal gm./3 hr.	
Subjects			
Diabetics			
JA	58	13	19
BA	47	38	26
HO	48	36	12
HA	65	41	43
JE	56	18	22
IN	32	17	13
BO	64	46	28
Mean ±S.E.	53±4	30±5	23±5
Controls			
Mean ±S.E.	40±3	15±3	3±0.3
P*	<0.02	<0.02	<0.001

*Significance of difference between diabetic and control groups.

In figure 4 estimated splanchnic blood flow (ESBF) is shown for the normal and diabetic subjects. ESBF was slightly but not significantly greater in the diabetics in the basal state. In both groups, following glucose ingestion, ESBF rose rapidly to levels 30 per cent above basal and then returned to baseline by 90 to 120 minutes. In the diabetics, ESBF was 20 to 27 per cent higher than in controls at 30 to 75 minutes.

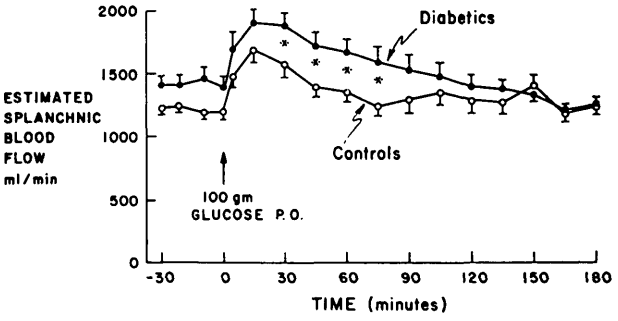

FIG. 4. Estimated splanchnic blood flow in diabetic and control subjects before and after glucose ingestion. The asterisks indicate that the values were significantly higher in the diabetic group ($p<0.05$) at 30 to 75 minutes.

DISCUSSION

In the current study the response to glucose ingestion was examined in maturity-onset diabetics and compared with that of healthy controls. As expected, the diabetics demonstrated a greater rise in blood glucose and a persistence of hyperglycemia throughout the study. Of particular interest were the differences between the two groups with respect to splanchnic glucose output (SGO).

Following glucose ingestion in the diabetic group, SGO remained significantly elevated above basal levels throughout the three-hour period of observation. In contrast, in the controls the values returned to baseline by 90 minutes and remained at that level (save for a transient rise at 150 minutes). As a consequence, total SGO during the three-hour period after glucose feeding was 33 per cent greater in the diabetic group than in controls (table 3) and accounted for over 50 per cent of the administered 100-gm. oral glucose load. Even more striking was the demonstration that the increase in glucose delivery

above the basal rate in the diabetics (30 gm. in three hours) was 100 per cent greater than that observed in controls (15 gm.). These data thus indicate that a greater proportion of an ingested glucose load escapes hepatic uptake and enters the systemic circulation in diabetic than it does in normal subjects.

In keeping with the present findings are previous indirect efforts aimed at quantitating hepatic glucose escape after glucose ingestion. Perley and Kipnis used the intravenous glucose load required to replicate the oral blood glucose profile as an index of the quantity of glucose escaping hepatic uptake in normal subjects and maturity-onset diabetics.[12] By this technique they estimated that, after ingestion of a 100-gm. oral glucose load, glucose release from the liver to the systemic circulation is less than 40 gm. in normal individuals but is in excess of 50 gm. in maturity-onset diabetics.[12] Those figures agree well with the direct observations in the present study (table 3).

The data on splanchnic glucose balance and glucose accumulation in body fluids also provide an estimate of the contribution of augmented hepatic glucose escape to postprandial hyperglycemia in the diabetic group. At the end of the three-hour period of observation the accumulation of glucose in the glucose space of the diabetics exceeded that of controls by 20 gm. (table 3). During the three-hour period, the mean rise in SGO above basal levels in the diabetic group exceeded that of controls by 15 gm. (table 3). Thus, augmented glucose escape from the splanchnic bed could account for 75 per cent (15/20) of the extra glucose that had accumulated in the body fluids of the diabetics. These findings thus indicate the relatively greater importance of diminished hepatic rather than peripheral glucose utilization in the development of postprandial hyperglycemia. These observations are also in keeping with the data in normal subjects, indicating the relatively minor role of peripheral tissues (muscle and adipose tissue) in the disposal of an oral glucose load.[3]

With respect to the mechanism of the augmented splanchnic glucose escape in the diabetics, insulin deficiency, insulin resistance, and altered glucagon secretion are possible contributing factors. Inasmuch as glucagon levels were comparable in the two groups and fell equally (figure 1), it is unlikely that this hormone contributed to the failure to retain ingested glucose within the splanchnic bed. Furthermore, studies of infusions of glucagon indicate that elevations in this hormone cannot of themselves bring about a deterioration in oral glucose tolerance.[13]

Concerning changes in insulin secretion, previous studies have indicated that seeming hypersecretion of insulin in maturity-onset diabetes may be a reflection of coincident hyperglycemia.[12,14] The higher absolute insulin levels in the diabetic group in the basal state and at 120 to 180 minutes after glucose ingestion thus may be a result of the markedly higher blood glucose levels in these subjects (figure 1). On the other hand, when the insulin levels are examined with respect to per cent changes from basal, it is apparent that the diabetic group demonstrated a 35 to 65 per cent reduction in insulin response over the initial 90 minutes of the study (figure 2). These findings are in agreement with previous observations indicating a diminished early insulin response to glucose ingestion in the maturity-onset diabetic.[12,15]

With regard to insulin sensitivity, studies with combined infusions of insulin, epinephrine, propranolol, and glucose have suggested that insulin resistance is an important pathogenetic factor in maturity-onset diabetes.[16,17] Inasmuch as the absolute insulin levels were normal or increased in the diabetic group while splanchnic glucose output was increased, the current findings may be interpreted as supporting the presence of hepatic resistance to insulin in maturity-onset diabetes. However, in view of the diminished increment in insulin levels above basal in the diabetics at 30 to 90 minutes (figure 2), and inasmuch as portal insulin levels were not measured in the two groups, firm conclusions regarding hepatic sensitivity to insulin cannot be drawn from the present data.

The possibility must also be considered that glucose absorption was accelerated in the diabetic group,[18] thereby accounting for increased glucose delivery from the splanchnic bed. Consistent with this possibility is the higher splanchnic blood flow in the diabetic group at 30 to 75 minutes. However, large differences in splanchnic glucose output between the diabetics and controls were observed at 90 to 180 minutes (figure 3), at which time splanchnic blood flow was virtually identical in the two groups (figure 4). Regardless of the operative mechanism, the current data provide evidence that splanchnic retention of ingested glucose is diminished in diabetics and is largely responsible for postprandial hyperglycemia in such patients.

In addition to the observations on the response to glucose ingestion, the current study provides data on basal exchange of gluconeogenic substrates. In previous studies in insulin-withdrawn juvenile-onset diabetics with more severe fasting hyperglycemia (200 to

250 mg./100 ml.), splanchnic uptake of alanine, lactate, pyruvate, and glycerol was noted to be 100 per cent greater than in controls.[5] In contrast, in the maturity-onset diabetics an increase in splanchnic uptake was observed only for glycerol (table 2). These observations suggest that the rate of hepatic utilization of gluconeogenic substrates may reflect the magnitude of hyperglycemia and insulin deficiency in the diabetic state. In the more severely hyperglycemic and insulin-deficient juvenile-onset diabetics there is thus a greater increase in gluconeogenic substrate uptake than is observed in the maturity-onset diabetics.

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