Glucose Fluxes and Oxidation After an Oral Glucose Load in Patients With Non–Insulin-Dependent Diabetes Mellitus of Variable Severity

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The relative contribution of liver and peripheral tissues to the postprandial glucose response has been examined in 19 obese non–insulin-dependent diabetes mellitus (NIDDM) patients and 11 matched nondiabetic control subjects during a 5-hour oral glucose tolerance test (OGTT) performed with a load of 75 g, corresponding to approximately 67 g/1.73 m^2. A dual-tracer technique was used to measure exogenous and endogenous glucose fluxes separately. Glucose oxidation was measured by indirect calorimetry. Diabetic patients were subdivided into two subgroups designated as "mild" (n = 7) and "severe" (n = 12) NIDDM according to postabsorptive glucose concentration with a cut-off point of 140 mg/dL. In the basal state, glucose concentrations averaged 99, 117, and 194 mg/dL, respectively, in control subjects and in the two diabetic subgroups, but insulin concentrations were not significantly different between groups. In comparison to control subjects, the basal hyperglycemia of mildly diabetic patients was entirely caused by a reduced metabolic clearance rate (118 *v* 144 mL/min; $P < .05$), whereas in severely diabetic patients basal hyperglycemia resulted from a combination of increased hepatic glucose output (187 *v* 139 mg/min; $P < .001$) and decreased metabolic clearance rate (97 *v* 144 mL/min; $P < .001$). A similar situation prevailed during the initial 2 hours after glucose ingestion. In patients with mild NIDDM, glucose concentration increased by 121 ± 10 mg/dL as compared with 36 ± 7 mg/dL in control subjects ($P < .001$). This difference was entirely due to a reduction in tissue glucose uptake (31 ± 2 *v* 42 ± 3 g/2 hours; $P < .005$), with the rates of total glucose appearance (R_a) being almost identical in the two groups (43 ± 2 *v* 46 ± 3 g/2 hours; NS). Average 0- to 2-hour insulin levels were not significantly different between diabetic and control subjects (73 ± 16 *v* 92 ± 10 μU/mL; NS). On the other hand, in severely diabetic patients in whom the integrated 0- to 2-hour insulin levels were markedly decreased (36 ± 3 *v* 92 ± 10 μU/mL; $P < .001$), the excessive increase in glycemia (+158 mg/dL at 2 hours) was accounted for in similar proportions by higher rates of total glucose entry (53 ± 2 *v* 46 ± 3 g/2 hours; $P < .01$) and decreased tissular disposal (33 ± 2 *v* 42 ± 3 g/2 hours; $P < .005$). The elevated total glucose entry rate was solely related to higher rates of residual hepatic glucose output (15 ± 1 *v* 8 ± 1 g/2 hours; $P < .001$), with the R_a of exogenous glucose not being affected by the presence of diabetes. The reduction in uptake resulted in approximately equal proportion from an impairment in oxidative and nonoxidative disposal. The persistence of elevated levels of glucose and insulin in the diabetic patients beyond 2 hours allowed them to normalize their rates of glucose disposal and oxidation within the 5 hours following glucose ingestion. It is suggested from these data that during the transition from the normal state to overt NIDDM, reduced glucose tolerance is due initially to an impaired peripheral glucose disposal related mainly to peripheral insulin resistance. The additional participation of an impaired suppression of hepatic glucose output in the abnormal glycemic response could only be identified in a more severe diabetic state associated with a grossly deficient insulin response.

IN RECENT YEARS, several studies have attempted to evaluate the relative participation of the splanchnic bed and peripheral tissues in glucose homeostasis after glucose ingestion in both obese and non-obese patients with non–insulin-dependent diabetes mellitus (NIDDM).[1-6] However, it is still unclear whether it is glucose overproduction or impaired glucose uptake that represents the most important determinant of postprandial hyperglycemia in these patients.[1-4]

Since it has been suggested[3] that differences in the degree of insulin deficiency could be one possible explanation for discrepancies among results, we reexamined this question in patients with NIDDM of variable intensity in an attempt to correlate the severity of the disorder with the degree of abnormality detected in the several components of the metabolic response to glucose ingestion. The experimental approach used in the present study included a dual-isotope technique to trace both total and orally derived glucose combined with indirect calorimetry so as to gain insight into the pattern of glucose utilization. The results in diabetic patients were compared with those in nondiabetic subjects matched by age and body mass index.

SUBJECTS AND METHODS

Subjects

The studied subjects included 19 obese NIDDM patients with a known duration of diabetes varying between 1 and 20 years (mean, 6 ± 1 years). Four of them had been previously treated with insulin, eight had received sulfonylurea therapy, and seven had been treated with diet alone. All medications had been discontinued for at least 1 week before the study. The 19 NIDDM patients were distributed into two groups (Table 1 and 2) according to their fasting glucose level measured while off therapy using 140 mg/dL as the cutoff point[7]; the 12 "severely" diabetic patients had basal glucose levels exceeding 140 mg/dL with a mean of 194 ± 11 mg/dL, whereas the seven "mildly" diabetic patients had basal glucose levels below 140 mg/dL (mean, 117 ± 3 mg/dL), but 2-hour oral glucose tolerance test (OGTT) levels above 200 mg/dL (mean, 237 ± 10 mg/dL). A control group was composed of 11 age- and weight-matched obese subjects with no family history of diabetes. The characteristics of the three groups are presented in Table 1. For 3 days before the test, subjects of all the groups were instructed to consume a weight-maintaining diet containing at least

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Table 1. Characteristics of Subjects

	Control Subjects	P_1	Mild NIDDM	P_2	Severe NIDDM	P_3
n	11		7		12	
M/F	5/6		5/2		9/3	
Age (yr)	47 ± 4	NS	41 ± 5	NS	53 ± 2	NS
Weight (kg)	82.9 ± 4.4	NS	85.6 ± 8.1	NS	79.7 ± 3.3	NS
Height (cm)	167 ± 2	NS	167 ± 2	NS	170 ± 3	NS
Body mass index (kg/m^2)	29.8 ± 1.3	NS	30.4 ± 2.5	NS	27.6 ± 1.1	NS
BSA (m^2)	1.91 ± 0.05	NS	1.94 ± 0.09	NS	1.91 ± 0.05	NS
Known duration of diabetes (yr)	—		4 ± 1	NS	7 ± 2	
HbA_{1c} (%; normal, 4%-6%)	—		5.9 ± 0.5	<.005	7.8 ± 0.3	
Treatment of diabetes (diet/OHA/insulin)	—		5/1/1		2/7/3	

NOTE. P_1 is the statistical significance of differences between patients with mild NIDDM and control subjects; P_2, severe NIDDM *v* mild NIDDM; and P_3, severe NIDDM *v* control subjects.

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; OHA, oral hypoglycemic agents.

200 g carbohydrate/d. The nature, purpose, and potential risks of study were explained to the patients and their consent was obtained before participation. The protocol was approved by the Ethics Committee of the Faculty of Medicine of the University of Brussels.

Protocol

Subjects were studied at 8:00 AM in a semi-sitting position, after a 14-hour overnight fast. The double-tracer study was performed as previously described.[5] In brief, a primed continuous infusion of D-6-^{3}H-glucose (New England Nuclear, Boston, MA) was administered through an antecubital vein for 7 hours at a rate of approximately 0.55 μCi/min. The priming dose represented 120 times the amount infused per minute in control subjects and was increased in proportion to the degree of hyperglycemia in the diabetic patients. A period of 120 minutes was allowed for equilibration of the tracer in the glucose pool. During the last 45 minutes of the basal period, a steady-state level of plasma ^{3}H-glucose activity was achieved in all subjects, with the difference between values recorded at −45 and 0 minutes amounting to +0.8% ± 0.8% in the control group and −1.3% ± 0.6% in the diabetic group; these figures were not significantly different from zero. At the end of the equilibration period, each subject ingested 75 g glucose dissolved in 320 mL flavored water and labeled with 100 μCi D-1-^{14}C-glucose (New England Nuclear). The glucose load represented approximately 67 g/1.73 m^2 in the three groups (Table 3). Glucose concentration and specific activity of the oral load were determined for each test. Arterialized venous blood was obtained from a dorsal vein of the hand opposite to the infusion side. The hand was maintained at 41°C with an electrical heating pad to provide adequate arterialization of the venous blood, as indicated elsewhere.[5] Samples were obtained every 15 minutes during the last 45 minutes of the basal period and the first hour following glucose ingestion, and every 30 minutes for the remaining 4 hours. Subjects voided before the start of the study, and urine was collected at the end of the experiment. The respiratory gas exchanges were determined during the basal period and for 15-minute periods every 30 minutes during the 5 hours after glucose ingestion using a Deltatrac Metabolic Monitor (Datex, Helsinki, Finland) equipped with a ventilated hood placed over the subject's head.

Analytical Procedures

Blood samples were collected in heparinized tubes kept on ice, centrifuged at 4°C, and separated for storage at −20°C until assayed. Plasma glucose concentration was determined using a

Table 2. Substrate and Hormone Concentrations in the Basal State and During OGTT

	Control Subjects (n = 11)	P_1	Mild NIDDM (n = 7)	P_2	Severe NIDDM (n = 12)	P_3
Glucose (mg/dL)						
Basal	99 ± 3	NS	117 ± 3	<.001	194 ± 11	<.001
Mean OGTT	122 ± 4	<.001	184 ± 10	<.001	283 ± 13	<.001
Insulin (μU/mL)						
Basal	13 ± 2	NS	23 ± 6	NS	19 ± 2	NS
Mean OGTT	57 ± 6	NS	61 ± 12	<.01	32 ± 2	<.01
C-Peptide (ng/mL)						
Basal	2.1 ± 0.2	NS	2.9 ± 0.4	NS	2.4 ± 0.2	NS
Mean OGTT	6.7 ± 0.6	NS	5.9 ± 0.7	<.05	4.2 ± 0.3	<.005
Glucagon (pg/mL)						
Basal	174 ± 26	NS	204 ± 34	NS	247 ± 33	NS
Mean OGTT	150 ± 27	NS	142 ± 30	NS	195 ± 25	NS
FFA (mmol/L)						
Basal	0.52 ± 0.06	NS	0.53 ± 0.05	NS	0.66 ± 0.06	NS
Mean OGTT	0.25 ± 0.03	NS	0.22 ± 0.03	NS	0.32 ± 0.04	NS
Lactate (mmol/L)						
Basal	0.99 ± 0.10	NS	1.14 ± 0.13	NS	1.26 ± 0.15	NS
Mean OGTT	1.25 ± 0.09	NS	1.28 ± 0.13	NS	1.69 ± 0.18	NS

NOTE. Mean OGTT values are calculated for the entire 5-hour study period; significance of P_1, P_2, and P_3 as in Table 1.

Table 3. Glucose Fluxes and Oxidation in the Basal State and During OGTT

	Control Subjects (n = 11)	P_1	Mild NIDDM (n = 7)	P_2	Severe NIDDM (n = 12)	P_3
Total R_a						
Basal (mg/min)	139 ± 8	NS	131 ± 7	<.001	187 ± 9	<.001
Mean OGTT (g/5 h)	79.2 ± 2.7	NS	73.2 ± 2.4	<.005	87.6 ± 2.1	<.05
Exogenous R_a						
Oral load (g)	66.9 ± 1.8	NS	66.8 ± 3.9	NS	67.5 ± 2.0	NS
Mean OGTT (g/5 h)	58.8 ± 2.1	NS	57.6 ± 3.0	NS	59.4 ± 1.8	NS
Endogenous R_a						
Basal (mg/min)	139 ± 8	NS	131 ± 7	<.001	187 ± 9	<.001
Mean OGTT (g/5 h)	19.8 ± 1.5	NS	15.6 ± 1.8	<.005	28.2 ± 1.8	<.05
Total R_d						
Basal (mg/min)	141 ± 8	NS	136 ± 7	<.001	192 ± 10	<.001
Mean OGTT (g/5 h)	80.4 ± 2.4	NS	74.1 ± 2.1	<.01	87.9 ± 2.4	NS
Urinary R_d						
Basal (mg/min)	0	NS	0	NS	4 ± 2	NS
Mean OGTT (g/5 h)	0	NS	1.8 ± 0.9	<.001	11.7 ± 1.8	<.001
Tissular R_d						
Basal (mg/min)	141 ± 8	NS	136 ± 7	<.001	188 ± 9	<.001
Mean OGTT (g/5 h)	80.4 ± 2.4	NS	72.3 ± 1.8	NS	76.2 ± 2.1	NS
MCR						
Basal (mL/min)	144 ± 9	<.05	118 ± 6	NS	97 ± 3	<.001
Mean OGTT (mL/min)	220 ± 10	<.001	137 ± 7	<.01	93 ± 6	<.001
Glucose oxidation						
Basal (mg/min)	74 ± 11	NS	66 ± 10	NS	61 ± 9	NS
Mean OGTT (g/5 h)	39.9 ± 2.1	NS	33.0 ± 3.9	NS	34.5 ± 3.6	NS
Nonoxidative glucose disposal						
Basal (mg/min)	66 ± 7	NS	72 ± 12	<.001	132 ± 11	<.001
Mean OGTT (g/5 h)	40.6 ± 2.3	NS	39.3 ± 3.3	NS	41.8 ± 3.2	NS

NOTE. All values including oral glucose load have been normalized to a BSA of 1.73 m^2; significance of P_1, P_2, and P_3 as in Table 1.

glucose oxidase method (Test Combination Glucose, Boehringer Mannheim Diagnostica, Germany). Plasma ^{3}H-glucose and ^{14}C-glucose concentrations were determined using a method that was recently described in detail.[8] In brief, plasma was successively deproteinized, purified by ion exchange, evaporated to remove ^3H_2O, reconstituted with water, and counted for ^{14}C and ^{3}H by dual-channel scintillation spectrometry. The amount of ^{14}C present in the first carbon of glucose was determined with a fermentation method using *Leuconostoc Mesenteroides*. This technique is based on the unique property of this bacteria to convert C-1 in CO_2, C-2 and C-3 in ethanol, and C-4 to C-6 in lactic acid.[9] The procedure has been extensively described with regard to methodology, accuracy, and specificity.[8] The concentrations of insulin,[10] C-peptide (RIA-Mat C-peptide, Byk-Sangtec Diagnostica, Dietzenbach, Germany), and glucagon[11] were determined by radioimmunoassay. Free fatty acids (FFA) were assayed with an enzymic method (NEFA Quick, Boehringer Mannheim Yamanouchi, Tokyo, Japan). Total urinary nitrogen content was measured with the method of Kjeldahl using a Kjeltec I Apparatus (Tecator, Höganäs, Sweden).

Calculations

Rates of total glucose appearance (R_a) and disappearance (R_d) were calculated for each time period between two consecutive samples from the ^{3}H-glucose infusion rate and the ^{3}H-glucose data in plasma using the non–steady-state equations of Steele.[12] For these calculations it was assumed that the functional volume of distribution of glucose represents 65% of extracellular fluid (ECF).[13] Since the studied subjects were overweight, the ECF volume was calculated as a function of body surface area ([BSA] m^2) according to the following equations: for males, ECF = 8.46 (BSA − 0.52), and for females ECF = 11.74 (BSA − 0.90). These equations were computed from those proposed by Hume and Weyers relating measured total body water to calculated BSA in obese subjects,[14] assuming that ECF represents 27% of total body water in males and 33% in females.[15] Tissular R_d was calculated at each time period by subtracting from total R_d the estimated rate of urinary loss assuming that glucosuria only occurred at levels greater than 180 mg/dL and was proportional to glucose concentration above this level. The metabolic clearance rate (MCR) of total glucose was calculated as the ratio between tissular R_d and the corresponding mean glucose concentration. The 1-^{14}C-glucose data were used to calculate the R_a of oral glucose. Therefore, the contribution to plasma glucose concentration made by ingested glucose was estimated by dividing the plasma concentration of 1-^{14}C-glucose by the ^{14}C specific activity of the glucose drink. With the use of this calculated glucose concentration of exogenous origin and the measured ^{3}H-glucose counts, the exogenous R_a was estimated as indicated above for total R_a. The R_a of endogenous glucose was subsequently obtained as the difference between the R_a for total and oral glucose.

Carbohydrate and lipid oxidations were calculated from CO_2 production, O_2 consumption, and urinary nitrogen output.[16] Nonoxidative glucose metabolism was calculated as the difference between tissular R_d and glucose oxidation.

All data including the administered glucose load were normalized to a BSA of 1.73 m^2 and expressed as means ± SE. Results were analyzed using a two-factor (group × time) ANOVA with repeated measures on time, and whenever a difference was detected at a statistically significant level ($P < .05$), simultaneous pair-wise comparisons between groups were made by a modified t test using the standard error derived from the ANOVA. Areas

under the curves were calculated by the trapezoidal rule and compared using an ANOVA.

RESULTS

The three groups of subjects were comparable with regard to age, weight, body mass index, and BSA (Table 1).

Concentrations of Substrates and Hormones

The fasting hyperglycemia observed in the two diabetic subgroups (Table 2) was associated with nonsignificant elevations in insulin, C-peptide, glucagon, FFA, and lactate levels. A mild glycosuria (4 ± 2 mg/dL) occurred only in severely diabetic patients.

Following glucose ingestion (Fig 1), glycemia peaked at 197 ± 13 mg/dL after 45 minutes in control subjects and at 248 ± 10 mg/dL and 354 ± 12 mg/dL after 90 minutes in the two subgroups of diabetic patients ($P < .001$ for the three comparisons). Glucose concentration returned to baseline levels in approximately 3 hours in the control group and in 4.5 to 5 hours in both diabetic groups. The mean glucose concentration during the 5-hour study period in control, mildly diabetic, and severely diabetic subjects averaged, respectively, 122 ± 4, 184 ± 10, and 283 ± 13 mg/dL ($P < .001$ for the three comparisons; Table 2). C-Peptide and insulin responses were more sluggish and more sustained in mildly diabetic patients compared with control subjects (Fig 1), but the mean- 0 to 5-hour concentrations were equivalent in these two groups (5.9 ± 0.7 *v* 6.7 ± 0.6 ng/mL for C-peptide, and 61 ± 12 *v* 57 ± 6 μU/mL for insulin; $P > 0.05$; Table 2). In contrast, severely diabetic patients had average C-peptide (4.2 ± 0.3 ng/mL) and insulin (32 ± 2 μU/mL) concentrations that were significantly lower than those of the two other groups. As shown in Fig 1, changes in FFA levels mirrored those of glucose and insulin, with the observed decrease being less abrupt and more sustained in diabetic patients. Mean FFA values during the OGTT were not significantly different between groups. Glucagon levels decreased in the three groups following glucose ingestion. Mean 0- to 5-hour values were slightly but not significantly higher in severely diabetic patients than in control subjects (Table 2).

Glucose Fluxes

In the basal state (Table 3), hepatic glucose production was comparable in mildly diabetic patients and control subjects (131 ± 7 *v* 139 ± 8 mg/min; $P > .05$), whereas the severely diabetic patients had significantly elevated rates of production (187 ± 9 mg/min) compared with those of the two other groups ($P < .001$ for both comparisons). The MCR was reduced by approximately 18% and 33%, respectively, in mildly and severely diabetic patients compared with control subjects, with the difference between groups being statistically significant (Table 3).

After glucose ingestion, the R_a of exogenous glucose peaked at approximately 350 mg/min after 45 minutes in the three groups, and then slowly decreased (Fig 2). The cumulative amount of exogenous glucose reaching peripheral circulation in 5 hours was almost identical in the three groups (~59 g/5 h representing ~88% of the oral load;

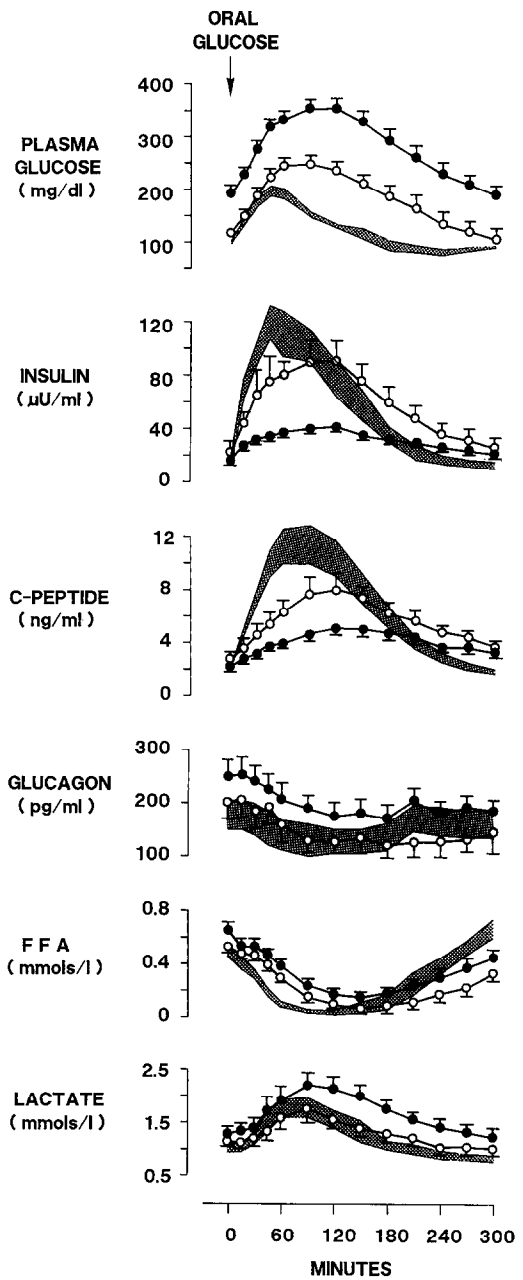

Fig 1. Substrate and hormone concentrations during an OGTT in patients with mild (○) and severe (●) diabetes. Shaded areas denote the responses of control subjects (mean ± SE).

Table 3). Endogenous glucose production decreased in nondiabetic subjects to a nadir of 39 ± 8 mg/min at 105 minutes, increasing to 96 ± 8 mg/min at 300 minutes. Suppression was more prolonged in diabetic patients so that glucose production rates at 300 minutes in mildly (36 ± 12 mg/min) and severely (66 ± 6 mg/min) diabetic patients were lower than corresponding values in control subjects, but the differences between groups were not statistically significant. Residual hepatic glucose production integrated over the 5-hour study period averaged 19.8 ± 1.5 g/5 h in the control group. Compared with this value, rates

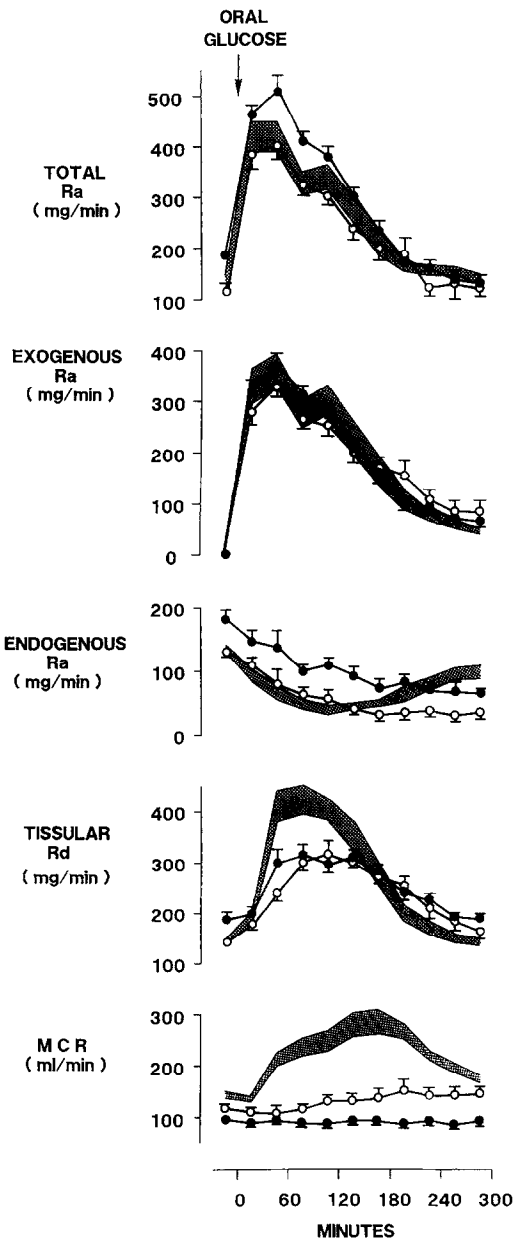

Fig 2. R_a, R_d, and MCR of glucose during an OGTT in patients with mild (○) and severe (●) diabetes. Shaded areas denote the responses of control subjects (mean ± SE).

of production were slightly but nonsignificantly lower in mildly diabetic patients (15.6 ± 1.8 g/5 h) and significantly ($P < .05$) higher in severely diabetic patients (28.2 ± 1.8 g/5 h). Consequently, the R_a of total glucose (exogenous + endogenous) was comparable in control (79.2 ± 2.7 g/5 h) and mildly diabetic subjects (73.2 ± 2.4 g/5 h), but values in severely diabetic patients (87.6 ± 2.1 g/5 h) exceeded those of the control ($P < .05$) and mildly diabetic ($P < .005$) groups. Since glucose concentrations had returned to baseline values in all groups by the end of the test, integrated total R_d compared very closely with total R_a in each group, and thus total R_d in severely diabetic patients (87.9 ± 2.4 g/5 h) was higher than in control (80.4 ± 2.4 g/5 h) and mildly diabetic subjects (74.1 ± 2.1 g/5 h), but the difference reached statistical significance only between the two diabetic groups ($P < .01$). Tissular R_d in mild (72.3 ± 1.8 g/5 h) and severe (76.2 ± 2.1 g/5 h) NIDDM patients was not significantly different from that of control subjects (80.4 ± 2.4 g/5 h). However, since diabetic patients displayed higher mean glucose levels during the OGTT, their 0- to 5-hour integrated MCR of glucose was reduced to 137 ± 7 and 93 ± 6 mL/min, respectively, in mildly and severely diabetic patients as compared with 220 ± 10 mL/min in control subjects, with all differences between groups being highly significant ($P < .01$ or less). In fact, as shown in Fig 2 and Table 3, severely diabetic patients did not stimulate their MCR to any extent following glucose ingestion.

Carbohydrate and Fat Oxidation

In control subjects, carbohydrate oxidation (Table 3) averaged 74 ± 11 mg/min in the basal state and increased by approximately 80% during the OGTT. Comparable figures were observed in the two subgroups of diabetic patients both before and after glucose-loading. Basal nonoxidative glucose disposal was comparable in mildly diabetic patients (72 ± 12 mg/min) and in control subjects (66 ± 7 mg/min; $P > .05$), but was significantly higher in severely diabetic patients (132 ± 11 mg/min) than in the two other groups ($P < .001$). During the OGTT, nonoxidative glucose disposal rates amounted to approximately 40 g/5 h in all three groups.

Fat oxidation rates were comparable (~60 mg/min) in the three groups in the basal state. Inhibition of lipid oxidation following glucose ingestion was more delayed and prolonged in diabetic patients compared with control subjects. Only in diabetic patients was lipid oxidation still below the baseline value at the end of the test. An overall inhibition of approximately 30% was observed in all groups during the 0- to 5-hour period.

DISCUSSION

Our results indicate that significant differences exist in the metabolic response to glucose ingestion between mild NIDDM patients with near-normal basal glycemia and severely diabetic patients with glucose levels in the range of 160 to 280 mg/dL. Part of the discussion will therefore be handled separately for the two diabetic subgroups.

Severely Diabetic Patients

In the basal state, the elevation in glucose levels observed in these patients in comparison to nondiabetic subjects is related to the combination of increased hepatic production (187 *v* 139 mg/min; $P < .001$) and decreased extraction of glucose by peripheral tissues as estimated by the reduced MCR (97 *v* 144 mL/min; $P < .001$). These two anomalies occur despite similar insulin and C-peptide levels in the two groups, suggesting that both the liver and peripheral tissues are resistant to the effect of insulin in NIDDM patients, in agreement with other studies.[1,2] However, it should be noted that comparisons of insulin and C-peptide levels

between nondiabetic and diabetic subjects should be interpreted with caution, since the proportion of immunoreactive insulin and C-peptide due to proinsulin is increased in NIDDM subjects.[17]

The abnormally elevated glucose levels observed in diabetic patients during the 5 hours of the OGTT are also associated with excessive glucose R_a, with cumulative R_a averaging 88 g/5 h in NIDDM patients and 79 g/5 h in nondiabetic subjects ($P < .05$). This phenomenon is entirely due to the persistence of higher rates of hepatic production in diabetic patients (28 *v* 20 g/5 h; $P < .05$). In fact, as observed in most[1,2,5,6] but not all[3] previous studies, percent suppression of hepatic glucose output is equivalent to that observed in nondiabetic controls; however, because basal rates of glucose production are greater in diabetic individuals, residual postglucose hepatic production remains elevated. On the other hand, the rate of entry of exogenous glucose is virtually identical in the two groups (~59 g/5 h), representing approximately 88% of the oral load. Because it is generally accepted that glucose absorption from the gut is virtually terminated after 5 hours, the portion of the oral load not appearing at the periphery (~8 g) represents the initial splanchnic extraction, a process that is not modified by diabetes in the present study. It should be noted that totally discordant results have been hitherto published regarding this issue, with the fraction of oral glucose reaching the systemic circulation in NIDDM patients having been reported as normal,[2] increased,[3,5] or reduced.[4]

The possible contribution of a reduced glucose uptake to the abnormal glycemic response of NIDDM patients to glucose ingestion should be evaluated with caution. If the data are analyzed over the entire 5-hour experiment, it is found that total and tissular R_d in diabetic patients are not significantly different from corresponding values in the control group. This is an expected finding since plasma glucose levels return to baseline in both groups after 5 hours so that cumulated input and output of glucose have to be similar between the two groups. These observations are consistent with other studies that showed that in diabetic patients both total tissular glucose uptake[3] and forearm muscle glucose uptake[3-5] are normal during the 5 to 7-hours following glucose ingestion. This type of data has been interpreted[3] as indicating that reduced glucose disposal in absolute terms does not participate in postprandial hyperglycemia in diabetic patients, leaving hepatic overproduction of glucose as the main cause of postprandial hyperglycemia in NIDDM. However, such a formulation tends to mask physiological reality. Indeed, in agreement with other studies,[1-3] we observed that the mean 0- to 5-hour MCR of glucose was more than 50% lower in NIDDM patients compared with control subjects, indicating a reduced ability of peripheral tissues to take up glucose. Muscle glucose clearance has been shown to be reduced to a similar extent.[3] As a consequence, a given rate of entry of glucose in diabetic patients results in higher plasma glucose concentrations, which in turn are capable of normalizing absolute uptake by a simple mass effect. It is acknowledged that the interpretation of MCR data is complicated by the fact that hyperglycemia per se reduces the MCR of glucose independent of changes in insulin levels, but the expected effect of hyperglycemia alone (10% to 35%)[18,19] is quantitatively insufficient to account entirely for the observed difference between mean postprandial MCR values in the two groups.

To evaluate the relative contribution of excessive R_a and deficient disposal of glucose to postprandial hyperglycemia of diabetic patients without relying on MCR data, it is necessary to limit the analysis to a shorter period of time that does not allow glycemia to return to its baseline value. Table 4 provides such an analysis for the 0- to 2-hour period during which glycemia increases by 158 mg/dL in NIDDM patients and by only 32 mg/dL in control subjects. During that period, total glucose entry in systemic circulation was 8 g higher in severely diabetic patients than in nondiabetic control subjects, and tissular disposal was reduced by approximately 9 g. In control subjects, the difference between total R_a and tissular R_d (~3 g) accumulates entirely in the glucose pool. The much larger difference (~20 g) observed in diabetic patients causes an accumulation of approximately 15 g in the glucose pool, while 6 g are eliminated in urine. Thus, according to this balance sheet, excessive R_a and reduced tissular R_d of glucose participate almost equally in the increased glycemic response of severely diabetic patients in whom the 0- to 2-hour integrated insulin concentrations were markedly reduced (36 ± 3 *v* 92 ± 10 μU/mL; $P < .001$). These observations are intermediate between those of Ferrannini et al,[2] who found that the excessive postprandial increase in plasma glucose level in NIDDM patients is mainly related to deficient uptake, and those of Mitrakou et al, who found that exaggerated glucose input is the only responsible factor. The abnormal hepatic and peripheral responses observed in our patients

Table 4. Balance Sheet of Glucose During the Initial 2 Hours of the OGTT

	Control Subjects (n = 11)	P_1	Mild NIDDM (n = 7)	P_2	Severe NIDDM (n = 12)	P_3
Oral load (g)	66.9 ± 1.8	NS	66.8 ± 3.9	NS	67.5 ± 2.0	NS
Systemic appearance of oral glucose (g/2 h)	37.8 ± 2.7	NS	33.1 ± 2.0	NS	38.3 ± 1.6	NS
Residual hepatic glucose output (g/2 h)	7.7 ± 0.8	NS	9.4 ± 0.7	<.001	14.8 ± 1.0	<.001
Total glucose R_a (g/2 h)	45.5 ± 2.5	NS	42.5 ± 2.3	<.005	53.1 ± 1.6	<.01
Tissular disposal (g/2 h)	42.2 ± 2.7	<.005	30.8 ± 1.6	NS	33.2 ± 1.6	<.005
Urinary loss (g/2 h)	0	NS	1.2 ± 0.5	<.001	6.0 ± 0.8	<.001
Total glucose R_d (g/2 h)	42.2 ± 2.7	<.01	32.0 ± 1.9	<.05	39.2 ± 1.5	NS
Change in glucose pool (g at 2 h)	3.5 ± 0.7	<.001	11.8 ± 1.3	<.05	14.8 ± 0.9	<.001

NOTE. All values including oral glucose load have been normalized to a BSA of 1.73 m^2; significance of P_1, P_2, and P_3 as in Table 1.

with overt diabetes are obviously related to the deficient insulin response (Fig 1, Table 2), and it is likely that insulin resistance further deteriorates these processes. Whether the mildly (and nonsignificantly) elevated levels of glucagon and FFA play an additional role in enhancing hepatic glucose production cannot be determined from the present data.

Mildly Diabetic Patients

As already reported by others,[20] we found that the modest elevation in basal glycemia (mean, 117 mg/dL) prevailing in mild NIDDM does not result from an augmented hepatic production of glucose, which tends even to be slightly lower than that of control subjects (131 *v* 139 mg/min), but rather from a decreased ability of peripheral tissues to take up glucose, as indicated by the lower MCR (118 *v* 144 mL/min; $P < .05$). The same conclusion holds true for the 5 hours of the OGTT. Integrated total R_a and its exogenous and endogenous components are normal, and the MCR of glucose is drastically reduced (137 *v* 220 mL/min; $P < .001$). This effect is probably mediated by peripheral insulin resistance, since the defective glucose disposal coexists with normal 0- to 5-hour integrated insulin and C-peptide levels. It is likely that some degree of insulin resistance also exists at the hepatic level because hyperglycemia per se has a suppressive effect on hepatic glucose production, and therefore the existence of a normal rate of hepatic glucose output in the presence of an elevated glucose concentration suggests that insulin is not fully active at the hepatic site.

Analysis of the glucose balance over the initial 2 hours shows that the greater increment in glycemia (+121 *v* +36 mg/dL; $P < .001$) is not related to an elevated R_a (42.5 *v* 45.5 g/2 h; $P > .05$), but rather to a marked reduction in tissular (30.8 *v* 42.2 g/2 h; $P < .005$) and total (32.0 *v* 42.2 g/2 h; $P < .01$) glucose disposal (Table 4) coexisting with a slight and nonsignificant reduction in the 0- to 2-hour integrated insulin level (73 ± 16 *v* 92 ± 10 μU/mL). Thus in mild NIDDM patients, as opposed to severely diabetic patients, reduced ability of peripheral tissues to dispose of glucose stands out as the only cause of postprandial hyperglycemia.

Figure 3 examines the relative participation of hepatic glucose overproduction and reduced efficacy of peripheral glucose uptake (MCR) in the abnormal postprandial glycemic response for all individual diabetic patients. It shows that the integrated 0- to 5-hour glucose levels are correlated positively with residual endogenous glucose production ($r = .74$, $P < .001$) and negatively with MCR ($r = .93$, $P < .001$). In addition, it demonstrates that the deterioration of the MCR is an early abnormality, already apparent in mild diabetes, whereas excessive hepatic glucose output is a later phenomenon that participates in postprandial hyperglycemia only in the severely diabetic state when absolute insulin deficiency is superimposed on diminished insulin action.

To our knowledge, there are no other isotope studies available on glucose production and disposal in mildly diabetic patients during an OGTT. However, interestingly, our observations in these patients are in total agreement with those of Sacca et al[22] in patients with glucose intoler-

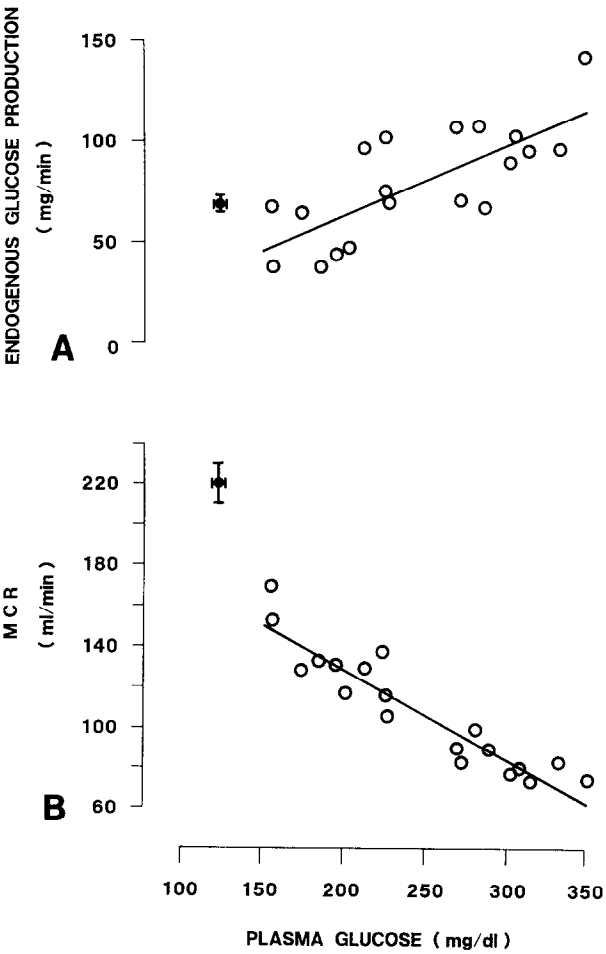

Fig 3. Relationships between mean plasma glucose concentrations and mean endogenous glucose production (A) or mean MCR of glucose (B) during a 5-hour OGTT in diabetic patients. A: $r = 0.74$, $P < .001$; B: $r = -.93$, $P < .001$. (●) Average values ± SE for the control group.

ance. They tested their subjects with intravenous glucose infusion using a combination of ^{3}H-glucose infusion and hepatic vein catheterization and showed that the altered glycoregulation resides entirely in peripheral tissues, whose ability to dispose of the glucose load is drastically reduced with no detectable anomaly in splanchnic glucose uptake or in hepatic glucose production. After termination of the present study, Mitrakou et al[23] published data on patients with glucose intolerance studied with the dual-isotope technique. They found that the excessive glycemic response during a 5-hour OGTT was entirely related to a reduced suppression of hepatic glucose output (−27% in obese glucose-intolerant patients *v* −46% in obese controls). Our data on mildly diabetic patients are in disagreement with these results. Comparative analysis of the two sets of data does not allow a satisfactory explanation for this difference. In the two studies, the control obese groups have similar endogenous production rates of glucose both basally and during the 5 hours of the OGTT, excluding systematic differences between the results of the two laboratories. Comparing the glucose-intolerant patients of Mitrakou et al[23] with our mildly diabetic subjects again shows similar

glucose production rates in the basal state (149 *v* 131 mg/min/1.73 m^2), but much higher 0- to 5-hour residual hepatic glucose output in glucose-intolerant subjects (110 *v* 52 mg/min/1.73 m^2) despite slightly lower levels of glucose and comparable levels of insulin and glucagon. It should be mentioned that in another study of more severely diabetic patients,[3] the same group observed only a 20% reduction in hepatic glucose production during a 5-hour OGTT, a figure well below the approximately 50% reduction generally reported in the literature[1,2] and confirmed in the present study.

Relative Importance of Oxidative and Nonoxidative Pathways in Postprandial Glucose Disposal

Since tissular glucose disposal and oxidation rates were virtually identical in the two subgroups of diabetic patients during the OGTT, all diabetic patients were handled as a single group for discussion of this topic. Over the 5-hour period, tissular glucose disposal and the proportions of glucose metabolized by oxidative versus nonoxidative pathways were comparable in diabetic and nondiabetic subjects. This observation indicates that the prolonged postprandial hyperglycemia characterizing diabetic patients restores normal rates of glucose disposal[24,25] and oxidation[26] through mass action in the face of a reduced concentration and/or efficiency of insulin. More interestingly, the reduction in glucose uptake observed in diabetic versus control subjects during the initial 2 hours of the study (32.5 *v* 42.2 g/2 h; $P < .001$) was equally due to an impairment in oxidative (14.4 *v* 18.6 g/2 h; $P < .05$) and nonoxidative (18.1 *v* 23.6 g/2 h; $P < 0.01$) pathways. These changes were not associated with significant differences in lipid oxidation (5.3 *v* 4.7 g/2 h; NS) or energy expenditure (124 *v* 123 kcal/2 h; NS) between groups. Our data on glucose metabolism are in sharp contrast with those published by Felber et al,[27] who reported that during a 3-hour OGTT, 80% of the reduction in glucose disposal observed in NIDDM patients can be accounted for by an impairment in nonoxidative disposal. It was suggested on this basis that deficient storage is the main cause of postprandial hyperglycemia in obese NIDDM patients. This discrepancy among results is mainly due to the fact that these investigators did not measure glucose uptake and calculated nonoxidative glucose uptake by subtracting from the oral load the amount of glucose oxidized and that accumulated in the ECF and eliminated in urine during the 3 hours of the test. Among other approximations, this mode of calculation assumes that hepatic glucose production is totally shut down after oral glucose, which is obviously not the case. On the contrary, a significant amount of glucose is still produced by the liver under these circumstances and, more importantly, residual glucose output is greater in diabetic than in nondiabetic subjects. Ignoring this fact leads to an underestimation of nonoxidative glucose disposal in NIDDM patients in comparison to nondiabetic controls. Interestingly, recalculating our own data from severely diabetic patients with this approximate method leads to the same conclusion as that formulated by Felber et al,[29] ie, approximately 75% of the impaired glucose uptake results from a deficiency in nonoxidative glucose disposal. Our observation that during both the initial 2 hours and entire 5 hours of the OGTT nonoxidative glucose disposal represents the same fraction of tissular R_d in diabetic and nondiabetic subjects does not necessarily imply that the pathways of nonoxidative glucose disposal are entirely normal in NIDDM. In addition to glycogen synthesis, nonoxidative glucose disposal includes a component due to glycolysis, and it has been clearly shown in forearm studies[3] that muscles of NIDDM patients oxidize a normal proportion of glucose taken up, but that storage as glycogen is deficient while lactate and alanine production are increased. Our data are compatible with these results. Although plasma lactate concentrations do not necessarily reflect lactate production rates, the slightly higher lactate levels observed during the OGTT in the severely diabetic group suggest that a greater proportion of glucose could have been converted to lactate in these patients, with less glucose being available for storage as glycogen.

In conclusion, in patients with overt diabetes as compared with control subjects, the excessive glycemic response to glucose ingestion is due to the combination of a higher R_a and a lower R_d of glucose. Since the amount of oral glucose reaching systemic circulation is normal, the excessive R_a is entirely due to an impaired inhibition of hepatic glucose production. On the other hand, in mild NIDDM patients with near-normal basal glycemia the abnormal postprandial glycemic response is exclusively due to deficient glucose uptake, with hepatic glucose production being normally suppressed. It is therefore suggested that during the transition from the normal state to overt NIDDM, the reduced glucose tolerance is initially due to an impaired peripheral glucose disposal reflecting mainly insulin resistance, inasmuch as a near-normal insulin secretion is maintained. The additional participation of impaired suppression of hepatic glucose output in the abnormal glycemic response can only be identified in a more severe diabetic state associated with a grossly impaired insulin response. The reduction in glucose uptake observed in NIDDM patients is related in equal proportions to an impairment in oxidative and nonoxidative glucose disposal.

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