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Research Article

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Abnormal Meal Carbohydrate Disposition in Insulin-dependent Diabetes

Relative Contributions of Endogenous Glucose Production and Initial Splanchnic Uptake and Effect of Intensive Insulin Therapy

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Abstract. Postprandial hyperglycemia in insulin-deficient, insulin-dependent diabetic subjects may result from impaired suppression of endogenous glucose production and/or abnormal disposition of meal-derived glucose. To investigate the relative contributions of these processes and to determine whether 2 wk of near normoglycemia achieved by using intensive insulin therapy could restore the pattern of glucose disposal to normal, meal-related and endogenous rates of glucose appearance were measured isotopically after ingestion of a mixed meal that contained deuterated glucose in seven lean insulin-dependent and five lean nondiabetic subjects. Diabetic subjects were studied once when insulin deficient and again during intensive insulin therapy after 2 wk of near normoglycemia. Total glucose production was determined by using tritiated glucose and the contribution of meal-related glucose was determined by using the plasma enrichment of deuterated glucose.

The elevated basal and peak postprandial plasma glucose concentrations (252 ± 33 and 452 ± 31 mg/dl) of diabetic subjects when insulin deficient were decreased by intensive insulin therapy to values (82 ± 6 and 193 ± 10

mg/dl, $P < 0.01$) that approximated those of nondiabetic subjects (93 ± 3 and 140 ± 15 mg/dl, respectively). Total and endogenous rates of glucose appearance ($3,091 \pm 523$ and $1,814 \pm 474$ mg/kg per 8 h) in the diabetic subjects were significantly ($P < 0.02$) greater than those in nondiabetic subjects ($1,718 \pm 34$ and 620 ± 98 mg/kg per 8 h, respectively), whereas meal-derived rates of glucose appearance did not differ. Intensive insulin therapy decreased ($P < 0.01$) both total ($1,581 \pm 98$ mg/kg per 8 h) and endogenous (478 ± 67 mg/kg per 8 h) glucose appearance to rates that approximated those observed in the nondiabetic subjects, but did not alter meal-related glucose appearance.

Thus, excessive entry of glucose into the peripheral circulation in insulin-deficient diabetic patients after ingestion of a mixed meal resulted from a lack of appropriate suppression of endogenous glucose production rather than impairment of initial splanchnic glucose uptake. Intensive insulin therapy restored postprandial suppression of endogenous glucose production to rates observed in nondiabetic subjects.

Introduction

In normal man the liver can minimize postprandial hyperglycemia after ingestion of carbohydrate by increasing its uptake and/or by suppressing its production of glucose. Estimates of the relative contributions of these two processes have varied depending on the techniques used for their measurement (1–5). Recent studies using hepatic vein catheterization have suggested that only 30–35% of ingested glucose is cleared by the liver (4). Since this technique measures net differences across the splanchnic bed, the relative contributions of changes in hepatic glucose uptake and suppression of endogenous glucose release cannot be assessed. The observation that endogenous glucose production decreases after oral (5) and intravenous glucose (6, 7) administration in nondiabetic man

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suggests this latter process may be an important factor in preventing postprandial hyperglycemia. Studies using double-isotope techniques indicate that ~90% of a 100-g oral glucose load reaches the peripheral circulation (5, 8, 9). However, since there is a 60–70% concomitant reduction of endogenous glucose production, the net effect of these two factors is that the liver “prevents” 20–35 g from reaching the peripheral circulation. Thus, an abnormality in hepatic response to an oral glucose load can potentially lead to a marked impairment in glucose tolerance.

Excessive postprandial excursions of plasma glucose are a common feature of patients with insulin-dependent diabetes mellitus (10). In vitro studies of livers from experimental diabetic animals indicated abnormalities in glycogenolysis, gluconeogenesis, and glycogen synthesis (11, 12). Whether similar defects in patients with insulin-deficient diabetes mellitus result in impaired postprandial suppression of endogenous glucose production or altered initial clearance of meal-derived glucose by the splanchnic bed is not known.

Therefore, the present studies were undertaken to determine (a) whether hyperglycemia after ingestion of a mixed meal in insulin-deficient patients with insulin-dependent diabetes mellitus is due to an excessive rate of glucose entry into the peripheral circulation, decreased glucose utilization, or a combination of both; (b) whether the excessive rate of postprandial glucose entry into the peripheral circulation, if present, is due to impaired suppression of endogenous glucose production or decreased initial splanchnic clearance of meal-derived glucose; and (c) whether insulin replacement sufficient to achieve near normoglycemia can correct the abnormal postprandial pattern of glucose disposition.

Methods

Informed, written consent was obtained from five healthy nondiabetic volunteers (three females, two males, aged 36 ± 5 yr, range 20–46 yr, weight 69 ± 8 kg) who had no family history of diabetes mellitus and from seven insulin-dependent diabetic subjects (two females, five males, aged 36 ± 3 yr, range 23–45 yr, weight 73 ± 5 kg). All the diabetic subjects were documented to have little or no residual beta cell function as indicated by minimal or no plasma C-peptide response to glucagon stimulation. All subjects were healthy at the time of the study and were within 25% of their ideal body weights (Metropolitan Life Insurance tables). None had a clinical history of autonomic neuropathy.

Studies were performed at the inpatient facility of the General Clinical Research Center at the Mayo Clinic. Nondiabetic subjects were studied once. Postprandial glucose disposition was measured in seven diabetic subjects when insulin deficient from suboptimal diabetic control and in five of these subjects after an average of 17 d (range 14–27 d) of optimized glycemic control by using continuous subcutaneous insulin infusion (Miles-Mayo Minipump, Life Science Instruments, Elkhart, IN) as previously described (11). Before the initial study the diabetic patients were maintained on their customary insulin regimens for the 7 d before the study. On the day before the initial study the insulin doses in the diabetic patients were reduced by ~20% to produce insulin deficiency. No insulin was given on the morning of

the insulin deficient study day. On the morning of the optimal diabetic control study day, diabetic subjects received a dose of regular insulin appropriate for the caloric content of the test meal via the insulin pump.

During the week before both study days blood glucose concentrations were measured four times daily with glucose oxidase reagent strips (Chemstrip BG, Bio-Dynamics, Boehringer Mannheim Corp., Indianapolis, IN) 30 min before each major meal and before the bedtime snack. During the interval of optimized control, patients also measured blood glucose concentrations before each meal and were supervised in insulin adjustment by daily telephone contact with the investigators.

Diabetic subjects were admitted the evening before each study day and nondiabetic subjects the morning of the study day. Between 7 a.m. and 8 a.m. a forearm vein was cannulated with an 18-g plastic catheter (Cathlon IV, Critikon, Inc., Tampa, FL) and used for isotope infusion. A contralateral dorsal hand vein was cannulated retrogradely with a 19-g butterfly needle (Turumo Corp., Tokyo, Japan) and maintained at 50°C for intermittent sampling of arterialized venous blood as previously described (12).

Between 8 a.m. and 9 a.m. a primed ($9.1 \mu\text{Ci}$) continuous ($0.09 \mu\text{Ci/min}$) infusion of $[2\text{-}^3\text{H}]\text{glucose}$ (New England Nuclear, Boston, MA; sp gr 14.1 Ci/mmol) was begun for isotopic determination of rates of glucose appearance and disappearance. After a 2-h equilibration period, a mixed meal containing 10 kcal/kg was ingested (0 time) and entirely consumed within 15 min. The meal calories were partitioned so that 45% of total calories were given as a dextrose solution enriched to 5 mol/100 mg with D- $[6,6\text{-}^2\text{H}_2]\text{glucose}$ (MDS Isotopes, Merck Frosst Canada, Inc., Montreal). 35% of total calories was given as fat, in the form of pure corn oil (Mazola 100% Corn Oil, Best Foods, CPC International, Inc., Englewood, NJ); and 20% of total calories was given as mixture of amino acids (MSUD-Aid, Mead-Johnson, Evanston, IL). This formula, which is devoid of branched-chain amino acids, was supplemented with isoleucine, leucine, and valine, such that the final mixture contained 6, 9, and 8% of these branched-chain amino acids, respectively. In each case the meal was ingested with two flasks. The isotope-enriched dextrose solution contained in a single 250-cm³ flask was consumed initially. The contents of the second flask containing the fat and amino acids were ingested next. Both flasks were rinsed four times with 25-cm³ of an unsweetened caffeine-free carbonated beverage, and the rinse solution was consumed.

Blood samples were obtained at 30, 20, 10, and 0 min before and 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, and 480 min after meal ingestion. Blood was placed immediately on ice, centrifuged at 4°C, and plasma was separated. Blood used to determine plasma glucose and free insulin concentrations and glucose specific activity was collected as previously described (13). Blood for insulin determination was centrifuged and the resulting plasma was stored at –20°C until assay. Plasma for the measurement of deuterated glucose isotopic enrichment was stored at –80°C until assay. Triplicate 0.4-ml aliquots of the remaining plasma samples were deproteinized by addition of 0.4 ml chilled 0.5 M perchloric acid for subsequent measurement of tritiated glucose specific activity as previously described (14). Plasma-free immunoreactive insulin was measured by radioimmunoassay (15). Deuterated glucose enrichment was measured by gas chromatography-mass spectrometry, as previously described (16).

The rates of total glucose appearance (R_a) and disappearance (R_d) were calculated by using the equations of Steele et al. (17) and modified by DeBodo et al. (18).

The rate of appearance in the systemic circulation of the ingested glucose was determined as suggested by Cherrington et al. (19). Thus,

[2-³H]glucose was used to trace the rate of appearance of D-glucose-6,6-d₂ just as it was used to trace the rate of appearance of naturally occurring [¹²C]glucose. The plasma deuterated glucose concentration was obtained by multiplying the isotopic enrichment of deuterated glucose by the total plasma glucose concentration. The rate of deuterated glucose appearance was divided by the isotopic enrichment of the meal to yield the rate of meal-derived glucose appearance. The meal-derived rate of glucose appearance was subtracted from the total glucose production rate to yield the rate of endogenous glucose production.

Statistical analysis was performed on log-transformed data by using a two-tailed *t* test with a *P* of ≤ 0.05 being considered significant.

Results

Plasma glucose and insulin concentrations (Fig. 1). Mean preprandial blood glucose concentration derived from self blood-glucose monitoring was 175 ± 21 mg/dl for the week before study during conventional insulin treatment and 118 ± 28 mg/dl for the week before study during intensive insulin therapy ($P < 0.05$).

Fasting (252 ± 33 mg/dl) and peak postprandial (452 ± 31 mg/dl) plasma glucose concentrations in the diabetic patients when insulin deficient were greater than those of the nondiabetic subjects (93 ± 3 mg/dl and 140 ± 15 mg/dl, $P < 0.01$, respectively). Fasting plasma free insulin concentrations did not differ between the diabetic (9 ± 2 μ U/ml) and nondiabetic (7 ± 1 μ U/ml) subjects. The postprandial plasma free insulin concentrations (11 ± 2 μ U/ml) did not change in the diabetic patients and were significantly less than those of the nondiabetic subjects (58 ± 14 μ U/ml, $P < 0.01$).

During intensive insulin therapy both fasting (82 ± 6 g/dl) and peak postprandial (193 ± 10 mg/dl) plasma glucose concentrations were significantly decreased compared with those in the insulin-deficient state ($P < 0.01$). Although the fasting plasma glucose concentrations during intensive insulin therapy did not differ from those in the nondiabetic subjects, the peak postprandial plasma glucose concentrations were greater (P

< 0.02). The fasting plasma insulin concentrations during intensive insulin therapy (15 ± 2 μ U/ml) were greater than those observed in the diabetic patients when insulin deficient ($P < 0.05$) and in the nondiabetic subjects ($P < 0.02$). Peak postprandial free insulin concentrations during intensive insulin therapy (66 ± 13 μ U/ml) were greater than those in the insulin-deficient diabetic patients ($P < 0.01$) but did not differ significantly from those observed in the nondiabetic subjects.

Rates of total glucose appearance and disappearance (Figs. 2 and 3). Rates of total glucose appearance after an overnight fast in the diabetic subjects when insulin deficient (4.4 ± 1.0 mg/kg per min) were greater than those in the nondiabetic subjects (2.4 ± 0.2 mg/kg per min) but the difference did not reach statistical significance. After meal ingestion both peak (8.8 ± 1.6 mg/kg per min) and total integrated glucose appearance ($3,091 \pm 523$ mg/kg per 8 h) were greater ($P < 0.01$) than those observed in the nondiabetic subjects (4.8 ± 0.3 mg/kg per min and $1,718 \pm 34$ mg/kg per 8 h, respectively). During intensive insulin therapy, glucose appearance rates after an overnight fast (1.7 ± 0.3 mg/kg per min) were significantly lower than those in the insulin-deficient state ($P < 0.02$) and slightly but not significantly lower than those in the nondiabetic subjects. Both the peak postprandial rates (6.3 ± 0.8 mg/kg per min, $P < 0.01$) and total integrated ($1,581 \pm 93$ mg/kg per 8 h) rates of glucose appearance were reduced ($P < 0.01$) as a result of intensive insulin therapy.

In general the changes in the rates of glucose utilization paralleled the changes in rates of glucose appearance. The total postprandial integrated response during intensive insulin therapy ($1,611 \pm 90$ mg/kg per 8 h) was less ($P < 0.05$) than that in the insulin-deficient state ($3,020 \pm 525$ mg/kg per 8 h) but no different from that observed in the nondiabetic subjects ($1,728 \pm 36$ mg/kg per 8 h).

Meal-derived and endogenous glucose production (Figs. 3 and 4). Meal-derived rate of glucose appearance in the insulin-deficient diabetic subjects ($1,277 \pm 65$ mg/kg per 8 h) did not

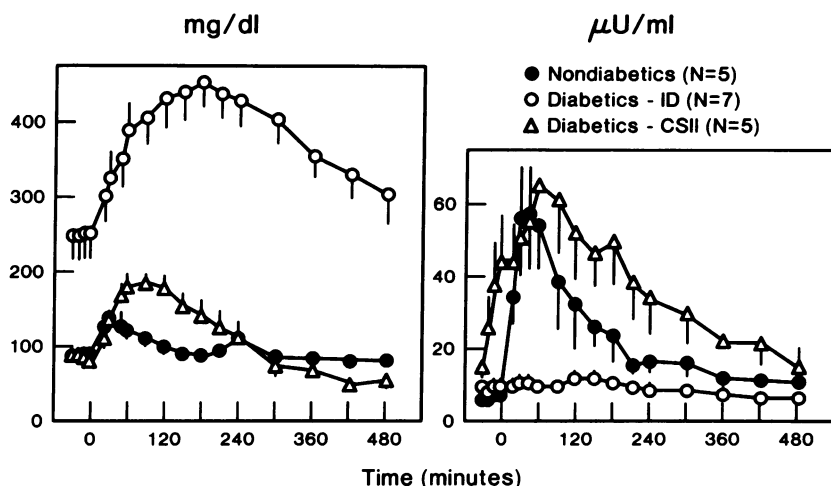


Figure 1. Plasma glucose (left) and free insulin concentrations (right) in nondiabetic subjects and diabetic subjects when insulin deficient (ID) and while treated with continuous subcutaneous insulin infusion (CSII). The meal was taken at 0 min.

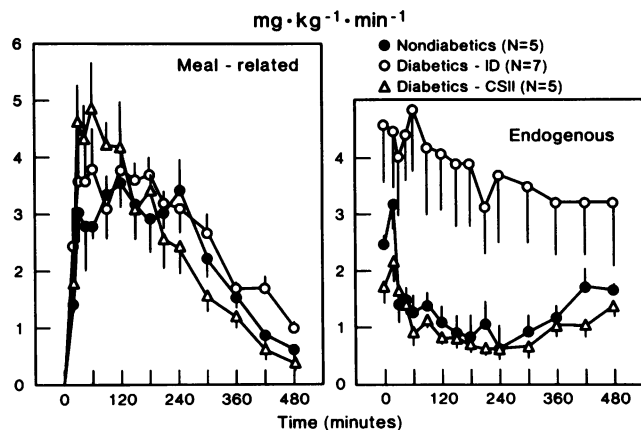


Figure 2. Meal-derived and endogenous rates of glucose appearance in nondiabetic subjects and diabetic subjects when insulin deficient (ID) and while treated with continuous subcutaneous insulin infusion (CSII). Meal was taken at 0 min.

differ from that observed in the nondiabetic subjects ($1,098 \pm 85$ mg/kg per 8 h) or from that in the diabetic subjects during intensive insulin therapy ($1,108 \pm 44$ mg/kg per 8 h). However, the rate of appearance of meal-derived glucose in the systemic circulation over the initial 2 h of the study after meal ingestion was greater ($P < 0.05$) in the diabetic subjects during intensive insulin therapy than in the nondiabetic subjects (450 ± 36 vs. 319 ± 31 mg/kg per 2 h).

After meal ingestion in the nondiabetic subjects there was a prompt decrease in endogenous glucose production, which reached a nadir of 0.6 ± 0.4 mg/kg per min. As the plasma glucose concentrations returned toward base line, endogenous glucose production returned toward preprandial rates. In contrast, in the insulin-dependent diabetic subjects, despite a 200

mg/dl increase in plasma glucose concentrations, endogenous glucose production rates decreased slightly but remained significantly greater than those in the nondiabetic subjects. Thus, endogenous glucose production over the 8 h after meal ingestion in the insulin-deficient diabetic subjects ($1,814 \pm 474$ mg/kg per h) was threefold greater ($P < 0.02$) than that observed in the nondiabetic subjects (620 ± 98 mg/kg per 8 h). During intensive insulin therapy the pattern of suppression of endogenous glucose production was restored to that observed in the nondiabetic subjects. The amount of endogenous glucose produced over the 8-h postprandial period during intensive insulin therapy (473 ± 67 mg/kg per 480 min) was less ($P < 0.01$) than that observed in the insulin-deficient state but not different from that observed in the nondiabetic subjects.

The amount of the ingested glucose load that reached the systemic circulation when expressed as percentage of the total oral glucose load was $98 \pm 7\%$ for the nondiabetic subjects, $113 \pm 6\%$ for diabetic subjects when insulin deficient, and $99 \pm 5\%$ for the diabetic subjects during intensive insulin therapy.

Discussion

The current studies demonstrate that impaired postprandial glucose tolerance observed in insulin-deficient diabetic subjects is due in part to a lack of appropriate suppression of endogenous glucose production rather than an abnormality in initial splanchnic clearance of meal-derived glucose. This abnormality in hepatic glucose regulation is restored to normal by intensive insulin therapy.

In nondiabetic man ingestion of a liquid mixed meal resulted in a 44% suppression of endogenous glucose production within 30 min that reached a maximal suppression of 74% by 240 min. As plasma glucose and insulin concentrations decreased to preprandial levels, endogenous glucose production

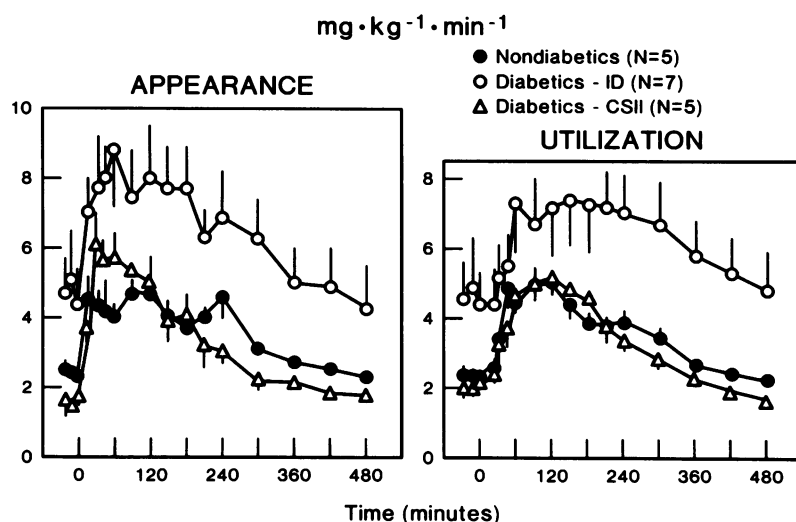


Figure 3. Total rates of glucose appearance and utilization in nondiabetic subjects and diabetic subjects when insulin deficient (ID) and while treated with continuous subcutaneous insulin infusion (CSII). The meal was taken at 0 min.

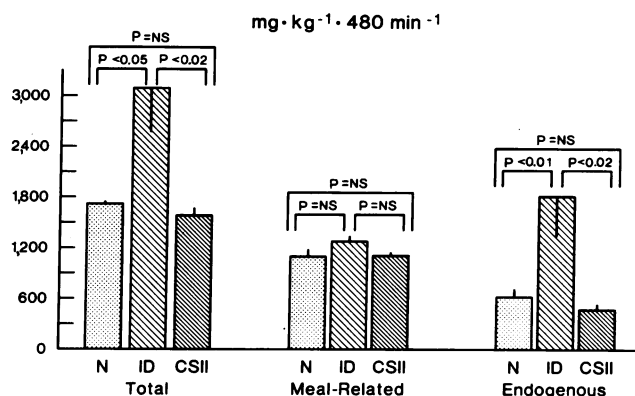


Figure 4. Total, meal-derived, and endogenous rates of glucose production in nondiabetic subjects (N) and diabetic subjects when insulin deficient (ID) and while treated with continuous subcutaneous insulin infusion (CSII).

returned toward base-line values. Comparable suppression of glucose production after ingestion of glucose has been reported by Radziuk et al. (5) in nondiabetic man, and Issekutz et al. (8) and Steele et al. (9) in healthy dogs using a similar dual-isotope method. In those experiments, as in the present studies, essentially all of the meal-derived glucose appeared in the systemic circulation over the period of study.

Although these findings may appear to be in conflict with reports of net glucose uptake by the liver after glucose ingestion (20, 21), the results obtained with dual-isotope methodology do not preclude incorporation of enteric glucose into hepatic glycogen either by recycling through two carbon precursors (22) or by direct hepatic extraction. The dual-isotope technique quantitates only the initial glucose clearance (i.e., the amount of glucose cleared by the splanchnic bed during the "first pass" from the gut to the peripheral circulation). Subsequent hepatic glucose uptake, once the meal-derived glucose has mixed with the systemic pool, is measured by the isotopic technique as glucose disappearance and cannot be distinguished from glucose uptake by extrahepatic tissues. Although the dual-isotope technique cannot quantitate hepatic glucose uptake after the first pass, since virtually all of the meal-related glucose reached the peripheral circulation after ingestion of a mixed meal, our data are consistent with those of earlier studies using a dual glucose challenge and imply that factors that regulate hepatic glucose uptake do not differ between intravenous and enterally derived glucose.

Therefore, it is evident that the liver contributes to postprandial glucose homeostasis in nondiabetic man by suppressing endogenous glucose production. The current studies indicate that this process is profoundly disturbed in insulin-deficient diabetic man. In the postabsorptive state, endogenous glucose release was greater in the insulin-deficient diabetic patients than in the nondiabetic controls and failed to suppress normally

after meal ingestion. Thus, ~1,200 mg/kg (or ~87 g) more glucose reached the peripheral circulation postprandially in the diabetic than in the nondiabetic subjects.

The increased glucose delivery in the diabetic patients could be totally accounted for by a lack of appropriate suppression of endogenous glucose production since no difference in the amount of the meal-derived glucose that reached the peripheral circulation was observed between groups. Postprandial glucose utilization was greater in the diabetic subjects than in the nondiabetic subjects, presumably due to "mass action" and urinary glucose losses. This should not be interpreted as indicating that glucose utilization was normal in the diabetic patients since these rates occurred at substantially elevated plasma glucose concentrations. It is likely that impaired peripheral glucose utilization also contributes to the postprandial hyperglycemia in the insulin-deficient diabetic subjects. Nevertheless, since the absolute rate of glucose utilization was not decreased in the diabetic subjects, overproduction of glucose by the liver rather than underutilization by tissues was clearly the initiating event in the postprandial hyperglycemia.

The improved postprandial suppression of endogenous glucose production during intensive insulin therapy could have been anticipated on the basis of previous reports. Insulin therapy has been shown to enhance hyperglycemic-induced glycogen synthesis and the inhibition of glycogenolysis in vitro (11) to restore fasting rates of glucose production in diabetic subjects to the nondiabetic range (23, 24), and to restore the suppression of hepatic glucose release by intravenous glucose administration (6). Improved hepatic processing of glucose has also been implicated by the finding that insulin administration via an artificial pancreas decreases hyperglycemia after oral glucose without altering forearm glucose uptake (7).

It should be emphasized, however, that the current studies do not necessarily indicate that insulin therapy completely normalizes the hepatic glucose handling of glucose after a meal. While the total amount of meal-related glucose that reached the peripheral circulation in the diabetic and nondiabetic subjects was equivalent, its temporal pattern of appearance differed in the two groups. Over the initial 2 h meal-related glucose appearance of the insulin-treated subjects exceeded that of the nondiabetic subjects. Since the rate of increase of glucose utilization was comparable in both groups during this interval, plasma glucose concentrations increased more in the insulin-treated diabetic patients. Although the reason for this initial greater appearance of the meal-derived glucose in the systemic circulation of the diabetic patients is speculative, rates of gastric emptying may have differed between groups.

The limitations of the isotopes used in the current study should be borne in mind when interpreting the current results. [2-³H]glucose was used to trace total systemic glucose production since this label loses its tritium during the passage into and out of glycogen (25). This label, however, can also be lost during futile cycling between glucose-6-phosphate and fructose-

6-phosphate (25). In the nondiabetic state this process may result in 10–20% overestimate of glucose turnover both in the basal state and after a glucose challenge (26, 27). The extent of futile cycling in diabetic man is not known. However, since glucokinase is decreased in diabetes (28) and since regulation of glucose-6-phosphate and fructose-6-phosphate during hepatic perfusion with glucose is similar in diabetic and nondiabetic animals, with only slight decreases in activity being observed in the diabetic animals (29), if anything a decrease in futile cycling would be anticipated in the diabetic group. If futile cycling is indeed decreased in diabetic man, this would result in an underestimate of differences in total glucose production between the diabetic and nondiabetic man.

In contrast to [2-³H]glucose, 6,6-dideuterated glucose, which was used to trace the mixed meal, can be incorporated into and released from glycogen without losing its label. In the current study, therefore, cycling of glucose through glycogen would not alter the measurement of total glucose production but would result in an overestimate of meal-derived glucose production and an underestimate of endogenous glucose production. In nondiabetic subjects, cycling of glucose through glycogen after an oral glucose challenge appears to be negligible (5). If the meal-derived glucose label cycled through glycogen in the insulin-deficient diabetic subjects, this would result in an underestimate of endogenous glucose production and mean that the actual difference in endogenous glucose production between the diabetic and nondiabetic subjects was greater than that observed in the current studies. In view of the above considerations, our results should be considered qualitative rather than quantitative.

Previous studies using a challenge of glucose alone suggest that absorption of a glucose load is complete within 3–4 h (5). In contrast, in the current study where glucose was ingested along with amino acids and fat, absorption appeared to continue in excess of 5 h as evidenced by persistent elevations of both total and meal-related glucose production over this interval. This prolonged absorption of the meal-derived glucose is most likely the result of slowed gastric emptying by virtue of the higher caloric content and lipid content of the challenge meal. If this postulate is correct, then the current study suggests that a longer interval of observation may be needed after ingestion of mixed meals rather than after ingestion of a simple carbohydrate load.

Although the current study indicates that in diabetic subjects excessive amounts of glucose are released into the peripheral circulation after meal ingestion, this should not be interpreted as the sole explanation of their postprandial hyperglycemia. A lack of an appropriate increase in glucose utilization also contributes to the impaired glucose tolerance. While the postprandial rates of glucose utilization were greater in the insulin-deficient diabetic subjects than in the nondiabetic subjects, these increased rates occurred in the presence of marked increases in circulating plasma glucose concentrations. Glucose utilization at comparable plasma glucose concentrations in

nondiabetic subjects capable of secreting insulin would presumably be far greater. After intensive insulin therapy, glucose utilization rates in the diabetic and nondiabetic subjects were virtually identical despite the fact that the plasma glucose and peripheral insulin concentrations were higher in the diabetic subjects. Taken together this data suggests that either the ability of insulin to stimulate glucose uptake or of glucose to modulate its own uptake was impaired in the diabetic subjects. Whether more prolonged near normalization of glycemic control or a more physiologic route of insulin administration (portal venous rather than subcutaneous) would reverse this (these) defect(s) is not known.

In summary, the present study indicates that the excessive entry of glucose into the peripheral circulation in insulin-deficient diabetic man is due to lack of appropriate suppression of endogenous glucose uptake rather than a decrease in initial splanchnic glucose uptake. Intensive insulin therapy restored postprandial suppression of endogenous glucose production to rates observed in nondiabetic subjects.

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