Effect of Insulin Therapy on Insulin Resistance in Type II Diabetic Subjects

Evidence for Heterogeneity

HENRY GINSBERG AND ELLIOT J. RAYFIELD

SUMMARY

Insulin resistance has been demonstrated previously in both glucose-intolerant and untreated type II diabetics. Although the former group had hyperinsulinemia in the fasting state and after an oral glucose load, the hyperglycemic type II subjects were relatively insulin deficient after carbohydrate ingestion. In an attempt to define the role that insulin deficiency might have played in the pathophysiology of insulin resistance in this latter group, we measured the steady-state plasma glucose level (SSPG) during a constant infusion of glucose (6 mg/kg/min) and insulin (80 mU/min) in 15 nonobese insulin-deficient type II diabetics before and after insulin replacement therapy. Hepatic glucose output (HGO) and plasma clearance of glucose (PCG) during these studies were also determined using an infusion of 3-^{3}H-glucose.

Before insulin treatment, 13 of 15 subjects had SSPG levels above the range reported in normal subjects. Two type II patients appeared to be normally sensitive to insulin. Although all subjects were more sensitive to insulin after 1–8 wk of insulin therapy, they could be clearly divided into two groups. Thus, five patients were now normally sensitive to insulin (SSPG:75 ± 5.3 mg/dl) while 10 patients were still significantly resistant (SSPG:227 ± 11.3 mg/dl). HGO during the infusion studies was high in the resistant group pretreatment and did not change posttreatment (3.54 ± 0.32 vs. 3.14 ± 0.78 mg/kg/min). HGO was lower before insulin therapy and decreased by > 50% after therapy in the sensitive group (1.93 ± 0.07 vs. 0.71 ± 0.32 mg/kg/min). PCG determinations revealed a similar pattern of response. Retrospective analysis of the two groups revealed no significant differences in their baseline characteristics. Fasting plasma glucose and hemoglobin A_{1c} levels also did not differ between the two groups before or after insulin therapy.

These results indicate that heterogeneity exists among subjects with type II diabetes mellitus. One-third of the subjects studied appear to have only insulin deficiency as the basis of their diabetes, while two-thirds seem to have an underlying resistance to insulin that is not corrected by insulin therapy.

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A large number of studies reported during the past decade have indicated that diabetes mellitus is a heterogeneous syndrome rather than a single disorder.[1–3] Recently, a new classification of diabetes mellitus has been developed in which the majority of subjects can be divided into two groups, type I and type II.[4] This division is based primarily on the presence or absence of an absolute requirement for insulin therapy. Population and family studies show differences in the patterns of HLA determinants[5–8] and modes of inheritance[9–11] between subjects in these two groups.

Furthermore, a growing body of data demonstrates differences in insulin sensitivity between subjects with type I and type II forms of the diabetic syndrome. Thus, while insulin-treated ketosis-prone type I patients exhibit normal sensitivity to exogenous insulin,[12] older, untreated type II diabetics have been found to be resistant to insulin in several studies.[13–15] Although these untreated hyperglycemic type I patients were clinically stable at the time of study, the role of insulin deficiency in the etiology of their insulin resistance remained unanswered. The demonstration of insulin resistance in both untreated alloxan-diabetic dogs[16] and type I diabetics during episodes of ketoacidosis[17] underscores the need to clarify this point. In both studies, treatment with insulin resulted in a rapid return of normal sensitivity to insulin. Thus, it was the purpose of the present study to investigate the effect of insulin therapy on the insulin resistance present in untreated subjects with type II diabetes mellitus.

METHODS

Subjects. Patients were recruited from the Diabetes Clinic at the Mount Sinai Medical Center. Criteria for admission to the study included the presence of significant hyperglycemia that required pharmacologic intervention in nonobese

From the Division of Arteriosclerosis and Metabolism, Department of Medicine, Mount Sinai School of Medicine, New York, New York 10029.
Address reprint requests to Dr. Henry Ginsberg at the above address.
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TABLE 1
Patient characteristics

Subject	Sex	Age	Wt. (lbs)	Ht.	%IBW*
1	M	40	170	5′8″	1.13
2	M	36	167	5′8″	1.11
3	M	47	170	5′9″	1.10
4	M	44	167	6′0″	1.01
5	M	40	148	5′8″	1.00
6	M	68	170	5′7″	1.20
7	F	52	130	5′1″	1.24
8	M	53	172	5′9″	1.10
9	F	47	132	5′2″	1.11
10	M	47	134	5′4″	1.00
11	M	57	178	6′0″	1.07
12	M	58	119	5′3″	0.97
13	F	70	135	5′7″	0.97
14	M	72	152	5′7″	1.02
15	M	51	165	6′0″	0.98

* Percent ideal body weight, as calculated from the Metropolitan Life Insurance Co. tables.

subjects who had newly diagnosed, untreated diabetes mellitus, or in whom therapy with diet alone or diet and oral hypoglycemic agents had been inadequate. Some subjects had been treated with insulin in the past, but none had been treated for longer than a 6-mo duration and no patient had received insulin for at least 1 yr before entry into the study. Subjects taking oral hypoglycemic agents had their medication discontinued at least 3 wk prior to study. No subjects were losing weight in the immediate prestudy period. All subjects had demonstrated resistance to ketosis in the absence of therapy and could therefore be classified as having type II diabetes mellitus. The clinical characteristics of the study group are presented in Table 1. The subjects ranged in age from 36 to 70 yr and from 0.97 to 1.24 in percent ideal body weight. No subject was taking any other medication known to affect insulin sensitivity. All subjects had normal thyroid, renal, and hepatic function.

Protocol. All studies were carried out while the subjects were inpatients in the General Clinical Research Center. After admission, patients were placed on a diet consisting of 45% carbohydrate, 40% fat, and 15% protein. Simple sugar was restricted. Calories were adjusted to maintain stable weight. After 3 days of diet stabilization, an oral glucose tolerance test was performed with ingestion of 75 g of glucose and blood sampling at 0, 30, 60, 90, 120, and 180 min. After an overnight fast, insulin resistance was determined using a constant i.v. infusion of glucose (6 mg/kg/min) and insulin (80 mU/min). In 10 subjects, endogenous glucose production and plasma clearance of glucose was determined using 3-^{3}H-glucose.[18] A priming dose of 20–30 μCi of radiolabeled glucose was followed by a constant infusion of 0.2–0.3 μCi/min. The solution was administered via a Harvard pump (Harvard Apparatus Co., Inc., Millis, Massachusetts) over a period of 150 min. Blood samples (10 ml) were withdrawn at 0, 90, 120, 130, 140, and 150 min from an i.v. line in the opposite arm for measurement of plasma glucose and insulin and determination of glucose specific radioactivity. Blood for HbA_{1c} determination was obtained at the start of this study. Under the conditions of this protocol, all subjects receive equivalent glucose loads intravenously, and steady-state plasma glucose (SSPG) levels are attained by 90 min and maintained for the duration of the infusion. In addition, similar steady-state plasma insulin (SSPI) levels are attained in all subjects.[12,13,17] If endogenous glucose production is suppressed equally in all subjects, the SSPG levels can be used as a direct estimate of the efficiency with which each subject utilizes the infused glucose loads. The SSPG level would thus estimate insulin resistance (or sensitivity) in any individual and SSPG levels of different subjects or of the same subject under differing conditions could be directly compared. However, endogenous glucose production may not be equally suppressed in all subjects. We have therefore directly measured endogenous (essentially hepatic) glucose production and plasma glucose clearance rates during the infusion studies by using radiolabeled glucose. These determinations enable us to compare insulin sensitivity in subjects whose total glucose utilization (turnovers) may differ during the infusion studies.

After completion of the infusion study, insulin therapy was initiated using a regimen of an intermediate-acting insulin injected once daily in the morning. Insulin with a short duration of action was added as necessary. All patients achieved adequate control of plasma glucose levels (all fasting and premeal levels less than 150 mg/dl) after 4–6 days of further hospitalization. After discharge on weight-maintaining diets, the subjects were followed at weekly or biweekly intervals by one of the investigators (HG) and a dietitian. Therapeutic goals included negative results for urine glucose in greater than 80% of tests and fasting glucose levels less than 150 mg/dl on three consecutive follow-up visits. Fourteen subjects returned to the Clinical Research Center after 4–8 wk of treatment. One subject (no. 12) was retested after only 1 wk of therapy because of a normal response to the initial infusion study. On readmission, all subjects underwent repeat diet stabilization for 3 days, repeat measurement of fasting plasma glucose and HbA_{1c} levels, and a second infusion study. No subject had a significant weight change during the period between infusion studies.

Laboratory. Blood samples were centrifuged at 4°C and plasma was stored at −70°C until assayed. Plasma glucose was measured with a glucose-oxidase method using an Abbott ABA-100 Dichromatic Analyzer (Abbott Laboratories, North Chicago, Illinois). Plasma insulin levels were determined with a double antibody assay.[19] Plasma free insulin levels were determined in those patients who had developed significant anti-insulin antibodies by the time of their repeat studies (no patients had anti-insulin antibodies during their initial studies). Free insulin concentration was measured by the method of Kuzuya et al.[20] Plasma ^{3}H-glucose specific radioactivity was determined by the method of Katz and Dunn.[18] This entailed deproteinization of plasma by Ba(OH) and $ZnSO_4$ followed by evaporation of the supernatant (containing ^3H_2O). The residue was used for both radioactivity and glucose measurements. HbA_{1c} levels were determined by column chromatography[21] in the laboratory of Dr. F. Ginsberg-Fellner. The upper limit for normal values in adults in her laboratory is 5.0% .

Analysis. The calculation of total glucose turnover during these infusion studies is based on the presence of steady-state kinetics. The presence of steady-state glucose metabolism is attested to by the constant plasma glucose and insulin levels achieved in these studies during the final 30

min of infusion.[12,13,17] Attainment of steady-state condition for tracer kinetics was confirmed by constant specific activities for each 10-min sampling period during the final 30 min of the infusion studies (data not shown). In addition, the use of a priming dose of 3-^{3}H-glucose at a 100:1 ratio with the constantly infused dose of radiolabeled glucose assured achievement of steady state during the course of the next 2 h, before sampling was initiated.

The total rate of glucose turnover during the infusion study can be calculated from the equation:

$$\text{Total glucose turnover (mg/kg/min)} = \frac{\text{infusion rate (cpm/kg/min)}}{\text{glucose specific activity (cpm/mg)}}$$

During the steady-state period of the infusion study, total glucose turnover equals the glucose infusion rate plus the rate of endogenous glucose production. Assuming insignificant renal glucose output, endogenous glucose production equals hepatic glucose production. This can be calculated by:

$$\text{Hepatic glucose production (mg/kg/min)} = \text{total glucose turnover-glucose infusion}$$

Finally, the metabolic clearance rate of glucose from plasma can be determined from:

$$\text{Metabolic clearance rate (ml/kg/min)} = \frac{\text{total glucose turnover (mg/kg/min)}}{\text{plasma glucose (mg/ml)}}$$

Statistical analysis was performed using paired and nonpaired *t* tests to compare both individual subjects with themselves and the sensitive group to the resistant group (vide infra), respectively, during both the pre- and posttherapy periods. Correlations were carried out using linear regression analysis.

RESULTS

Table 2 depicts the SSPG and SSPI levels of all 15 subjects during each study period. It is clear that all subjects had increased sensitivity to insulin after insulin therapy. However, on closer examination, it becomes evident that five subjects (nos. 1, 5, 9, 12, and 14) had significantly lower SSPG levels after insulin therapy than the other 10 subjects. These data are graphically presented in Figure 1. Here the overall group has been subdivided on the basis of their SSPG levels post-insulin therapy. The division is based on the very close clustering of the five sensitive subjects posttherapy as well as data in age-matched normal subjects we have previously studied (mean ± SD = 125.7 ± 11.2 mg/dl, N = 30).[22] It should also be noted that two of these five subjects actually had SSPG levels clearly in the range of normal subjects during the pretreatment study, while another two had SSPG levels at the upper end of the normal range (Table 2).[22] It can be seen that there were clear differences in insulin sensitivity between the two groups, both in the pre- and posttherapy studies. Furthermore, although both groups had increased insulin sensitivity after insulin treatment, the difference in insulin responsiveness between the two groups was increased after therapy. There were no significant differences in the SSPI levels attained within or between groups during the two study periods. Based on these differences in the SSPI levels attained within or between groups during the two study periods. Based on these different responses to the infusion studies, the two groups were defined as either insulin resistant (10 subjects) or insulin sensitive (5 subjects) for purposes of further data analysis.

TABLE 2
Effect of insulin therapy on insulin resistance

	SSPG* (mg/dl)		SSPI† (μU/ml)	
Subject	Pre	Post	Pre	Post
1	325	89	89	95
2	270	213	90	95
3	367	210	91	79
4	334	202	83	84
5	184	84	61	60‡
6	346	245	74	80
7	353	247	96	106
8	361	253	113	125‡
9	190	68	85	80
10	346	211	83	77‡
11	350	155	64	56
12	105	72	128	118
13	393	272	110	105
14	122	60	87	75
15	251	265	67	95‡

* Steady-state plasma glucose obtained from four blood samples during final 30 min of infusion study. See METHODS.
† Steady-state plasma insulin levels obtained in same manner. See METHODS.
‡ Plasma free insulin levels. See METHODS.

Table 3 presents the clinical data for the subjects in each of the two groups. There were no significant differences in age or percent ideal body weight between the two groups (Table 1). While fasting plasma glucose levels improved significantly in both groups after insulin therapy, there were no significant differences between the two groups in either the pre- or posttherapy study periods. Fasting plasma insulin and HbA_{1c} levels were similar in the two groups at pretreatment. Furthermore, although HbA_{1c} concentration, an integrated measure of glucose control, decreased in 10 of 11 patients after several weeks of insulin therapy, the mean values of the two groups were nearly identical. To further assess the effect of each subject's clinical status on insulin sensitivity, the relationship between fasting plasma glucose and SSPG was studied. When the data from the two groups were combined, there was a significant positive correlation

FIGURE 1. The steady-state plasma glucose (SSPG) and steady-state plasma insulin (SSPI) levels during an i.v. infusion of glucose (6 mg/kg/min) and insulin (80 mU/min) in 10 subjects who remained resistant to insulin after insulin therapy (open bars) and 5 subjects who were normally sensitive to insulin after insulin therapy (striped bars).

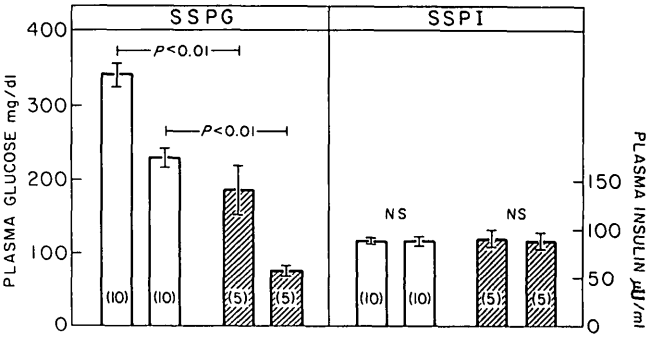


TABLE 3
Clinical characteristics of insulin-sensitive and resistant groups

Group	No.	FPG (mg/dl)* Pre	FPG (mg/dl)* Post	FI (μU/ml)† (Pre)	HbA_{1c} (%)‡ Pre	HbA_{1c} (%)‡ Post	GTT: Glucose area§ (Pre)	GTT: Insulin area§ (Pre)
Sensitive	1	262	171	—	—	—	—	—
	5	290	102	11.1	4.3	4.5	237.5	220.5
	9	204	94	20.0	7.7	5.5	286.2	−252.0
	12	206	103	6.9	6.4	6.2	104.6	510.0
	14	250	117	5.9	9.0	7.8	159.8	561.0
Mean ± SD		242.4 ±37	117.4 ±31	10.9 ±6.4	6.9 ±2.0	6.0 ±1.4	197.0 ±81	210.2 ±261
Resistant	2	156	90	—	—	—	—	—
	3	453	135	—	—	—	—	—
	4	366	209	—	—	—	—	—
	6	272	160	13.2	6.5	4.7	256.1	253.5
	7	247	84	12.0	10.0	5.4	222.9	199.5
	8	274	150	6.3	7.5	6.4	116.3	244.5
	10	299	158	11.4	6.8	4.0	189.0	1486.5
	11	291	182	14.5	6.3	4.5	160.9	627.5
	13	399	185	26.5	8.7	7.2	284.0	270.5
	15	271		5.6	10.6	6.2	199.7	−171.0
Mean ± SD		302.8 ±84	149.5 ±39.6	12.8 ±6.9	8.1 ±1.7	5.5 ±1.2	204.1 ±57	415.9 ±511

* Fasting plasma glucose at the start of the glucose-insulin infusion protocol.
† Fasting plasma insulin at the start of the glucose-insulin infusion protocol.
‡ Sample obtained the day of the glucose-insulin infusion protocol.
§ Area above baseline for plasma glucose (mg·min/ml) and plasma insulin (μU·mm/ml) after ingestion of 75 g of glucose. Subjects 1–4 did not undergo the test.

between SSPG levels and the fasting plasma glucose concentrations in the pretreatment period. However, after insulin therapy, no correlation was observed (Figure 2).

Plasma glucose and insulin levels in the two groups after ingestion of 75 g of glucose (Figure 3) revealed no significant differences between the groups for either variable at any time point. Analysis of the data as area under the curve above baseline also revealed no intergroup differences. Both groups had very little insulin response above basal levels to the oral glucose load (Table 3).

Hepatic glucose output and plasma glucose clearance during the infusion studies in both periods are depicted in Figure 4. In both study periods, the insulin-sensitive group had lower rates of hepatic glucose production during the infusion of glucose and insulin than did the resistant group, although the difference was not statistically significant in the posttreatment period because of individual variability. Thus, under conditions where equal levels of plasma insulin existed and similar exogenous loads of glucose were administered, the resistant subjects as a group produced approximately twice as much endogenous glucose as the sensitive subjects. It should also be noted that after insulin therapy, the sensitive group had a greater than 50% reduction in hepatic glucose output versus the pretreatment study, while there was no change in hepatic glucose output in the resistant group. Plasma clearance of glucose, on the other hand, tended to rise in most subjects after insulin ther-

FIGURE 2. Relationship between fasting plasma glucose (FBS) and steady-state plasma glucose (SSPG) in the fifteen subjects before (left panel) and after (right panel) insulin therapy. Open circles refer to the insulin-sensitive subjects and closed circles refer to the insulin-resistant subjects.

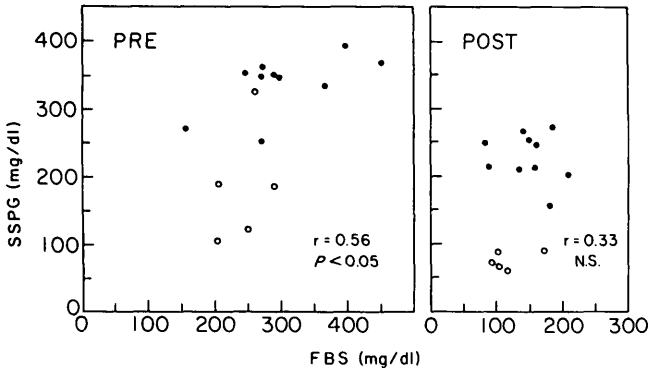
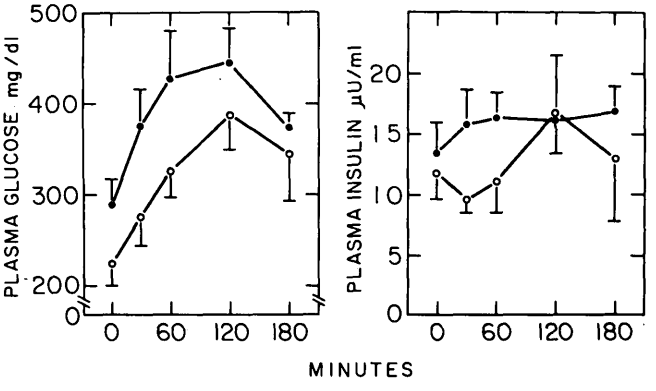


FIGURE 3. Plasma glucose (left panel) and insulin (right panel) concentrations after ingestion of 75 g of glucose in seven subjects who remained insulin resistant after insulin therapy (closed circles) and four subjects who were normally sensitive to insulin after insulin therapy (open circles). The oral glucose load was administered to all subjects during the first study period, prior to insulin treatment. No significant differences were present between the two groups at any time for either plasma glucose or plasma insulin concentrations.



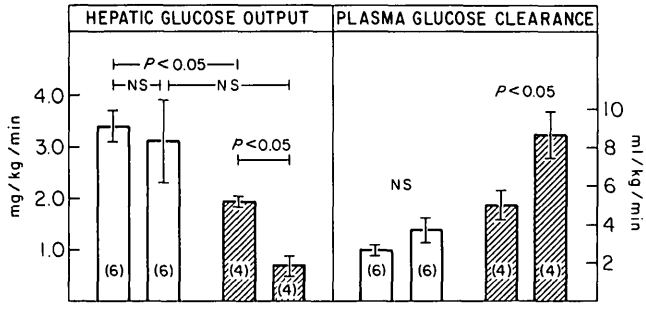


FIGURE 4. Hepatic glucose output (left panel) and plasma glucose clearance (right panel) in six subjects who remained insulin resistant after insulin therapy (open bars) and four subjects with normal insulin sensitivity after insulin therapy (striped bars). Studies were carried out by infusing trace amounts of 3-^{3}H-glucose simultaneously with glucose and insulin (see Figure 1).

apy. However, the increase in clearance postinsulin therapy was only significant in the sensitive group. In addition, plasma clearance of glucose was greater in the sensitive group during both study periods.

DISCUSSION

Recently, data derived from family, population, and physiologic studies have been used to form the basis of a new system of classification for diabetes mellitus.[4] This system attempts to use physiologic criteria to a greater degree than either epidemiologic or purely clinically derived data in order to separate diabetic subjects into subgroups. Thus, the two major groups, type I and type II, differ primarily in their absolute dependence on insulin for maintenance of metabolic stability, i.e., the absence of ketoacidosis. This classification is independent of age of onset so that young, non-insulin-dependent subjects ("maturity onset diabetes of youth") fall within the type II class, while elderly ketosis-prone diabetics are grouped with the type I subjects. While this new approach to classifying diabetes offers the potential advantage of allowing investigators to study apparently physiologically homogeneous subpopulations of diabetic patients, this may not be the case.

In the present investigation, insulin sensitivity was studied in one such subpopulation comprised of nonobese type II diabetics. However, the results clearly indicate heterogeneity within this group. Thus, during the pretreatment study period, 2 subjects were normally sensitive to insulin, 2 were minimally insulin resistant, and 11 were significantly resistant to insulin. Insulin therapy resulted in a clearer division of the group into two subgroups: one group of 5 subjects with quite normal insulin sensitivity and one group of 10 subjects with persistent insulin resistance. These two subgroups were similar in their degree of hyperglycemia and insulin deficiency at the time of enrollment into the study and achieved equivalent control of carbohydrate metabolism with insulin therapy. However, they exhibited significant differences in their pathophysiology. Thus, in one-third of these patients, insulin deficiency alone could explain their inability to maintain normal plasma glucose levels in the absence of insulin therapy. In contrast, two-thirds of the subjects appeared to have two independent defects: insulin deficiency and insulin resistance. In these latter subjects, this subnormal responsiveness to insulin could be demonstrated both by estimating the degree of suppression of hepatic glucose production by insulin and by measuring insulin-mediated glucose uptake by tissues.

Neither the cellular mechanism nor the site of this resistance to the action of insulin is known at present. It should be pointed out that we have used insulin resistance in a general sense and have not attempted to differentiate between insensitivity and unresponsiveness, terms that have been used to signify resistance at the receptor and intracellular (postreceptor) levels, respectively.[23,24] Previous workers have demonstrated diminished numbers of insulin receptors in circulating monocytes in nonobese type II subjects in the untreated state[14,25] and these findings have been indirectly corroborated by multistage glucose clamp experiments in which a shift to the right in the dose-response curve (indicative of decreased receptor activity) has been observed. Controversy exists, however, regarding the coexistence of postreceptor defects in these same patients.[26,27] Similarly, we have no information concerning the role of counterregulatory hormones or substrates in the etiology of the persistent insulin resistance in the majority of our subjects. However, in studies of untreated nonobese type II subjects, cortisol, growth hormone, and glucagon all appeared to respond normally to an infusion protocol similar to the one used in this study.[13,28] Free fatty acid levels, in contrast, were found to be less responsive in the diabetics than in the normal control subjects,[13] suggesting a pathophysiologic role for this substrate.[29] Whether a similar defect in the regulation of free fatty acids persists in the treated, resistant subjects remains to be determined.

The data presented here indicate, therefore, that insulin resistance may be a primary defect in the majority of nonobese type II diabetic subjects. There are, however, several intriguing questions concerning this point. First, one might ask whether more aggressive insulin replacement therapy might have eliminated the insulin resistance that persisted in two-thirds of the subjects in this study, i.e., whether all the insulin resistance was secondary to insulin deficiency. We believe this unlikely because equal degrees of control were attained in the two groups, but did not result in uniform sensitivity to insulin, because two of the insulin-sensitive subjects had nearly normal responsiveness to insulin even in their untreated state at a time when they were quite insulin deficient and because insulin-resistant ketoacidotic type I patients become normally sensitive to insulin rather quickly after initiation of insulin therapy.[17] There was a significant positive relationship between fasting plasma glucose levels and SSPG pretreatment (Figure 2), suggesting an interaction between clinical status and insulin sensitivity. However, the significance of this relationship was derived mainly from the presence of three subjects with very high fasting plasma glucose levels. While these data indicate that a component of insulin resistance in the subjects pretherapy was secondary to insulin deficiency (as does the reduction in SSPG in all subjects after insulin treatment), the lack of correlation between SSPG and either fasting plasma glucose or HbA_{1c} levels posttherapy is indicative of an underlying insensitivity to insulin in the resistant group that was independent of the degree of severity of the diabetes.

A more puzzling issue is the apparent dual defect of insulin deficiency and insulin resistance in the resistant group. Although we have no data directly addressing this point, two reasonable possibilities suggest themselves. First, the com-

bination of a more common genetic trait that causes decreased tissue sensitivity to insulin with a less common trait that is associated with pancreatic beta-cell dysfunction (of viral or autoimmune etiology) would result in clinically significant diabetes mellitus. The previous demonstration of insulin resistance (of a similar degree to that observed in the treated resistant subjects in this report) in nonobese hyperinsulinemic subjects with impaired glucose tolerance[21] is supportive of this hypothesis. Second, diminished beta-cell responsiveness to an environment of steadily increasing hyperglycemia (the result of diminished insulin action) might trigger a vicious cycle that would result in the significant insulin deficiency observed in our insulin-resistant patients. The fact that increased beta-cell function can be demonstrated after improvement in carbohydrate metabolism has been achieved in type II diabetics as a result of weight reduction, the use of oral hypoglycemic agents, or insulin therapy[30–35] supports this hypothesis.

A third question concerns the relevance of the present findings to the total type II diabetic population. Surveys have demonstrated that as much as 80% of the type II population is obese.[36] We chose to study nonobese individuals to eliminate the effect of obesity-related insulin resistance. While we agree that a similar study in obese type II diabetics should be carried out, we feel that it is reasonable to assume that heterogeneity will exist within this subgroup of diabetics in which the degrees of obesity and hyperglycemia vary greatly. More importantly, our data suggest that if "idiopathic" insulin resistance can play a significant role in the pathophysiology of both carbohydrate intolerance[21] and type II diabetes mellitus in nonobese subjects, it may be additive to, or synergistic with, whatever defect in insulin sensitivity develops as a concomitant of obesity. Recent evidence from a study of Pima Indians indicated that obese glucose-intolerant subjects were significantly more resistant to insulin than weight-matched Pimas with normal glucose tolerance.[37]

Finally, the demonstration of heterogeneity within this subgroup of type II diabetics suggests that the present classification scheme[4] may require further refinement. Thus, if the complexity of the diabetic syndrome is to be unraveled and the unique etiologies and pathophysiologies defined, subgroups of subjects that are truly uniform will have to be identified. Specific physiologic and/or biochemical markers will be needed to characterize these various subgroups before family and population studies can be interpreted correctly. Similarly, various therapeutic regimens can only be tested in appropriate, well-characterized groups if we are to obtain meaningful data regarding the association between control of diabetics and incidence of sequelae.

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