The Disposal of an Oral Glucose Load in Patients With Non-Insulin-Dependent Diabetes

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Following glucose ingestion, tissue glucose uptake is enhanced and endogenous glucose production is inhibited, thus contributing to the maintenance of normal glucose tolerance. To examine whether these responses are disturbed in diabetes, glucose kinetics after oral glucose administration were studied in 12 non-insulin-dependent diabetic and 10 age- and weight-matched control subjects. A double tracer approach was used, whereby the endogenous glucose pool was labeled with 3-^{3}H-glucose and the oral load with 1-^{14}C-glucose. The two glucose tracers were separated in plasma by a two-step chromatographic procedure, and the two sets of isotopic data were analyzed according to a two-compartment model for the glucose system. Basally, glucose production was slightly higher in diabetics than in controls (2.51 ± 0.24 *v* 2.28 ± 0.11 mg/kg · min, NS) even though the former had higher plasma glucose (189 ± 19 *v* 93 ± 2 mg/dL, $P < .001$) and insulin (23 ± 4 *v* 12 ± 1 μU/mL, $P < .05$) concentrations. Following the ingestion of 1 g/kg of glucose, oral glucose appeared in the peripheral circulation in similar time-course and amount in the two groups (75 ± 2% of the load over 3.5 hours in the diabetics *v* 76 ± 3% in controls). Endogenous glucose production was promptly inhibited in diabetic and normal subjects alike, but the mean residual hepatic glucose production after glucose ingestion was significantly greater in the diabetic group (17 ± 2 *v* 10 ± 3 g/3.5 h, $P < .05$). At the end of the 3.5-hour study period, hepatic glucose production was still partially suppressed in both groups (by about 50%). This impairment in suppression of hepatic glucose production in the diabetics occurred despite the presence of marked hyperglycemia (mean plasma glucose following glucose ingestion = 298 ± 23 *v* 147 ± 7 mg/dL in controls, $P < .001$) and similar plasma insulin concentrations (46 ± 10 *v* 60 ± 7 μU/mL, NS). In the diabetics, endogenous glucose production was directly correlated with plasma glucose concentration both basally ($r = .92$, $P < .001$) and after glucose ($r = .63$, $P < .05$). At the end of 3.5 hours the healthy subjects had disposed of 60 ± 4 g by tissue uptake; this amount represented nearly 100% of the glucose (both oral and endogenous) that had appeared in the peripheral circulation. In contrast, in the diabetics tissue glucose disposal was only 44 ± 4 g over 3.5 hours ($P < .05$ *v* controls); 11 ± 3 g were lost into the urine and 16 ± 3 g had accumulated in the glucose space. In the diabetic group the mean plasma glucose concentration postload was inversely correlated with tissue glucose disposal ($r = -.70$, $P < .01$). We conclude that, in non-insulin-dependent diabetic patients: (1) the peripheral appearance of an ingested glucose load follows a normal pattern; (2) suppression of endogenous glucose production after oral glucose ingestion is impaired when compared with controls despite a twofold higher plasma glucose concentration and comparable plasma insulin levels; (3) tissue uptake of oral and endogenous glucose is markedly impaired; and (4) reduced tissue glucose uptake and relative overproduction of glucose by the liver both contribute to postprandial hyperglycemia.

THE PRESENCE of insulin resistance in patients with non-insulin-dependent diabetes (NIDDM) has been documented by a variety of techniques (reviewed in references 1 and 2), all of which involve the intravenous administration of glucose and/or insulin. Oral administration of glucose, however, remains the most common test for the diagnosis of diabetes and represents the normal route of glucose consumption in daily life. Although carbohydrate intolerance is clearly the hallmark of NIDDM, the site(s) and mechanism(s) responsible for the impaired response during oral glucose testing have not been elucidated. An altered response to glucose ingestion could result from an increased rate of appearance of oral glucose in the peripheral circulation, a diminished inhibition of endogenous (hepatic) glucose release, or an impaired uptake of glucose in peripheral or splanchnic tissues. To quantitate each of these dynamic processes, a double-tracer approach has been used.[3,4] With this technique, one tracer of glucose is infused intravenously at a constant rate while another tracer is given by mouth with the glucose load. The two sets of isotopic data thus obtained are analyzed according to a two-compartment model for the glucose system to yield estimates of the rates of appearance of oral and endogenous glucose. These estimates, and the concurrently measured rates of total glucose disposal, provide a quantitative description of the glycemic response to oral glucose administration, and locate the site, peripheral or hepatic, of any defect in glucose homeostasis.

In the present study, we have applied the double-tracer technique to measure the disposal of a standard oral glucose load in a group of nonobese, non-insulin-dependent diabetics, and have compared these results with those obtained in an appropriately matched group of nondiabetic subjects.

MATERIALS AND METHODS

Subjects

Two groups of subjects were studied (Table 1): 12 non-insulin-dependent diabetic and 10 age-matched healthy volunteers. All subjects were within 20% of their desirable body weight (based on the Metropolitan Life Insurance Co Tables, Chicago, 1959). The mean ± SEM duration of diabetes was 7 ± 1 years with a range of 1

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Table 1. Clinical Characteristics of the Study Subjects

	Controls (n = 10)	Non-Insulin-Dependent Diabetics (n = 12)
Sex (M/F)	7/3	8/4
Age (yr)	66 ± 3	59 ± 2
Weight (kg)	68 ± 4	71 ± 3
Obesity index (%)	100 ± 4	104 ± 4
Fasting plasma glucose (mg/dL)	93 ± 2	189 ± 19*
Fasting plasma insulin (μU/mL)	12 ± 1	23 ± 4†

*$P < .001$ *v* controls.

†$P < .05$ *v* controls.

to 19 years. Six of the diabetics had previously been treated with sulphonylurea agents while six had received dietary therapy only. All of the diabetics had been off all medications for at least 4 weeks prior to the study. For three days prior to study subjects consumed a weight-maintaining diet containing at least 200 g of carbohydrate per day. None of the control subjects had a family history of diabetes mellitus or were taking any medication. The nature, purpose, and potential risks of the study were explained to all subjects, and their informed, voluntary, written consent was obtained prior to their participation. The study protocol was reviewed and approved by the Human Investigation Committee at Yale University School of Medicine.

Experimental Protocol

Subjects were studied in the recumbent position at 8 AM after a 12-hour overnight fast. The double-tracer study was performed as previously described.[4] In brief, a primed-continuous infusion of D-3-^{3}H-glucose (New England Nuclear, Cambridge, MA) was started and continued throughout the study via an antecubital vein. The constant infusion rate was approximately 0.4 μCi/min, and the ratio of the priming dose to the constant infusion rate was 100 in the controls. In the diabetics the prime was increased in proportion to the increase in fasting plasma glucose concentration. A period of 120 minutes (normal subjects) or 180 minutes (diabetics) was allowed for equilibration of tritiated glucose; the end of this equilibration period was taken to be time zero. A steady state of 3-^{3}H-glucose specific activity was achieved in all control and diabetic subjects during the last 30 minutes of the equilibration period. At time zero, each subject ingested 1 g of glucose per kg body weight (as a 45% aqueous solution) containing 100 μCi of D-1-^{14}C-glucose (New England Nuclear) over five minutes. Blood was drawn from a wrist vein cannulated retrogradely and heated to 70°C in a hot box[4] to allow arterialization of venous blood. Blood samples were obtained every 5 minutes for 20 minutes before time zero, and then every 15 minutes for 210 minutes following glucose ingestion. Subjects voided just prior to ingestion of the glucose load, and urine was collected at the end of the experiment for determination of urinary glucose loss.

Analytical Procedures

Plasma glucose was assayed by the glucose oxidase method on a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA). Plasma insulin concentration was measured by radioimmunossay using talc to separate bound from free insulin.[5] Plasma ^{3}H-glucose radioactivity was determined as previously described.[4] Plasma ^{14}C-glucose radioactivity was measured as ^{14}C-gluconic acid after reaction with glucose oxidase and column chromatographic separation.[6] ^{14}C radioactivity in position 6 of the glucose molecule was determined by the method of Reichard et al.[6] Aliquots of the infused (^{3}H-glucose) and the ingested (^{14}C-glucose) glucose tracer were run in triplicate for the precise determination of the ^{3}H-glucose infusion rate and the specific activity of the glucose drink, respectively. Counting was performed in a two-channel liquid scintillation counter (TriCarb, Packard, Downers Grove, IL), with corrections for counting efficiency and for spillover of ^{14}C counts into the ^{3}H channel.

Calculations

Basal rates of glucose appearance in the systemic circulation (Ra) were measured as the ratio of the ^{3}H-glucose infusion rate to the steady-state plasma ^{3}H-glucose specific activity (mean of five determinations until time zero). During the last 30 minutes prior to ingestion of the glucose drink, all subjects had achieved a steady-state equilibrium of plasma tritiated glucose specific activity. After glucose ingestion, total rates of glucose appearance and of glucose disappearance from the peripheral circulation (Rd) were computed from the ^{3}H-glucose data with the use of a two-compartment model for the glucose system previously described in detail.[4] Calculations were based on a total glucose distribution volume of 200 mL/kg, an initial glucose distribution volume of 65 mL/kg, and a clearance rate of glucose from the first compartment of 29 mL/kg · min. Urinary glucose loss was subtracted from the rate of total glucose disappearance that was integrated over 210 minutes to obtain total tissue glucose disposal during the entire test. The ^{14}C-glucose data were used to calculate the appearance of oral glucose (RaO).[4] ^{14}C-Glucose counts were corrected for recycling in three-carbon glucose precursors. This recycling was estimated by multiplying by 4 the ^{14}C counts in position 6, and then subtracting these "recycled" counts from the total ^{14}C-glucose counts.[6] The corrected ^{14}C-glucose radioactivity represents only the tracer originally added to the drink. This plasma radioactivity was divided by the specific activity of the glucose drink to calculate the plasma "oral" glucose concentrations, ie, the levels that glucose would attain in the systemic circulation if the sole source of glucose were the oral load. These calculated "oral" glucose concentrations and the ^{3}H-glucose data were then used to compute the rates of appearance of oral glucose in peripheral plasma (RaO) according to the same model of the glucose system as employed to derive total rates of glucose appearance.[4] The rate of appearance of endogenous glucose (RaE) was subsequently obtained as the difference between total and oral rates of glucose appearance. All rates of glucose turnover were averaged over 15-minute intervals.

All results are expressed as the mean ± SEM. Integration was performed by the trapezoidal rule. Comparisons between groups were performed using the two-tailed Student's *t*-test for unpaired data. *P* values greater than or equal to .10 are reported as not significant (NS). Linear regression was performed by the method of least squares analysis.

RESULTS

In the fasting state, both plasma glucose ($P < .001$) and plasma insulin ($P < .05$) concentrations were approximately twofold higher in the diabetic *v* the control group (Table 1). Following glucose ingestion, the diabetics showed a marked and sustained hyperglycemic response compared to control subjects (Fig 1). In contrast, the plasma insulin concentrations following glucose ingestion were not statistically different between the two groups. The mean plasma insulin level over the 210 minutes following glucose ingestion was 60 ± 7 μU/mL in the controls and 46 ± 10 μU/mL in the diabetics (NS). However, the increment in plasma insulin in the diabetic patients was significantly reduced when compared with controls whether expressed in absolute (23 ± 6 *v* 48 ± 7 μU/mL, $P < .01$) or relative (97 ± 22% *v* 414 ± 62%, $P < .001$) terms.

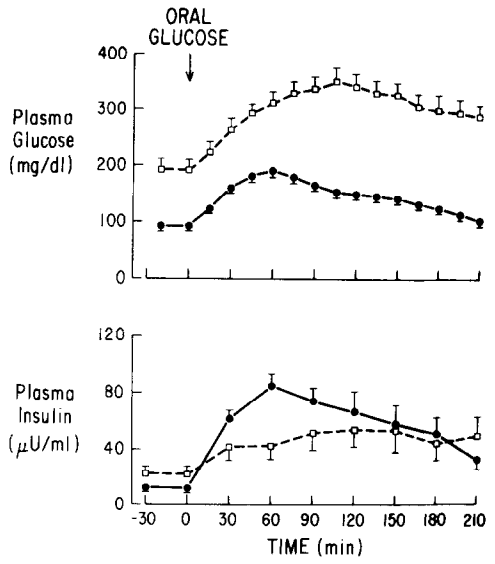

Fig 1. Plasma glucose and insulin concentrations in non-insulin-dependent diabetic (□---□) and healthy subjects (●—●) in the fasting state and following the ingestion of 1 g/kg of glucose.

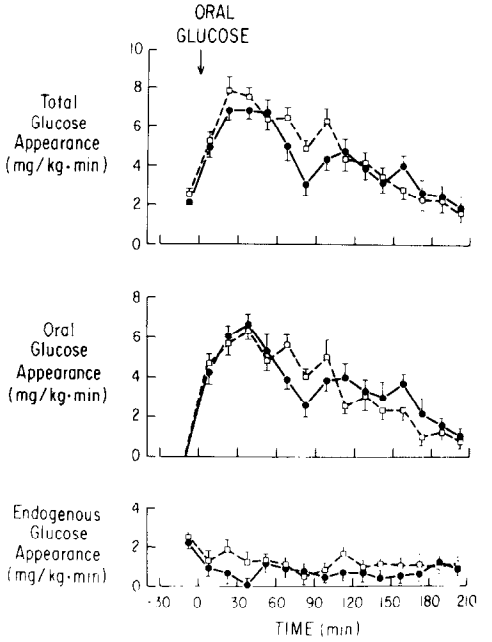

Fig 2. Rates of appearance of total (oral plus endogenous), oral, and endogenous glucose in diabetic (□---□) and control (●—●) subjects after oral glucose ingestion. The initial (basal) point represents the mean of five determinations from −20 to 0 minutes.

Basal endogenous glucose production was slightly, but not significantly, higher in the diabetics (2.51 + 0.24 mg/kg · min) compared to controls (2.28 ± 0.11 mg/kg · min). Because of fasting hyperglycemia, however, the calculated basal glucose clearance rate was markedly reduced in the diabetic *v* the control subjects (1.35 ± 0.05 *v* 2.46 ± 0.09 mL/kg · min, $P < .001$).

Following glucose ingestion, the total rate of glucose appearance (Ra) in the peripheral circulation rose to essentially the same extent and in similar time-course in both study groups (Fig 2). Peak values of 7 to 8 mg/kg · min were reached at 30 to 60 minutes with a second, smaller peak evident between 90 and 120 minutes. This pattern largely reflected the appearance of ingested glucose in peripheral plasma (RaO), whose profile paralleled those of total Ra and plasma glucose levels (Fig 2). Of note is that, at the end of 3.5 hours, oral glucose was still entering the periphery in both groups at rates that were significantly different from zero (0.81 ± 0.40 mg/kg · min in diabetics and 0.98 ± 0.34 mg/kg · min in controls). Basal endogenous glucose production was suppressed throughout the period of glucose absorption (Fig 2). The decline in endogenous glucose production was somewhat more rapid in the control compared to diabetic subjects; it reached a nadir of about 0.5 mg/kg · min between 75 and 105 minutes, and tended to return toward baseline thereafter. At the end of 3.5 hours, however, endogenous glucose Ra was still significantly inhibited by approximately 50% as compared to fasting values, both in diabetic and control groups.

The total rates of glucose disappearance (Rd) from the systemic circulation in controls rose above baseline between 30 and 90 minutes attained a plateau of 5 to 6 mg/kg · min, and remained significantly elevated for the entire absorption period (Fig 3). In the diabetics, the initial rise in Rd lagged roughly 30 to 90 minutes behind that of the controls but eventually reached equivalent levels (Fig 3). This apparently normal pattern, however, was obtained at the expense of greater hyperglycemia in the NIDD patients (whose mean glucose concentration during 3.5 hours of absorption was 298 ± 23 mg/dL) as compared to the controls (147 ± 7 mg/dL, $P < .001$). Thus, when a plasma glucose clearance rate is calculated (Fig 3), the diabetics failed to show any stimulation of this parameter above its fasting value. In

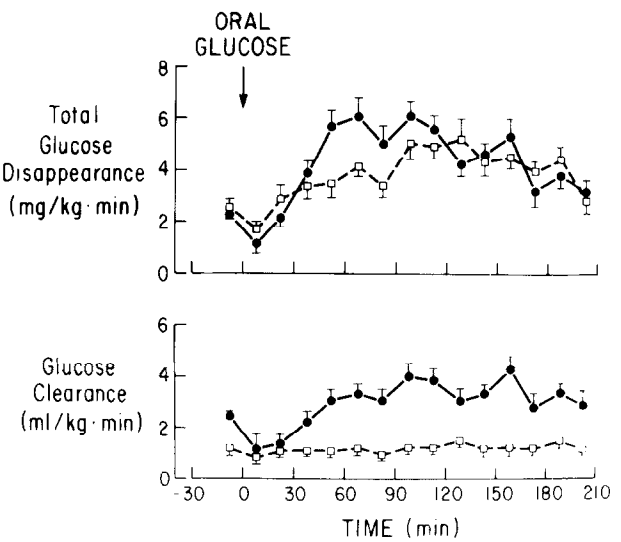

Fig 3. Rates of disappearance and clearance of plasma glucose from the peripheral circulation in diabetic (□---□) and control (●—●) subjects after oral glucose ingestion. The initial (basal) point represents the mean of five determinations from −20 to 0 minutes.

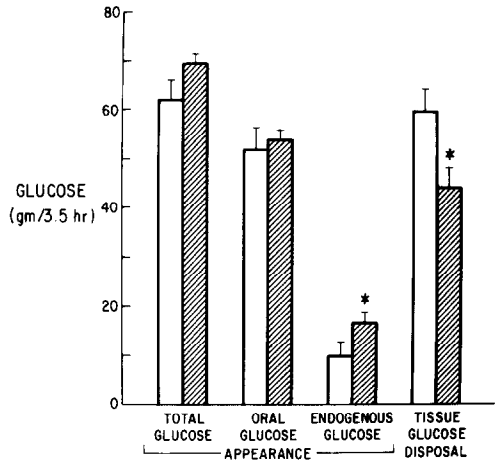

Fig 4. Cumulative glucose fluxes over 3.5 hours following glucose ingestion in diabetic (▨) and control (□) subjects. (*$P < .05$ vcontrols).

contrast, glucose clearance in controls, after an initial decline, increased significantly above baseline between 75 and 120 minutes and was still higher than basal at the end of the study. The mean glucose clearance during the 3.5-hour study was approximately threefold greater in the control subjects when compared to the diabetic group (2.98 ± 0.25 *v* 1.12 ± 0.17 mL/kg · min, $P < .001$).

Although the total Rd of glucose during the 3.5 hours after glucose ingestion was not significantly different in diabetic *v* control subjects (56 ± 2 *v* 60 ± 4 g/3.5 h, NS), one must consider that glucosuria was negligible in the control group whereas the diabetic patients lost 11 ± 3 g of glucose in the urine. Therefore, the total Rd of glucose overestimated actual tissue glucose uptake in the patients by an amount equal to their glucosuria. If one calculates the true rate of tissue glucose uptake (total Rd minus urinary glucose loss),

Table 2. Balance Sheet for the Disposal of an Oral Glucose Load in Non-Insulin-Dependent Diabetic and Healthy Subjects*

	Controls (n = 10)	Diabetics (n = 12)
Ingested load	68 ± 4	71 ± 3
Residual endogenous release (a)	10 ± 3	17 ± 2‡
Oral glucose appearance (b)	52 ± 5	54 ± 2
Total glucose appearance (a + b)	61 ± 4	70 ± 2
Tissue disposal (c)	60 ± 4	44 ± 4‡
Urine loss (d)	0	11 ± 3§
Change in glucose pool† (e)	1 ± 1	16 ± 3‖
Total glucose accounted for (c + d + e)	61 ± 4	72 ± 2
Glucose unaccounted for (a + b) − (c + d + e)	0	−1 ± 7¶

*Values are rounded off to the nearest gram.

†Change in glucose pool is calculated as the difference between the initial and final plasma glucose concentration multiplied by the distribution space of glucose (200 mL/kg).

‡$P < .05$ *v* controls.

§$P < .01$ *v* controls.

‖$P < .001$ *v* controls.

¶Not significantly different from zero.

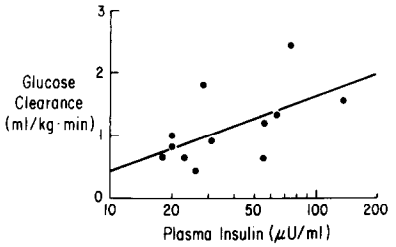

Fig 5. Relationship between glucose clearance and the mean plasma insulin concentration in diabetic subjects after glucose ingestion ($r = .57$, $P < .05$).

then a significant impairment of tissue glucose uptake in the diabetic patients is evident (44 ± 4 *v* 60 ± 4 g/3.5 h, $P < .05$; Fig 4, Table 2).

The cumulative glucose flux during the 210-minute period following glucose ingestion is shown in Fig 4 and Table 2. Total Ra of glucose was similar in both groups. Likewise, almost identical proportions of the administered glucose load were recovered in the systemic circulation: 75 ± 2% in the diabetics *v* 76 ± 3% in the controls. Suppression of endogenous glucose production was slightly greater in control *v* diabetic subjects whether expressed in absolute (10 ± 3 *v* 17 ± 2 g/3.5 h, $P < .05$) or relative (by 67 ± 6 *v* 54 ± 5%; $P = .09$) terms. Furthermore, tissue glucose disposal was impaired by approximately 25% in the diabetics. The mean plasma glucose clearance rate (MCR) during glucose absorption was reduced by over 60% in the diabetics as compared to the controls and was directly correlated with the mean plasma insulin levels during the 210 minutes of the study ($r = .57$, $P < .05$) (Fig 5).

In the NIDD patients, the magnitude of fasting hyperglycemia was directly related to basal endogenous glucose output ($r = .92$, $P < .001$) (Fig 6). In a similar manner,

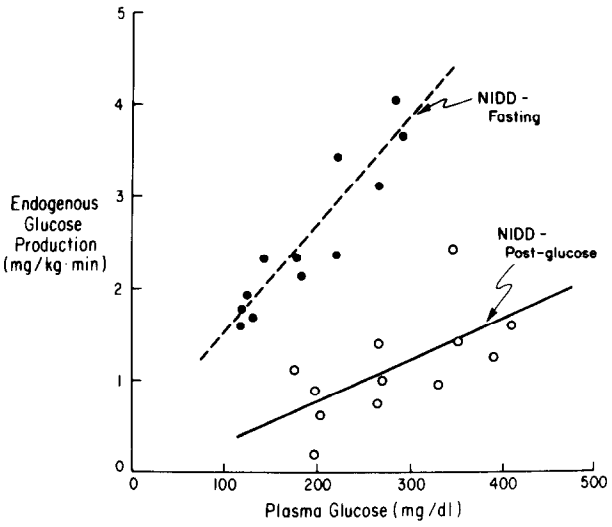

Fig 6. Relationship between endogenous glucose production and plasma glucose concentration in the fasting state ($r = .92$, $P < .001$) and following oral glucose administration (mean values over 3.5 hours, $r = .63$, $P < .05$) in non-insulin-dependent diabetic subjects.

residual glucose production following glucose ingestion was directly related to the level of postprandial hyperglycemia during the entire absorption period ($r = .63$, $P < .05$, Fig 6). Finally, in the diabetic group the mean postingestion glucose concentration was inversely related to the rate of plasma glucose disappearance ($r = -.70$, $P < .01$).

DISCUSSION

The principal findings of the present study can be summarized as follows. First, the appearance of an equivalent glucose load in the systemic circulation is the same in diabetic and nondiabetic subjects. Accelerated absorption of ingested glucose is, therefore, an unlikely cause of postglucose hyperglycemia in diabetics. Whether this conclusion would be changed by the presence of vascular or neuropathic complications in patients with longer-term diabetes remains to be ascertained. However, we believe this would be unlikely since the presence of autonomic neuropathy would be expected to delay, rather than enhance, the absorption of an oral glucose load. Second, whole-body tissue glucose uptake during glucose absorption is significantly depressed in diabetics despite their heightened glycemic response and their normal absolute insulin levels. It should be remembered that both hyperinsulinemia as well as hyperglycemia (by its mass action effect) contribute to the augmentation in glucose disposal following glucose ingestion. It is likely that both diminished insulin-mediated glucose uptake[1,2] and an impaired ability of hyperglycemia to promote glucose disposal[7] are responsible for the decreased oral glucose tolerance observed in our normal weight non-insulin-dependent diabetic subjects. The severity of the impairment in insulin action is further highlighted by the calculation of plasma glucose clearance. Although the glucose clearance may modestly overestimate (by 15% to 20%) the severity of insulin resistance, particularly when plasma glucose levels are very high and insulin levels are low,[8-10] it is nevertheless apparent that the diabetic patients have a substantial impairment (>60%) in their ability to clear glucose from the circulation during the postprandial period. Third, suppression of endogenous glucose production following glucose ingestion is impaired in NIDDM despite a much greater elevation in the plasma glucose level and a normal absolute insulin concentration.

The balance sheet shown in Table 2 for the cumulative glucose fluxes over 3.5 hours after glucose administration gives a clear quantitative picture of diabetic glucose intolerance. Whereas in healthy subjects essentially all of the glucose that appears in the systemic circulation, whether of endogenous or exogenous origin, is disposed of by tissue uptake in 3.5 hours, in the diabetics only about 60% is assimilated, the remainder being passed into the urine or accumulated in the glucose space.

It is of interest that the correlations found in the present study are similar to those observed in another group of NIDD subjects in whom insulin resistance was quantitated with the use of the euglycemic clamp technique.[11] Thus, glucose uptake and clearance during glucose absorption were reduced in the present study to the same extent as observed during insulin infusion, ie, by approximately 30% and 60%, respectively. Likewise, the fasting plasma glucose concentration was directly related to the fasting rate of glucose output in both the present and the previous series. Furthermore, in the diabetics in the present study, the mean postingestion plasma glucose level was linearly related to the residual rate of endogenous glucose production (Fig 6). This finding suggests that those patients who have the highest glucose output in the fasting state also have the highest (or least suppressed) rates of glucose release during oral glucose absorption and are more hyperglycemic under both circumstances. Indeed, basal hepatic glucose production in the diabetic patients was highly correlated with the rate of residual endogenous glucose release during the 3.5 hours following glucose ingestion ($r = .71$, $P < .01$). Therefore, it can be concluded that glucose overproduction is an important determinant of diabetic hyperglycemia, both in the postabsorptive state and postprandially. This is likely to be even more evident in type I diabetics, in whom endogenous glucose output has been reported not to be inhibited by glucose ingestion.[12]

Diminished glucose utilization, on the other hand, stands out as the major factor contributing to postprandial hyperglycemia. Among our patients, in fact, higher postload glucose levels were associated with lower rates of tissue glucose disposal ($r = -.70$, $P < .01$). It should be noted, however, that the decrease in tissue glucose disposal, although significant, may underestimate the defect in insulin action since both hyperglycemia and hyperinsulinemia are known to promote tissue glucose uptake. In order to obtain a measure of insulin action independent of hyperglycemia, calculation of the glucose clearance has been advocated. Although some previous studies have suggested that hyperglycemia produces a modest (15% to 20%) reduction in glucose clearance,[8-10] particularly when the plasma insulin concentration is maintained at basal levels,[8,9] we[13] as well as others[14] have demonstrated that glucose clearance provides a useful and reasonable index of insulin action in the insulin-stimulated state as long as one does not overinterpret small differences between groups. With these reservations in mind, we have compared the glucose clearance in diabetic and control subjects after oral glucose ingestion. As shown in Fig 3, the glucose clearnance in the diabetic patients failed to increase above basal levels and was reduced by over 60% when compared to controls (1.12 ± 0.17 v 2.98 ± 0.25 mL/kg · min, $P < .001$). This quantitatively large and statistically significant reduction in glucose clearance serves to emphasize the severity of the defect in insulin action in the diabetic group.

Our studies also suggest that relative hypoinsulinemia contributes to postprandial hyperglycemia in patients with NIDD. Although the absolute plasma concentrations of insulin were not different in control and diabetic subjects, these "normal" values in the diabetics occurred in the presence of plasma glucose levels that were more than twofold higher than in control subjects. Moreover, the increment in plasma insulin in control subjects (48 ± 7 μU/mL) in response to the glucose load was approximately twice as great as in the diabetic patients (23 ± 6 μU/mL, $P < .01$).

Finally, the diabetic patients with the lowest postprandial plasma insulin concentrations also exhibited the greatest reduction in glucose clearance after glucose ingestion (Fig 5).

Studies using the hepatic venous catheter technique have suggested that defective splanchnic uptake of glucose is the chief mechanism responsible for hyperglycemia in non-insulin-dependent diabetics following glucose ingestion.[15] The technique used in the current study measures total tissue glucose disposal. The relative contribution of splanchnic vis-à-vis peripheral glucose uptake could not, therefore, be determined in the present study. In healthy subjects, however, no more than 20% to 30% of an oral glucose load is retained within the splanchnic area over four hours.[16] This makes it unlikely, on a priori grounds, that reduced splanchnic glucose uptake is the major factor responsible for the postprandial hyperglycemia of non-insulin-dependent diabetes. Furthermore, the fact that diabetics exhibit approximately the same relative reduction in glucose uptake following glucose ingestion as during an insulin clamp, in which the majority of infused glucose is taken up by peripheral tissues,[17] is consistent with the notion that the periphery is the main site of glucose underutilization.

Finally, it should be noted that the choice of isotopes employed for the measurement of total glucose appearance (3-^{3}H-glucose) and oral glucose appearance (1-^{14}C-glucose) may quantitatively affect the results obtained with this technique. Both of these glucose tracers may be incorporated into glycogen via the direct pathway (ie, glucose → glucose-1-phosphate → glycogen) without loss of their respective labels so that re-release of labeled glucose may occur. This would lead to an underestimation of the rate of glucose appearance. However, several recent studies[18-20] have suggested that the majority of liver glycogen is repleted via the indirect pathway (ie, glucose → lactate/pyruvate → glucose-1-phosphate → glycogen). Since 3-^{3}H-glucose loses its label at the triose phosphate isomerase step in glycolysis, one would not expect substantial labeling of glycogen to occur with this tracer. Furthermore, following glucose ingestion plasma glucagon levels decline and the plasma insulin concentration rises. These hormonal changes, in combination with hyperglycemia, lead to a marked inhibition of hepatic glucose release. This would minimize the release of any small amounts of label that might have been incorporated into glycogen after glucose ingestion. This conclusion is consistent with previous studies by Radziuk et al[3] and Sacca et al[21] who have shown that after the administration of radiolabeled glucose, infusion of glucagon or epinephrine produces a negligible release of labeled glucose from liver glycogen. Finally, a recent paper by Bell et al[22] suggests that while the use of a glucose tracer that retains its label in glycogen (3-^{3}H-glucose) *v* a tracer that loses its label in glycogen (2-^{3}H-glucose) yields quantitatively small differences in the rates of glucose turnover during physiologic hyperinsulinemia in diabetic subjects, it does not qualitatively change the observation that diabetic patients are resistant to the action of insulin. Therefore, it is unlikely that our choice of radioisotopic tracers would alter the conclusions of our study or lead to a significant understimation of appearance rates of oral or endogenous glucose under the present experimental conditions.

In summary, defects in both tissue glucose uptake as well as suppression of hepatic glucose production contribute to the glucose intolerance observed in normal weight NIDDM following glucose ingestion. From the quantitative standpoint, however, the impairment in tissue glucose uptake (16 g/3.5 h) is the major disturbance responsible for the excessive rise in plasma glucose concentration. The impaired suppression of hepatic glucose production contributed only 7 g/3.5 h to the excessive hyperglycemic response observed in the diabetic subjects. Lastly, some caution should be introduced about extrapolating the present results to the obese NIDD patient since obesity per se (ie, independent of diabetes) is known to exert its own separate effects on insulin action.

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