Further Evidence that Insulin Resistance Exists in Patients with Chemical Diabetes

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SUMMARY

Insulin resistance was estimated in fifty nonobese subjects who were classified as normal (thirty subjects) or as having chemical diabetes (twenty subjects) on the basis of a standard oral glucose tolerance test. Insulin resistance was determined by administering a constant intravenous infusion of epinephrine, propranolol, glucose and exogenous insulin to each subject for 150 minutes and by measuring the resultant steady state plasma glucose levels attained during the last sixty minutes. Under these conditions, endogenous insulin secretion and hepatic glucose output are suppressed, and similar steady state plasma levels of the exogenously infused insulin are achieved in all subjects. Since all patients are challenged with comparable glucose loads, the height of the steady state plasma glucose response becomes a direct measure of an individual's resistance to insulin-mediated glucose uptake. With this approach we found that the mean (± S.E.) steady state plasma glucose level in patients with chemical diabetes was 224 ± 15 mg. per 100 ml. as compared to 126 ± 12 mg. per 100 ml. in control subjects. This difference was statistically significant ($p < .001$) and could not be attributed to differences in degree of obesity between the two groups. Furthermore, when individual values were examined it was apparent that relatively little overlap existed between steady state plasma glucose levels in normal and diabetic subjects. These results indicate that resistance to insulin-mediated glucose uptake is a characteristic of nonobese patients with chemical diabetes. DIABETES *23*:674-78, August, 1974.

In an earlier paper[1] we described an in vivo infusion technic that provided a direct estimate of the efficiency of insulin-mediated glucose uptake in an individual. This method is based upon the suppression of both endogenous insulin secretion and hepatic glucose output by the continuous infusion of epinephrine, propranolol, glucose and exogenous insulin, and specifically measures the ability of similar plasma levels of exogenous insulin to promote glucose uptake. In the original study we indicated that subjects with chemical diabetes mellitus had a marked decrease in their ability to remove glucose from the plasma when compared to normal subjects. The initial report was based upon comparison of seven normal subjects and seven patients with chemical diabetes mellitus. Although the differences in efficiency of insulin-mediated glucose uptake between the two groups were quite large, the question remained as to the frequency with which this abnormality is associated with the presence of chemical diabetes. We have continued to use this test in investigations of various aspects of carbohydrate metabolism, and in this report we present the results of this measurement in thirty normal subjects and in twenty patients with chemical diabetes.

METHODS

Fifty subjects were studied in the Stanford Clinical Research Center. These subjects were selected from a larger group of patients admitted over the past two years on the basis of their glucose tolerance and relative weight. Patients with fasting hyperglycemia (plasma glucose > 110 mg. per 100 ml.), with relative weight < 0.9 or > 1.2* or with oral glucose tolerance tests not clearly normal or abnormal are not included in this report. Glucose tolerance tests were evaluated by the revised criteria of Fajans and Conn,[2] and they were judged to be abnormal if plasma glucose levels exceeded 185 mg. per 100 ml. at one hour

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*Relative weights were estimated from Metropolitan Life Insurance Tables.

and 140 mg. per 100 ml. at two hours. A test was judged normal if plasma glucose levels were < 165 mg. per 100 ml. at one hour and < 135 mg. per 100 ml. at two hours. None of the subjects were taking medications known to modify carbohydrate metabolism, and they had no clinical or laboratory evidence of hepatic or cardiac diseases. They consumed a liquid weight-maintenance formula diet that consisted of 43 per cent carbohydrate, 42 per cent fat and 15 per cent protein three times daily in portions of one fifth, two fifths and two fifths of total calories. Daily weights were obtained and no significant weight changes occurred during the study period.

After at least three days of this diet, subjects were given an oral glucose load of 40 gm. per square meter body surface area, and blood samples were drawn during the following three hours for measurement of plasma glucose concentration. Two days later each subject received an intravenous injection of 5 mg. propranolol followed by a continuous intravenous infusion of glucose (6 mg./kg./min.), insulin (50 mU./min.), epinephrine (6 μg./min.) and propranolol (0.08 mg./min.) for 150 minutes using a Harvard constant infusion pump. We have previously shown that both endogenous insulin secretion and glucose output are suppressed during this infusion, and that steady state plasma levels of insulin and glucose are attained after ninety minutes.[1] Blood was sampled every ten minutes between ninety and 150 minutes for measurement of plasma glucose and insulin levels. During this steady state period, when the plasma glucose concentration is constant, the rate at which glucose is infused is equal to the rate of glucose uptake. Therefore, since all subjects are receiving glucose at the same rate and have similar plasma insulin levels, the higher the steady state plasma glucose concentration the lower the efficiency of insulin-mediated glucose uptake, i.e. the greater the insulin resistance.

Plasma glucose was measured by the method described by Hoffman;[3] plasma insulin was measured by a single antibody technic.[4] Statistical analysis was performed using the Student Test for nonpaired data. Correlation coefficients were calculated using a product moment method.

RESULTS

Patients were divided into two groups on the basis of their plasma glucose response during the oral glucose tolerance test. These results are seen in figure 1. Thirty subjects, twenty-five males and five females

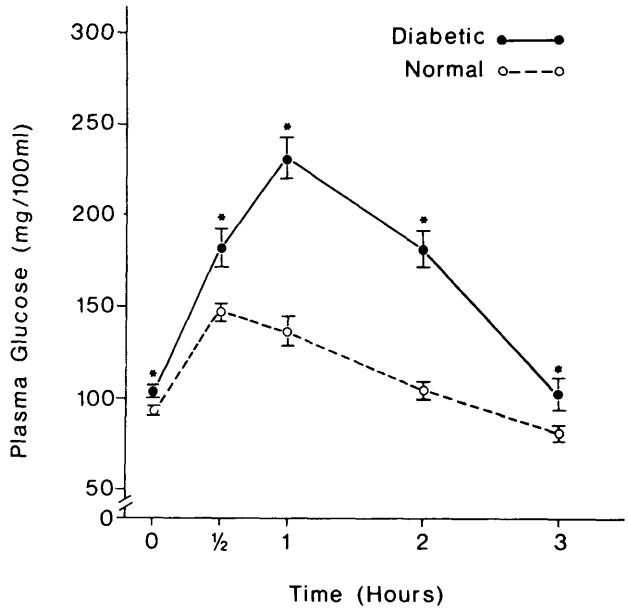

FIG. 1. Mean plasma glucose response during an oral glucose tolerance test in thirty normal subjects and twenty patients with chemical diabetes (* = p <0.01).

with a mean age (± S.D.) of 43 ± 14 years, had normal glucose tolerance. Twenty subjects, sixteen males and four females with a mean age (± S.D.) of 47 ± 9 years, had an abnormal tolerance test and were classified as having chemical diabetes. Plasma glucose levels were significantly higher in subjects with chemical diabetes at all time intervals. The age, sex, relative weight, oral glucose tolerance tests and steady state plasma glucose values for all patients are given in table 1. Figure 2 compares the mean relative weights and steady state plasma insulin and glucose levels during the infusion in the two groups. It is clear that the relative weights and plasma insulin levels of the two groups are essentially the same. However, the mean (± S.E.) steady state plasma glucose level of patients with chemical diabetes was 224 ± 15 mg. per 100 ml., as compared to the level of 126 ± 12 mg. per 100 ml. in the normal group. This difference was significant at the $p < 0.001$ level.

In figure 3, the individual steady state plasma glucose levels of the normal subjects are compared to the individual levels of the diabetic subjects. Although there is some variation in the steady state levels in both normal and diabetic subjects, there is relatively little overlap between the two groups. More specifically, over 90 per cent of the normal subjects were clearly separable from the diabetic group, while 85

TABLE 1

Summary of experimental data in thirty normal and twenty subjects with chemical diabetes

Normal Subjects									Chemical Diabetics								
			OGTT Plasma Glucose†									OGTT Plasma Glucose†					
Age	Sex	R.W.*	F	1/2	1	2	3	SSPG‡	Age	Sex	R.W.*	F	1/2	1	2	3	SSPG‡
51	M	0.95	90	163	163	122	60	47	43	M	1.05	110	180	205	149	113	60
25	M	0.93	90	141	140	110	73	50	69	M	1.04	108	96	246	258	53	104
22	M	0.90	91	119	147	133	54	53	47	M	0.95	109	211	204	206	131	122
64	M	1.05	101	128	144	97	70	63	42	M	1.10	95	167	191	183	166	206
45	M	0.95	97	136	119	70	74	76	36	M	1.16	91	146	234	158	74	211
23	M	1.10	90	147	155	101	101	76	26	M	0.98	109	156	206	198	165	211
34	F	0.91	90	132	164	100	69	90	60	F	1.13	92	196	213	163	65	226
43	M	1.00	70	156	164	106	70	90	45	M	1.03	99	100	216	156	86	231
20	F	0.95	94	143	130	105	99	91	53	F	1.08	105	212	274	156	67	233
63	M	0.99	97	156	153	123	78	98	37	M	1.05	96	175	192	170	90	235
59	M	0.94	100	192	160	115	90	100	47	M	0.96	106	200	254	226	110	236
58	M	0.94	105	144	135	83	72	103	50	M	1.03	99	100	216	156	86	236
47	M	1.04	90	155	114	112	116	108	42	F	0.98	95	167	191	183	166	241
46	M	0.94	102	163	113	111	90	118	53	F	1.06	107	191	201	193	74	253
69	F	0.91	100	151	115	125	77	119	41	M	0.91	103	191	229	198	92	264
48	F	0.97	90	150	127	97	74	124	43	M	1.05	110	180	205	149	113	268
24	M	1.20	93	132	115	93	84	134	61	M	1.16	101	166	186	172	98	271
22	M	1.10	85	125	109	100	71	135	49	M	1.02	108	246	290	266	154	279
55	M	1.13	100	163	113	111	90	140	46	M	0.96	110	214	264	143	97	286
46	M	0.96	98	107	106	98	79	142	49	M	1.12	107	232	228	146	84	300
26	M	0.98	80	128	164	132	107	142									
43	M	1.00	90	160	142	85	58	148									
38	M	1.00	86	126	136	104	69	150									
37	M	1.00	99	130	60	109	80	150									
54	F	1.16	98	216	161	82	82	154									
57	M	1.13	98	180	147	92	97	158									
46	M	0.95	93	152	163	100	69	159									
48	M	1.00	105	165	125	134	90	167									
41	M	0.91	90	132	162	106	77	273									
32	M	1.19	98	168	163	114	91	314									

*Relative weight was estimated from Metropolitan Life Insurance Tables.
†Individual plasma glucose levels after an oral glucose load of 40 gm. per meter^2 body surface.
‡Steady state plasma glucose levels.

per cent of the diabetic group had steady state plasma glucose levels well above those found in the normal group.

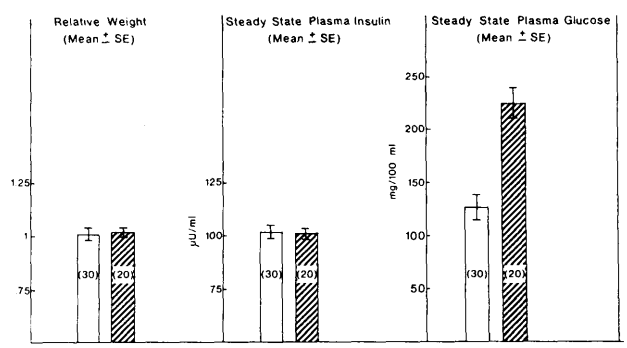

FIG. 2. Mean relative weights and steady state plasma insulin and glucose levels of thirty normal subjects (□) and twenty patients with chemical diabetes (▨).

Finally, there was a statistically significant correlation ($r = .42$, $p < .01$) between the fasting plasma glucose level and the mean steady state glucose response in these fifty subjects. An even higher degree of correlation existed ($r = .56$, $p < .005$) between the total glucose response during the oral glucose tolerance test (area under the curve) and the mean steady state plasma glucose level.

DISCUSSION

Before the introduction of radioimmunoassay as a means of specifically measuring plasma insulin levels, it was assumed that hyperglycemia in diabetes mellitus was due to insulin deficiency. However, the initial report of Yalow and Berson[5] clearly indicated that plasma insulin levels were not always low in nonketotic diabetic patients, and they concluded that hyper-

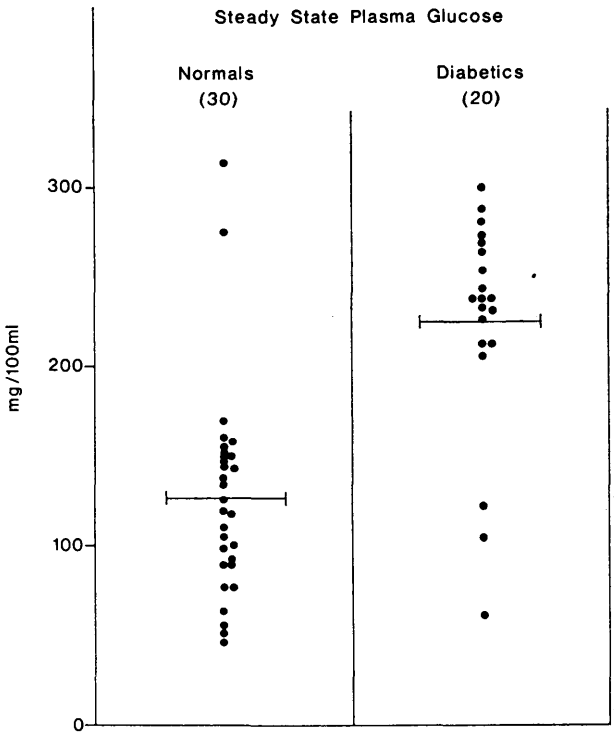

FIG. 3. Individual steady state plasma glucose levels of thirty normal subjects and twenty patients with chemical diabetes.

glycemia in these subjects could not be due solely to insulin deficiency. Since that time it has become increasingly apparent that the vast majority of patients who are classified as having diabetes on the basis of an abnormal glucose tolerance test have levels of plasma insulin which are, in absolute terms, equal to or greater than normal at all time intervals.[6-11] However, other investigators measuring insulin secretion relative to simultaneously measured plasma glucose levels have concluded that inappropriately low levels of plasma insulin are responsible for hyperglycemia in patients with chemical diabetes.[12-14] In an attempt to eliminate the issue of relative hypoinsulinemia in the genesis of hyperglycemia in these patients, we devised an in vivo infusion technic that provided a measure of an individual's ability to utilize glucose in the presence of insulin.[1] This technic takes advantage of the fact that the continuous infusion of epinephrine, propranolol, glucose and exogenous insulin can suppress endogenous insulin secretion and hepatic glucose output and allows us to compare the ability of various subjects to dispose of comparable glucose loads at a time when their plasma insulin levels are the same. With this approach the ability of seven normal subjects to dispose of a glucose load was clearly distinguished from that of an equal number of patients with chemical diabetes.[1] Thus, we could account for the hyperglycemia in these patients with chemical diabetes on the basis of their resistance to insulin-mediated glucose transport.

In the present report we have extended these studies and have estimated insulin resistance in thirty normal subjects and in twenty patients with chemical diabetes, the latter of whom were diagnosed on the basis of an abnormal oral glucose tolerance test. Normal subjects and patients with chemical diabetes, with comparable degrees of obesity, were clearly separable on the basis of their degree of insulin resistance. Given the likelihood that neither test used to estimate carbohydrate tolerance is infallible, the small degree to which the individual measurements of insulin resistance in the two groups overlapped seems remarkable. The fact that only three of twenty patients with chemical diabetes had mean steady state plasma glucose levels in the range of the normal subjects indicates that the majority of these patients are more insulin resistant than are normal subjects. This conclusion receives further support from the observation that only two of thirty normal subjects had mean steady state plasma glucose levels as high as the levels in patients with chemical diabetes. Therefore, these data demonstrate that resistance to insulin-mediated glucose transport is characteristic of patients with chemical diabetes. This defect is not dependent upon a greater degree of obesity in these patients, and it provides an explanation for the glucose intolerance of patients with chemical diabetes. This notion receives support from the significant correlation noted between the degree of glucose intolerance and the estimate of insulin resistance. Finally, the possibility that resistance to insulin-mediated glucose transport might also play a role in the hyperglycemia of patients with more severe diabetes remains to be evaluated.

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