Investigation of Insulin Sensitivity in Treated Subjects with Ketosis-prone Diabetes Mellitus

LCDR Henry N. Ginsberg, MC USN, San Diego

SUMMARY

Two similar intravenous infusion techniques have been utilized to investigate insulin sensitivity in young subjects with recent-onset ketosis-prone diabetes mellitus. All subjects presented initially with mild to moderately severe ketoacidosis and had been treated with daily insulin therapy for two to eight weeks at the time of study.

Six diabetics and 10 normal subjects (group A) received intravenous infusions of glucose (6 mg./kg./min.), insulin (80 mU./min.), epinephrine (6 μg./min.), and propranolol (0.08 mg./min.) for 150 minutes. Steady-state plasma glucose (SSPG) and insulin levels (SSPI) were reached by 90 minutes and maintained through the end of the study. As all subjects achieve similar SSPI while simultaneously receiving similar glucose loads, the SSPG can be used to measure individual insulin sensitivity. Under these conditions the diabetics in group A had a mean SSPG (± S.E.) of 99 ± 26 mg./100 ml., which was not different from the level of 98 ± 14 mg./100 ml. for their control subjects. Six diabetics and six normal subjects (group B) received infusions of only glucose (6 mg./kg./min.) and insulin (80 mU./min.). Similar SSPI levels were attained in both the diabetic and control subjects, and their mean SSPG (± S.E.) levels were not significantly different (83 ± 13 vs. 61 ± 6 mg./100 ml.).

One diabetic in group A and two diabetics in group B had SSPG levels above the highest values measured in their control groups. However, all three had markedly elevated fasting plasma glucose levels on the day of study. In contrast, nine well-controlled diabetics had normal insulin sensitivity. These results suggest that well-controlled subjects with ketosis-prone diabetes mellitus have normal sensitivity to insulin. DIABETES *26*:278-83, April, 1977.

In 1939, after studying the blood glucose responses of patients given oral glucose with and without an accompanying dose of intravenous insulin, Himsworth and Kerr[1] reported that subjects with diabetes mellitus could be classified as insulin-sensitive or insulin-insensitive. During succeeding years, other investigators using various approaches also found differences in the effectiveness of acutely administered insulin among their diabetic subjects.[2-6] While some of these studies indicated that the insulin-insensitive patients were usually older nonketotic diabetics and that the insulin-sensitive diabetics were younger and ketosis-prone,[2-4] the relationship between insulin sensitivity and clinical presentation of the patients was not always apparent.[5,6] More recently, a prolonged intravenous infusion of glucose and insulin has been utilized to demonstrate resistance to insulin in untreated adult subjects with both glucose intolerance[7,8] and nonketotic hyperglycemic diabetes mellitus.[9] This infusion technique allows the development of a steady-state period during which all subjects have similar plasma insulin levels at a time when they are all receiving identical glucose loads.[7] Therefore, a direct comparison can be made between a subject's insulin sensitivity (or resistance) and that of a normal group of subjects. In the present investigation this

From the Department of Internal Medicine and the Clinical Investigation Center, Naval Regional Medical Center, San Diego, California.

Address correspondence and requests for reprints to Henry Ginsberg, M.D., Department of Medicine, MO13, University of California San Diego, La Jolla, CA 92093.

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TABLE 1

Clinical characteristics

	Diabetics	Sex	Age	R.W.*	Admission data PG†	pH	Ketones‡	Insulin dose	Study data Duration of therapy	Fasting PG†
			(yr.)					(NPH)	(wk.)	
Group A	1	M	17	0.96	900	7.36	1:4	42	8	65
	2	M	19	1.02	860	7.20	1:16	40	2	133
	3	M	28	0.84	450	7.33	1:8	40	2	155
	4	M	21	0.87	500	7.31	1:8	30	2	136
	5	F	12	0.90	720	7.20	1:16	35	4	230
	6	F	22	0.84	300	7.31	1:8	15	2	130
	Controls (n=10)	M = 7 F=3	24 ± 1	0.96± 0.05						86±6
Group B	1	M	22	1.20	450	7.08	1:16	50	6	105
	2	M	22	1.00	680	7.37	1:4	24	3	109
	3	M	23	0.99	570	7.35	1:8	30	3	136
	4	M	22	0.94	670	7.32	1:8	32	3	273
	5	M	20	0.98	560	7.32	1:8	36	2	114
	6	F	12	0.90	2,000	7.13	1:32	32	7	223
	Controls (n=6)	M=3 F=3	23±1	1.01± 0.06						84±6

*Relative weight calculated from Metropolitan Life Tables.
†Plasma glucose in mg./100 ml.
‡Plasma dilutions largely positive by Acetest tablets (Ames).

infusion protocol has been used to determine insulin sensitivity in young subjects with ketosis-prone diabetes mellitus.

METHODS

Twelve subjects with recently diagnosed ketosis-prone diabetes mellitus were studied as either inpatients or outpatients at the Naval Regional Medical Center in San Diego. All 12 had entered the hospital two to eight weeks prior to study during their initial episode of diabetic ketoacidosis. They had been receiving insulin therapy from the time of admission. The 12 patients were divided into two groups, A and B (see below). The clinical characteristics and admission laboratory data of each group are presented in table 1. At the time of study, all were asymptomatic, had maintained or gained weight since admission, and were taking no medications other than insulin. The 16 control subjects were also divided into two groups. Group A consisted of 10 subjects. This group was comprised of all the normal subjects, 28 years or younger, who were studied over a period of several years at the Stanford University Medical Center.* Group B was comprised of six normal subjects studied at the Naval Regional Medical Center. None of the control subjects had a family history of diabetes mellitus, and all had normal oral glucose tolerance according to the revised criteria of Fajans and Conn.[10] The pertinent characteristics of the two control groups are shown in table 1.

The six diabetic subjects and the 10 control subjects in group A were studied after an overnight fast and, in the case of the diabetics, 24 hours after their last dose of an intermediate-acting insulin preparation. They received 5 mg. of propranolol intravenously, followed by a continuous infusion of glucose (6 mg./kg./min.), insulin (80 mU./min.), epinephrine (6 μg./min.), and propranolol (0.08 mg./min.). This solution was infused into an antecubital vein for 150 minutes via a Harvard infusion pump. Blood samples were drawn from a vein in the opposite arm through an indwelling needle kept patent by a slow saline infusion. Under these experimental conditions, endogenous insulin secretion is suppressed and steady-state plasma glucose (SSPG) and steady-state plasma insulin levels (SSPI) are achieved by 90 minutes and maintained for the duration of the study.[7] Since similar SSPI levels are attained in all subjects,[7] this technique allows us to compare the ability of different subjects to dispose of identical glucose loads under the same insulin stimulus. Therefore, the mean of several plasma glucose concentrations measured during the steady-state period from 90 to 150 minutes is a measure of a subject's efficiency of insulin-mediated glucose utilization—i.e., his insulin sensitivity or resistance. The six diabetics and the six control subjects in group B underwent study protocols

*Data kindly supplied by Dr. G. M. Reaven.

identical to those used on the subjects in group A except that epinephrine and propranolol were not included in their infusion mixtures. This technique was employed after it was noted in separate studies that SSPI levels were quite similar in patients and control subjects during infusions of glucose and insulin with and without epinephrine and propranolol (unpublished observations).

Blood for determination of plasma glucose and insulin levels was drawn into test tubes containing EDTA, the plasma was quickly separated, and aliquots were stored at −20° C. Plasma glucose was measured by an ortho-toluidine method,[11] and plasma insulin was determined by the method of Desbuquois and Aurbach.[12] None of the diabetic subjects had circulating antibodies to insulin at the time of their study. Statistical analysis was performed with the two-tailed Student *t*-test for nonpaired data. Correlation coefficients were calculated by linear regression analysis.

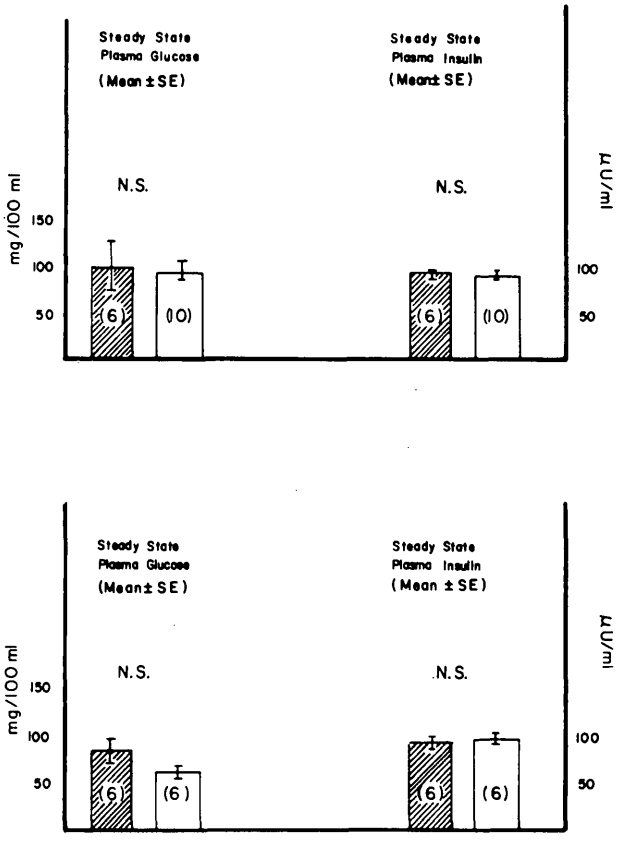

FIG. 1. Upper panel: Mean (± S.E.) SSPG and SSPI levels in six diabetics (striped bars) and 10 normal subjects (clear bars) in group A during infusion studies. All received intravenous infusions of glucose (6 mg./kg./min.), insulin (80 mU./min.), epinephrine (6 μg./min.), and propranolol (0.08 mg./min.) for 150 minutes. Steady-state levels of glucose and insulin were reached by 90 minutes, and the mean values of several samples drawn between 90 and 150 minutes were used as the SSPG and SSPI levels. Lower panel: Mean (± S.E.) SSPG and SSPI levels in six diabetics and six normal subjects (group B) during infusion studies. All received only glucose (6 mg./kg./min.) and insulin (80 mU./min.). Protocol was otherwise identical to that used in group-A studies.

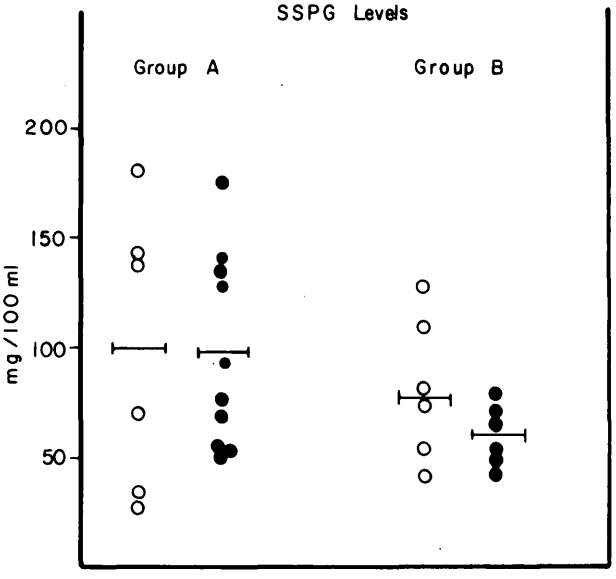

FIG. 2. Individual SSPG levels of each of the diabetics (open circles) and normal subjects (solid circles) in group A and group B during the infusion studies (see figure 1 legend).

RESULTS

Figure 1 depicts the results of the infusion studies in the diabetics and control groups. The upper panel compares the six diabetic patients and the 10 control subjects in group A, who received glucose, insulin, epinephrine, and propranolol in their infusates. It can be seen that with similar mean SSPI levels attained in both groups, there was no significant difference between the mean SSPG levels of the diabetic and control groups. The lower panel presents the same data for the six diabetic patients and the six control subjects in group B, who received only glucose and insulin in their infusion mixtures. Again, with similar mean SSPI levels present in both groups, there was no significant difference between the mean SSPG levels of the diabetic and control groups. From these data one might conclude that treated ketosis-prone diabetics have normal sensitivity to insulin. However, better insight into this question can be gained by inspection of the individual data of all the subjects.

Figure 2 compares the individual SSPG levels of the

diabetic and control subjects in both groups. In group A, both diabetics and controls had rather wide but quite similar ranges of values. While three of six diabetic subjects had SSPG levels lower than the majority of the normal subjects, one diabetic had an SSPG level that was slightly above the highest level measured among the control subjects. In group B, more striking differences between control subjects and diabetics were evident. While the SSPG levels of the six subjects in the control group were clustered over a narrow range, the six diabetics in group B showed more variability. In fact, two of these six diabetics had SSPG levels greater than two standard deviations above the mean level observed in their matched controls. Thus, if the individual data for both groups are combined, 10 of 12 treated ketosis-prone diabetics had insulin sensitivity comparable to that present in matched control subjects, while two of the diabetic subjects were relatively insulin-resistant.

In an effort to uncover differences between the insulin-sensitive and insulin-resistant diabetics, several of their clinical characteristics were compared. No differences were found regarding age, relative weight, or initial presentation. Clear-cut differences were noted, however, when each patient's fasting plasma glucose level at the time of study was compared with the SSPG levels measured.

Figure 3 represents the relationship between the fasting plasma glucose level and the SSPG level for each diabetic subject in both groups. It is clear that the one patient in group A and the two patients in group B with the highest SSPG levels had fasting plasma glucose levels significantly higher than those present in the rest of the subjects in their respective groups. It is suggested, therefore, that the elevated SSPG levels in these subjects were related to inadequate control of their diabetes.

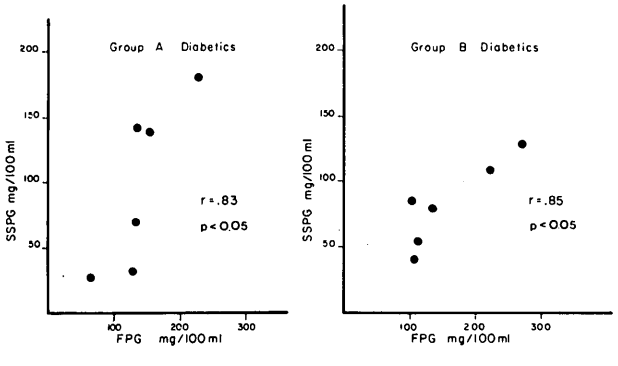

FIG. 3. Relationship between fasting plasma glucose level on the day of infusion study and the SSPG level for each diabetic in group A and in group B.

Finally, the data in figures 1 and 2 indicate that the mean and individual SSPG levels of both the diabetic and control subjects in group B tended to be lower than those of the subjects in group A. Even though the two groups were comprised of different individuals, these data suggest that the presence of epinephrine and propranolol in the infusate resulted in a moderate elevation of the SSPG levels. This effect seemed to be of equal significance in both diabetic and control subjects.

DISCUSSION

The results presented in this report indicate that the majority of a group of treated young ketosis-prone diabetic subjects had sensitivity to insulin that was equal to that present in normal subjects. These data, together with similar studies demonstrating insulin resistance in older subjects with both glucose intolerance[7,8] and nonketotic hyperglycemia,[9] support previous work that differentiated populations of diabetics into insulin-sensitive and insulin-insensitive or -resistant types.[1-6] While the present study adds weight to the hypothesis that different types of diabetes mellitus exist, it falls short of providing evidence that would allow diabetics to be uniformly categorized as insulin-sensitive or -resistant simply on the basis of their clinical presentation.

For example, although an attempt was made to study a narrowly defined group of diabetics—e.g., young newly treated subjects who had presented initially with ketoacidosis—a wide range of SSPG levels was observed. Thus, whereas both diabetics and controls in group A had similar ranges of insulin sensitivity, two of six diabetics in group B had SSPG levels outside the normal range of their controls. Therefore, even in this group of patients selected for their uniform clinical presentation, two of 12 diabetic subjects seemed to be insulin-resistant as compared with matched control subjects. On inspection of the individual data, however, these two resistant individuals in group B had fasting plasma glucose levels at the time of study that were much higher than those present in the other four more sensitive patients in that group. In addition, the patient in group A with the highest SSPG level also had a fasting plasma glucose level that was significantly greater than the other diabetics in her group. Because of the previous observation that untreated ketotic diabetics have marked insulin resistance that is significantly decreased after

insulin therapy,[13] it seems logical to conclude that the relative insulin resistance in these three subjects was secondary to poor clinical control of their diabetes at the time of the study. It is not unreasonable, however, to suggest that these patients did not have optimal control of the plasma glucose level at the time of study *because* they were more insulin-resistant than the rest of the patients. Although repeated studies of these individual patients after longer periods of therapy might have answered this question, practical circumstances made this impossible. In addition, development of circulating insulin antibodies in the patients, with concomitant variability in their plasma levels of free (active) insulin, would have made comparable SSPI levels unattainable. Interpretation of SSPG levels would, therefore, have been impossible. In conclusion, these studies indicate that well-controlled patients with ketosis-prone diabetes mellitus have normal insulin sensitivity. The possibility remains, however, that some patients with identical initial clinical presentations may have a primary resistance to insulin in addition to insulin deficiency.

In addition to the questions left unsolved by the present study, several questions concerning insulin sensitivity in diabetes mellitus must still be addressed. First, as outlined in a recent report,[14] insulin resistance in adults with glucose intolerance is associated with hyperinsulinemia, suggesting that resistance in these patients is a primary abnormality. However, the resistance to insulin demonstrated in untreated adults with nonketotic hyperglycemia is associated with chronic insulin deficiency. Therefore, the resistance in some of these patients might be secondary, and normal insulin sensitivity might be observed after optimal control of this group with insulin therapy. Similarly, children and adolescents with both glucose intolerance and nonketotic hyperglycemia may have a wide range of insulin secretory capacity.[15-17] No controlled determination of insulin sensitivity has been reported in these patients. Investigation of these questions might result in a more satisfactory classification of subjects with diabetes mellitus than that of juvenile versus adult or ketotic versus nonketotic types. In addition, such studies might give clearer meaning to recent reports concerned with the different patterns of inheritance apparent in diabetics.[17-19]

One final point concerns the effect(s) of epinephrine and propranolol on the SSPG levels of normal and diabetic subjects. In previous studies, where insulin resistance was demonstrated in older nonketotic diabetics,[7-9] consideration was repeatedly given to the possibility that the intense alpha-adrenergic stimulation that results from the combination of these two agents might have had a unique effect on the diabetic subjects. The elevated SSPG levels measured in these diabetics, therefore, might have been secondary to such an effect. The present studies indicate that, although the addition of epinephrine and propranolol to an infusion of glucose and insulin does seem to cause moderate elevation of SSPG levels, this effect is probably of equal magnitude in diabetics and normal subjects. Thus, it appears that while infusions of glucose and insulin alone can be used effectively to evaluate insulin sensitivity in insulin-deficient subjects, the addition of epinephrine and propranolol to the infusate to suppress endogenous insulin secretion in diabetics with normal or excessive pancreatic responsiveness to glucose will yield qualitatively comparable results.

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