Insulin Resistance is a Prominent Feature of Insulin-dependent Diabetes

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SUMMARY

Tissue sensitivity to insulin was examined in 36 control subjects and 19 insulin-dependent diabetics with diabetes of long-standing duration (mean = 10 ± 3 yr) employing the insulin clamp technique (Δ plasma insulin concentration ~100 μU/ml). Eleven of the diabetics (group I) were studied at their fasting hyperglycemic level (173 mg/dl); the remaining 8 diabetics (group II) were studied after lowering their plasma glucose concentration to euglycemic levels (90 mg/dl). Despite plasma glucose levels that were almost twice as great in the diabetics (group I, 173 versus 91 mg/dl, $P < 0.001$), insulin-mediated glucose metabolism, 4.77 ± 0.18 mg/kg·min, was reduced by 32% versus controls, 7.03 ± 0.22 mg/kg·min ($P < 0.01$). When the control subjects were restudied at plasma glucose levels (166 ± 2 mg/dl) that were comparable to those of the diabetics, insulin-mediated glucose metabolism was 12.14 ± 0.96 mg/kg·min ($P < 0.01$). In diabetics studied at euglycemic levels (group II) insulin-mediated glucose metabolism, 3.39 ± 0.30 mg/kg·min, was reduced even further. The metabolic clearance rate in the 19 diabetics, 3.31 ± 0.23 mg/kg·min, was reduced by 58% compared with controls, 7.83 ± 0.25 ($P < 0.001$). These results emphasize the severe degree of insulin resistance that exists in the insulin-dependent diabetics.

Basal hepatic glucose production in the diabetic group, 2.96 ± 0.24 mg/kg·min, was 26% greater than in the controls, 2.35 ± 0.04 ($P < 0.001$). The fasting plasma glucose concentration displayed a strong positive correlation ($r = 0.857$, $P < 0.001$) with basal hepatic glucose production and was weakly and inversely correlated ($r = -0.413$, $P = 0.07$) with the basal glucose clearance. Following hyperinsulinemia, however, suppression of hepatic glucose production was ~95% in both diabetics and controls, suggesting that peripheral tissues are primarily responsible for the observed impairment in insulin-mediated glucose uptake.

The present results indicate that impaired insulin action is a common feature of insulin-dependent diabetics, despite daily insulin requirements (35 ± 2 U/day) that would not clinically characterize them as being insulin resistant. DIABETES *31*:795–801, September 1982.

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Insulin resistance is a well-recognized feature of non-insulin-dependent, type II (maturity-onset) diabetes mellitus.[1–4] However, few studies have examined whether or not insulin resistance is also present in insulin-dependent, type I (juvenile-onset) diabetes mellitus. Himsworth and Kerr[5] were among the first to suggest that insulin action might be impaired in insulin-dependent diabetics (IDD). Using a combined insulin-glucose tolerance test they found that although most insulin-dependent diabetics whose disease started early in life were insulin sensitive, a significant percentage manifested resistance to the action of insulin. Employing the same insulin-glucose tolerance test, Martin and Stocks found that 22 of 43 insulin-dependent diabetics were insulin resistant.[6] Ginsberg,[7] using the quadruple infusion (propranolol, epinephrine, glucose, and insulin) technique to measure tissue sensitivity to insulin, found normal sensitivity in six insulin-dependent diabetics. However, a wide range was observed, with three of the six diabetics being well above the mean of the controls and three well below the mean control value. Harano et al.,[8] employing the somatostatin modification of the quadruple infusion technique, demonstrated significant insulin resistance in five of five insulin-dependent diabetics studied.

Most insulin-dependent diabetics require 35–40 U (often more) of insulin per day to achieve glucose control that is usually suboptimal (i.e., fasting hyperglycemia persists and wide swings in plasma glucose concentration after meals are common). Experience at Yale with 20 adult IDD treated with a portable insulin infusion pump system indicates that the average daily insulin dose to achieve good control is 50 ± 5 U/day (data kindly provided by Dr. Robert Sherwin). Since recent studies examining insulin kinetics in man have

estimated the mean daily insulin secretory rate to be in the order of 20–25 U,[9–14] it is obvious that most IDD must be resistant to the action of insulin.

Taken as a whole, the above studies would suggest that a significant percentage of IDD demonstrate insulin resistance. However, it is a common clinical teaching that in the absence of insulin antibodies, tissue sensitivity to insulin is normal in IDD and insulin-dependent diabetes is not listed as a cause of insulin resistance.[15] In the present study, we have employed the insulin clamp technique[16] to directly assess the presence of tissue insensitivity to insulin in young, insulin-dependent diabetic subjects.

METHODS

Subjects. The study population consisted of two groups. (1) 19 insulin-dependent diabetics, ranging in age from 18 to 49 yr (mean = 33 ± 2 yr) and in ideal body weight (based on medium frame individuals, Metropolitan Life Insurance Tables, 1959) from 86% to 120% (mean = 101 ± 2%), were studied. There were 8 males and 11 females (Table 1). The mean duration of diabetes was 12 ± 2 yr and the mean daily insulin dose was 35 ± 2 U of NPH or the equivalent. In addition to their long-acting insulin, three patients also took 10, 4, and 4 U of regular insulin every morning. Thirteen of the 19 diabetic subjects had a prior history of ketoacidosis. None had evidence of renal or hepatic disease as documented by routine laboratory determinations. (2) Thirty-six healthy volunteers, ranging in age from 21 to 49 yr (mean = 36 ± 1 yr) and in ideal body weight from 90% to 116% (mean = 102 ± 1%), served as the control population. There were 24 males and 12 females. None of the control subjects had any family history of diabetes mellitus. Other than insulin, none of the diabetic or control subjects were taking any medications. The last dose of insulin was administered 24 h before beginning the insulin clamp study. All subjects were consuming a weight-maintaining diet containing at least 200 g of carbohydrate per day for at least 3 days before study. All studies were performed at 8 a.m. following a 12-h overnight fast. The purpose, nature, and potential risks of the study were explained to all subjects and written consent was obtained before their participation. The protocol was reviewed and approved by the Committee on Human Investigation at the Yale University School of Medicine.

Insulin clamp study. Before each study, a catheter was inserted into an antecubital vein under local anesthesia for the administration of all test substances. A second catheter was inserted retrogradely into a forearm vein for all blood sampling. The hand was then inserted into a heated box that was maintained at 70°C to ensure arterialization of the venous blood.[17] Following the collection of at least three baseline blood samples, a primed-continuous (40 mU/m²·min) infusion of crystalline porcine insulin (Eli Lilly and Co., Indianapolis, Indiana) was administered to acutely raise and

TABLE 1
Summary of pertinent clinical and laboratory data in 19 insulin-dependent diabetics. Group I was clamped at their fasting glucose level. In group II, the plasma glucose concentration was allowed to decrease to 90 mg/dl, at which level they were clamped

Patient no.	Age (yr)	Obesity index	Duration of diabetes (yr)	Insulin dose* (U)	Fasting plasma glucose (mg/dl)	Glucose metabolism (mg/kg · min)	Glucose clearance (ml/kg · min)	Increase in insulin concentration (μU/ml)
Group I								
1	44	1.15	25	52	90	3.27	3.67	67
2	32	0.86	14	36	93	4.18	4.49	71
3	28	1.05	17	46	285	5.55	1.95	(110)†
4	20	0.94	0.5	35	185	6.44	3.48	87
5	18	1.04	0.5	20	270	3.36	1.24	66
6	44	0.90	3.5	34	238	5.75	2.42	82
7	18	0.96	1.5	30	105	3.60	3.43	(84)†
8	43	1.20	10	30‡	205	4.18	2.04	94
9	49	0.86	5	22	260	8.05	3.10	87
10	41	1.04	5	24	100	3.58	3.58	90
11	38	1.15	29	38	96	2.84	3.19	59
Mean	34	1.01	10	34	175	4.77	3.08	78
±SEM	±3	±0.04	±3	±3	±24	±0.48	±0.29	±4
Group II								
12	25	1.06	11	55	186	3.03	3.44	47
13	23	0.94	17	43	179	4.46	4.96	55
14	26	1.03	14	29	226	3.73	4.10	69
15	36	1.02	10	42	198	2.07	2.25	99
16	38	1.10	4	46‡	165	2.69	3.02	79
17	29	0.94	15	26	128	4.54	5.22	88
18	29	0.95	18	32‡	119	3.22	3.58	139
19	47	1.07	23	32	121	3.36	3.73	115
Mean	33	1.01	14	38	165	3.39	3.79	86
±SEM	±2	±0.02	±2	±4	±4	±0.30	±0.34	±11

* Refers to the daily dose of long-acting insulin (NPH, PZI, lente).
† Fasting plasma insulin could not be determined in these two diabetics; therefore, the mean fasting insulin value in the other 17 IDD (10 μU/ml) was subtracted from the steady-state value to calculate the increment in plasma insulin concentration above baseline.
‡ These three IDD were also taking 10, 4, and 4 U of regular insulin, respectively, from top to bottom.

maintain the plasma insulin concentration by approximately 100 μU/ml above fasting values. This same insulin infusion rate was employed in all control and diabetic subjects. In 11 subjects (group I; nos. 1–11 in Table 1) the plasma glucose concentration was kept constant at the fasting level by determination of the plasma glucose concentration every 5 min and the appropriate adjustment of the infusion rate of a 20% glucose solution as previously described.[10] In the remaining 8 diabetic subjects (group II: nos. 12–19 in Table 1) the fasting plasma glucose concentration was allowed to decrease to 90 mg/dl, at which level it was then maintained constant for 2 h. Since hyperglycemia is known to enhance glucose metabolism by a mass action effect,[18] five of the control subjects were restudied with a combined hyperglycemic-insulin clamp to simulate the mean plasma glucose and insulin levels observed in the diabetic group. Under steady-state conditions of either hyperglycemia or euglycemia, glucose input must equal glucose utilization. Glucose input is comprised of the exogenous glucose infusion required to maintain the plasma glucose concentration constant and the endogenous glucose production (see below); their sum thus serves as a measure of the body's sensitivity to the infused insulin.[16]

Endogenous glucose production. All insulin clamp studies were performed in conjunction with tritiated glucose to measure the effect of hyperinsulinemia on hepatic glucose production, as previously described.[1] For 180 min before starting the insulin clamp study, each subject's glucose pool was labeled by a primed-continuous infusion of [^{3}H-3]glucose (New England Nuclear, Boston, Massachusetts). The labeled glucose was administered as a 25-μCi bolus followed by a continuous infusion at the rate of 0.25 μCi/min in controls. In diabetics the priming bolus was increased in proportion to the elevation in fasting plasma glucose level. Plasma samples for the determination of glucose specific activity were taken at −60 and −30 min of this equilibration period, and then every 5 min until time 0 when the insulin infusion was begun. A steady state of glucose specific activity was achieved by this method in each study, and the specific activity plateau was used to calculate the rate of glucose appearance in the basal state. Since glucose production by nonhepatic tissues in the fasting state is negligible, the rate of basal glucose appearance equals hepatic glucose production. After this equilibration period, the insulin clamp was begun and the tritiated glucose infusion continued at the same rate. During the insulin clamp, plasma samples for glucose specific activity were obtained at 15-min intervals for the first 90 min, and then every 5 min for the final 20 min of the 2-h study.

Analytic procedures. Plasma glucose was determined by the glucose-oxidase method (Glucostat, Beckman Instruments, Inc., Fullerton, California). Methods for the determination of [^{3}H-3]glucose plasma specific activity have previously been published.[1] In control subjects plasma insulin concentration was determined by radioimmunoassay[19] using talc to separate bound from free insulin. In diabetic subjects plasma was treated with polyethylene glycol (PEG) to remove insulin antibodies and then the plasma free insulin concentration was determined as described by Kuzuya et al.[20] No preincubation was used since this was found to result in a time-related increase in free insulin levels. In 18 control subjects the plasma free insulin levels, determined after the addition of PEG, averaged 98 ± 4% of those determined directly by radioimmunoassay. In 11 of the diabetic subjects (nos. 1–11 in Table 1) plasma drawn during the fasting state was incubated with tracer insulin alone to determine whether or not significant amounts of insulin antibodies were present. Plasma from normal subjects served as the control for nonspecific binding of tracer insulin.

Calculations. For the insulin clamp studies, the glucose infusion rate was averaged over the 20–120-min time period of the clamp study. The total amount of glucose metabolized by the entire body (M) was calculated by adding the rate of endogenous glucose production (see below) to the exogenous glucose infusion rate required to maintain euglycemia. Steady-state plasma glucose and insulin levels were determined from the mean values for the 20–120-min time period.

Glucose turnover in the basal state was determined by dividing the tritiated glucose infusion rate (cpm/min) by the steady-state glucose specific activity (cpm/mg) achieved during the final 30 min of the tracer equilibration period. After the insulin infusion is begun, a non-steady-state condition for glucose specific activity exists. The total rate of appearance of glucose in the systemic circulation was then calculated from Steele's equations in their derivative form,[21] using a value of 0.65 for the pool fraction.[22] The rate of endogenous (hepatic) glucose production was estimated by subtracting the exogenous infusion rate from the total appearance rate as calculated by the isotopic tracer technique.

The glucose clearance was calculated by dividing the total amount of glucose metabolized (M) during the 20–120-min period by the mean plasma glucose concentration during the same time period.

All data are presented as the mean ± SEM. All statistical comparisons between groups were performed by unpaired *t* test analysis. Coefficients of correlation were determined by standard procedures.

RESULTS

Euglycemic insulin clamp. The fasting plasma glucose concentration in the diabetics, 171 ± 14 mg/dl, was approximately twofold higher than in the controls, 91 ± 1 mg/dl ($P < 0.001$). During the period of hyperinsulinemia the glucose concentration was maintained at 173 ± 24 mg/dl with a coefficient of variation of 3.1 ± 0.3% in the diabetic subjects (nos. 1–11 in Table 1) clamped at their fasting hyperglycemic level. In the remaining eight diabetics (nos. 12–19 in Table 1) the fasting plasma glucose concentration was clamped at 90 ± 1 mg/dl with a coefficient of variation of 3.4 ± 0.3%. In the 36 control subjects clamped at euglycemic levels, the fasting plasma glucose concentration was maintained at 90 ± 1 mg/dl with a coefficient of variation of 4.5 ± 0.2%. In the five control subjects who were clamped at hyperglycemic levels, the fasting plasma glucose concentration (89 ± 2 mg/dl) was maintained at 166 ± 2 mg/dl with a coefficient of variation of 4.0 ± 0.4%.

The fasting plasma insulin concentration in the control group, 14 ± 1 μU/ml, was raised and maintained at 107 ± 3 μU/ml. The increment in plasma insulin above baseline was 93 ± 3 μU/ml. In the five controls studied with the combined hyperglycemic-insulin clamp, the steady-state plasma insulin concentration was 107 ± 4 μU/ml. The

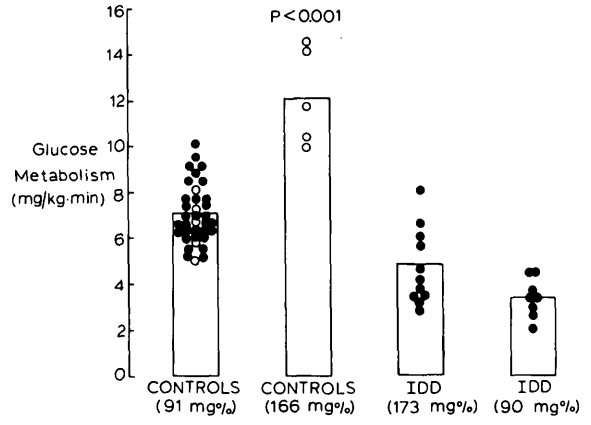


FIGURE 1. Insulin-mediated glucose uptake in insulin-dependent diabetics and control subjects studied at euglycemic and hyperglycemic levels. The steady-state plasma glucose level at which the insulin clamp study was performed is shown in parentheses. The height of the bar represents the mean ± SEM for the groups. The individual data points for each subject are shown by the circles. The open circles represent the five control subjects who were restudied at hyperglycemic levels.

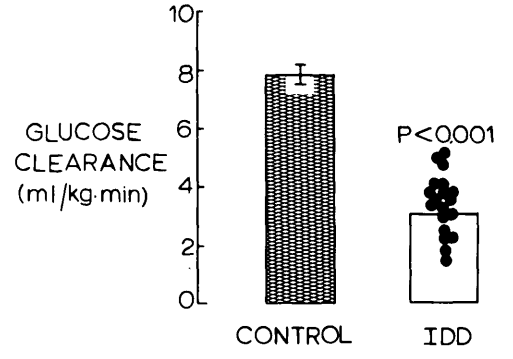


FIGURE 2. Glucose clearance (glucose uptake ÷ steady-state plasma glucose concentration) during the insulin clamp study in insulin-dependent diabetic and control subjects. The height of the bar represents the mean ± SEM for the groups. The individual data points for each of the 19 diabetics are shown by the solid circles.

fasting and steady-state plasma free insulin levels in the 19 diabetics averaged 10 ± 2 μU/ml (P = 0.08 versus controls) and 94 ± 6 μU/ml (P = 0.08 versus controls). The increment in plasma free insulin concentration above baseline was 82 ± 5 μU/ml (P = 0.06 versus controls).

The total amount of glucose metabolized by the control group during the euglycemic insulin clamp averaged 7.03 ± 0.22 mg/kg·min (Figure 1). In the diabetics (nos. 1–11) studied at hyperglycemic levels, insulin-mediated glucose metabolism, 4.77 ± 0.48 mg/kg·min, was reduced by 32% compared with controls (P < 0.001) (Figure 1). A positive correlation (r = 0.676, P < 0.05) between the fasting plasma glucose concentration and insulin-mediated glucose metabolism was observed in this diabetic group. For the five controls who were clamped at hyperglycemic levels comparable to the diabetics, glucose metabolism (12.14 ± 0.96 mg/kg·min) was 255% greater than in the diabetic group (P < 0.001). In the 8 diabetics (nos. 12–19) studied at euglycemic levels, the mean rate of insulin-mediated glucose metabolism was 3.39 ± 0.30 mg/kg·min (P < 0.001 versus controls).

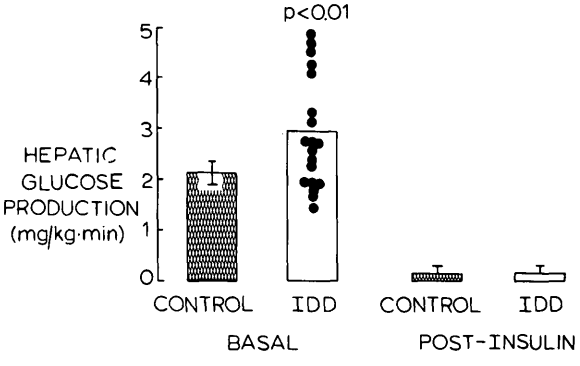
To compensate for the difference in plasma glucose levels between diabetics and controls, data were also calculated in terms of the glucose clearance. In the 36 controls receiving the euglycemic clamp study, the glucose clearance was 7.83 ± 0.25 ml/kg·min (Figure 2). This was 254% greater than in the diabetic group (nos. 1–11) studied at hyperglycemic levels, 3.08 ± 0.29 ml/kg·min (P < 0.001), and 207% greater than in the diabetic group (nos. 12–19) studied at euglycemic levels, 3.79 ± 0.34 ml/kg·min (P < 0.001). Glucose clearance during the insulin clamp in the diabetic group correlated inversely (r = −0.593, P < 0.01) with fasting plasma glucose concentration.

Endogenous glucose production. Basal hepatic glucose production (Figure 3) in the diabetics, 2.96 ± 0.24 mg/kg·min, was significantly elevated compared with controls, 2.35 ± 0.04 mg/kg·min (P < 0.02). The fasting plasma glucose concentration showed a strong positive correlation (r = 0.857, P < 0.001) with basal hepatic glucose production and was weakly inversely (r = −0.413, P < 0.07) correlated with the basal glucose clearance (Figure 4). In the control group, the fasting plasma glucose concentration also correlated positively with basal hepatic glucose production (r = 0.583, P < 0.001).

Following the hyperinsulinemia created during the insulin clamp, hepatic glucose production was suppressed by greater than 76% within the first 20 min in both groups and during the last hour of study averaged 0.11 ± 0.02 and 0.15 ± 0.04 mg/kg·min for the controls and diabetics, respectively. The percent suppression was 95% in both groups.

Insulin antibodies. The presence of insulin antibodies was screened for in diabetic patients nos. 1–11. In five, the amount of tracer ^{125}I-insulin precipitated by the diabetic's plasma was not greater than by the control plasma. In three, it was markedly greater by 4.3–10.7%. In the remaining three, it was slightly to moderately greater by 0.5–1.1%. In the five diabetics in whom no significant titer of insulin antibodies could be detected, the mean rate of insulin-mediated glucose metabolism (4.64 ± 0.62 mg/kg·min) and metabolic clearance rate of glucose (3.04 ± 0.34 ml/kg·min) were both significantly less than controls (7.03 ± 22 mg/kg·min and 7.83 ± 0.25 ml/kg·min, respectively, P < 0.001). In the remaining six diabetics with demonstrable insulin antibodies, the rate of insulin-mediated

FIGURE 3. Hepatic glucose production in the basal state and during the insulin clamp in insulin-dependent diabetics and controls. Although basal hepatic glucose production was significantly elevated in the diabetic group, insulin infusion resulted in a nearly complete suppression.



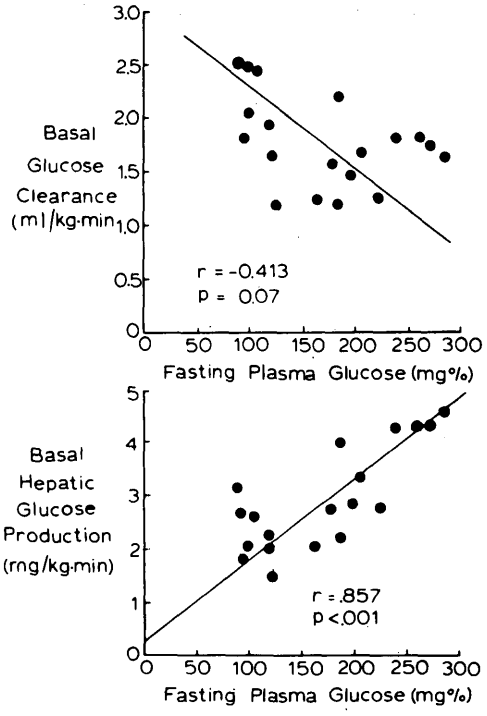


FIGURE 4. The relationship between the fasting plasma glucose concentration in insulin-dependent diabetics and (1) the rate of basal hepatic glucose production (bottom panel) and (2) the basal glucose clearance (top panel).

glucose metabolism (4.60 ± 0.79 mg/kg·min) and metabolic clearance rate of glucose (2.90 ± 0.47 ml/kg·min) were similar to those diabetics without antibodies.

DISCUSSION

Numerous studies employing a variety of different techniques[1–5,23–25] have demonstrated the presence of insulin resistance in the majority of non-insulin-dependent, type II diabetics. However, few studies have examined whether a similar degree of insulin resistance also exists in insulin-dependent, type I diabetics. Both Himsworth and Kerr[5] and Martin and Stocks,[6] using a combined insulin-glucose tolerance test, have provided evidence that insulin action is impaired in as many as half of insulin-dependent diabetics. More recent studies by Ginsberg[7] and Harano et al.,[8] carried out on small numbers of patients, have yielded conflicting results. The latter group demonstrated insulin resistance in all five diabetics studied whereas the former found normal sensitivity in six insulin-dependent diabetics.

In the present study, we have employed the insulin clamp technique to quantitate tissue sensitivity to insulin in 19 long-standing, insulin-dependent diabetics. Based on the insulin requirements of this group (mean daily NPH dose = 33 ± 2 U), none would be characterized clinically as being insulin-resistant. However, during the insulin clamp study performed in group I diabetics (i.e., those studied at fasting hyperglycemic levels), insulin-mediated glucose metabolism was diminished by 32% as compared with age- and weight-matched controls ($P < 0.01$). This impairment in glucose metabolism is even more striking when it is considered that the mean glucose level at which the insulin clamp studies were performed was almost twice as great in the diabetics versus controls (173 ± 24 versus 91 ± 1 mg/dl, $P < 0.001$). In this group I, the degree of insulin resistance can be better appreciated by comparing the glucose clearance in diabetic and control groups. This was 254% greater in the control group ($P < 0.001$). The severity of insulin resistance is also evident when the diabetics are compared with the five controls who were restudied at a similar level of hyperglycemia (166 mg/dl). Glucose metabolism by the control group was 255% greater than the diabetic group ($P < 0.001$). Thus, whether one compares the absolute rates of glucose metabolism in diabetics and controls or the rates of glucose clearance in the two groups, or glucose metabolism in control and diabetic subjects studied at comparable levels of hyperglycemia, a severe degree of insulin resistance is evident.

The insulin clamp studies performed in the 8 diabetics (group II) studied at euglycemic levels (90 mg/dl) adds further support for the presence of insulin resistance in IDD. In this group insulin-mediated glucose metabolism, 3.39 ± 0.30, was even lower than in group I diabetics studied at fasting hyperglycemic (173 mg/dl) levels, 4.77 ± 0.48 ($P < 0.02$). In every one of the 19 IDD, the metabolic clearance rate of glucose fell at least 1 SD below the controls and in 16 of the 19 it fell at least 2 SD beyond the controls. These results indicate the uniform presence of insulin resistance in our 19 IDD subjects. Since a relatively large number of diabetics was studied and since their clinical and laboratory characteristics are representative of most insulin-requiring diabetics, it is likely that tissue insensitivity to insulin in IDD is much more common than previously appreciated.

It could be argued that part of the insulin resistance observed in our IDD was due to the presence of circulating insulin antibodies. Although insulin antibody titers were not directly measured in the present study, several lines of evidence would suggest that factors other than insulin antibodies are responsible for the impairment in insulin action. (1) Only patients whose daily insulin dose (20–55 μU/ml) was not excessive were chosen for study. This was done since several previous studies have shown that, in general, diabetics with insulin requirements in this range do not have high circulating insulin antibody titers.[26–29] (2) In the 11 IDD in group I, tracer ^{125}I-insulin was incubated with the patient's plasma to screen for the presence of circulating insulin antibodies. In 5 of the 11, significant insulin antibody titers could not be detected with this screening procedure. The mean rate of insulin-mediated glucose metabolism (4.64 ± 0.62 mg/kg·min) and metabolic clearance rate of glucose (3.04 ± 0.34 ml/kg·min) were both significantly less than in controls ($P < 0.001$). In the remaining 6 IDD with insulin antibodies, the glucose metabolic rate (4.60 ± 0.79 mg/kg·min) and the glucose clearance rate (2.90 ± 0.47 ml/kg·min) were similar to those IDD without antibodies. (3) The steady-state plasma free insulin levels (94 ± 6 versus 107 ± 4 μU/ml, $P < 0.08$) as well as the increment in plasma insulin concentration above baseline (82 ± 5 versus 93 ± 3 μU/ml, $P = 0.06$) were reduced by 15% and 12%, respectively. These reductions are of borderline significance and are quantitatively small, suggesting that significant titers of insulin antibodies were not present in our IDD patients. (4) The severity of the impairment in the metabolic clearance rate of glucose is far in excess of that which could be explained by a 12–15% decrease in the plasma free insulin concentrations. The metabolic clearance rate of

glucose in the 19 IDD was reduced by 57% compared with controls (3.38 versus 7.83 ml/kg·min). Throughout the physiologic range of plasma insulin concentrations, glucose clearance and glucose metabolism are closely related to the plasma insulin concentration. It would not be possible for a 12–15% reduction in plasma insulin concentration to account for a 57% reduction in glucose clearance. The steady-state plasma free insulin level would have to be about 45–50 μU/ml (in contrast to the measured value of 94 μU/ml) to account for such a severe impairment in insulin action. In order for circulating antibodies to account for such a large reduction in plasma free insulin levels, they would have to be present in extremely high titers. As stated earlier, this is not compatible with the daily insulin requirement of our IDD, which averaged only 35 ± 2 U. (5) Lastly, even in diabetic patients with significant antibody titers only a small fraction of the antibody sites are occupied and plasma free insulin levels in the basal state are usually normal.[26,29–32] Furthermore, when the plasma of diabetic subjects is acutely exposed to insulin, the majority of the insulin remains in the free state because the equilibrium between antibody-bound insulin and free insulin is attained slowly (many hours) and the association-dissociation constants favor the free form of the hormone.[26,29]

The present results suggest that the primary site of insulin resistance resides in peripheral tissues. Although basal hepatic glucose output was significantly elevated in the diabetic group, when hyperinsulinemia was created during the insulin clamp, endogenous glucose production was suppressed normally by 95%. These results are in agreement with previous reports by Bearn et al.[33] and Sacca et al.,[34] who used the hepatic venous catheter and radioisotope dilution techniques, respectively, to document that suppression of hepatic glucose production was normal in IDD. The latter study is particularly noteworthy in that the insulin infusion rate was only 0.4 mU/kg·min, which presumably increased portal vein plasma free insulin levels by about 40 μU/ml. These results, in combination with ours, suggest that the liver of insulin-dependent diabetics retains normal sensitivity to suppression of glucose production throughout the physiologic range of plasma insulin concentrations (40–100 μU/ml). Hepatic glucose uptake was not measured in the present study. However, in previous studies in normal subjects during which the plasma glucose concentration was raised to greater than 200 mg/dl and portal insulin levels were well in excess of 100 μU/ml, splanchnic glucose uptake was only 1–1.2 mg/kg·min. Since the magnitude of the defect in insulin-mediated glucose uptake observed in insulin-dependent diabetics is well in excess of this value, our results suggest that a significant portion of the insulin resistance must reside in peripheral tissues. Whether or not an impairment in glucose uptake by the liver also exists remains to be determined.

The present results also help to clarify the determinants of the fasting plasma glucose concentration. In the diabetic subjects, a very strong positive correlation ($r = 0.857$, $P < 0.01$) was observed between the fasting glucose level and the rate of hepatic glucose production, suggesting that overproduction of glucose is an important contributor to the fasting hyperglycemia. A weaker, inverse correlation ($r = -0.413$, $P = 0.07$) was noted between the basal glucose clearance and the fasting glucose level, suggesting that an impairment in glucose disposal also contributes to the fasting hyperglycemia. It should be noted that the tracer methodology measures all glucose disappearance from the body and includes tissue uptake of glucose as well as glucose loss in the urine. Since the latter was not quantitated in the present study, it is likely that tissue glucose uptake is even more severely impaired than suggested by our results. It is also noteworthy that the degree of fasting hyperglycemia correlated positively ($r = 0.676$, $P < 0.05$) with the rate of insulin-mediated glucose metabolism and inversely with the glucose clearance ($r = -0.799$, $P < 0.01$) in the 11 IDD studies at fasting hyperglycemic levels. A similar relationship has previously been reported by us in non-insulin-dependent, type II diabetics.[1] It is interesting to speculate that the development of fasting hyperglycemia provides a compensatory mechanism that attempts to maintain glucose metabolism "relatively normal" in the face of insulin deficiency and insulin resistance. This would be similar to the situation in non-insulin-dependent diabetics.[1] In fact, the degree of insulin resistance in the present group of IDD is quite similar to that previously reported by us[1] as well as by others[35] who have employed the insulin clamp technique to examine tissue responsiveness to insulin in NIDD. These results indicate that both insulin deficiency as well as insulin resistance contribute to the impairment in glucose metabolism observed in both IDD and NIDD.

The cellular mechanism of the insulin resistance remains to be defined. Both an increase as well as a decrease in insulin receptor number has been reported in insulin-dependent diabetics.[36] In animal models where a state of absolute deficiency of insulin has been created, an increase in insulin binding has been reported uniformly.[37] In these animal models a prominent postreceptor defect in insulin-mediated stimulation of glucose transport and intracellular glucose metabolism by muscle[38,39] and adipose tissue[37,40] has been reported. It remains to be determined in man what the relative contributions of receptor versus postreceptor defects are to the observed insulin resistance.

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