Insulin Resistance in Diabetic Ketoacidosis

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SUMMARY

The effect of "low-dose" (6–10 U/h) insulin treatment on the rate of decline of plasma glucose concentration was determined in 15 diabetic subjects admitted in ketoacidosis (plasma glucose = 948 ± 79 mg/dl) and in six normal volunteers rendered hyperglycemic by a combined infusion of somatostatin and glucose (plasma glucose = 653 ± 28 mg/dl). The fractional glucose turnover and the half-time of the fall in plasma glucose during insulin treatment were both 10-fold reduced ($P < 0.001$) in the diabetics as compared with the controls. In the ketoacidotic subjects, the mean glucose clearance during insulin treatment was only 8% of that in the controls ($P < 0.001$). In the normal subjects, tissue glucose clearance during insulin treatment of the hyperglycemia (5.8 ± 0.7 ml/min · kg) was similar to that measured in the same subjects using a standard technique to quantitate insulin sensitivity (euglycemic insulin clamp).

In the ketoacidotic patients, a history of prior insulin therapy, but not the degree of hyperglycemia at the time of admission, was associated with a more rapid rate of decline of plasma glucose in response to insulin treatment. We conclude that marked insulin resistance is present in virtually all diabetics in ketoacidosis. DIABETES 31:923–928, October 1982.

While severe insulinopenia is acknowledged to cause ketoacidosis in man, the contribution of insulin resistance to the disordered glucose metabolism of ketoacidosis is uncertain. Many recent studies[1–4] have demonstrated that continuous intravenous infusion or intermittent intramuscular injection of insulin in doses between 3 and 8 U/h, combined with appropriate fluid and electrolyte replacement, effectively corrects the metabolic disturbances that accompany diabetic ketoacidosis (DKA). "Low-dose" and "high-dose" insulin infusions appear to have comparable efficacy in correcting the hyperglycemia of DKA in the vast majority of patients.[5,6] Low-dose insulin treatment lowered blood glucose despite the presence of metabolic acidemia[7] and increased circulating concentrations of free fatty acids,[8] and several hormones (e.g., glucagon,[9] cortisol,[10,11] catecholamines,[11,12] and growth hormone[13]) that are known to antagonize the action of insulin. Occasionally, patients are encountered in whom very large doses of insulin appear to be required to control glycemia and acidemia. Unquestionably, these unusual patients are severely insulin resistant. However, based on the observed effectiveness of low-dose insulin, investigators have questioned the presence of significant insulin resistance in the majority of patients with DKA.[5,6,14] It should be noted that even during "low-dose" insulin treatment plasma insulin levels are in the high physiologic or supraphysiologic range.[3–5] It is thus possible that this degree of hyperinsulinemia already exerts a maximal hypoglycemic effect, and that greater increments in plasma insulin concentration do not further enhance glucose disposal. The question arises whether the tissue sensitivity to "low-dose" insulin in ketoacidotic patients differs significantly from that seen in normal subjects.

The present study was consequently undertaken to ascertain whether insulin sensitivity is impaired in ketoacidotic diabetics, and, if so, to provide an estimate of this insulin resistance. We compared the rate of fall of plasma glucose after a primed-continuous insulin infusion in 15 ketoacidotic diabetics and in a group of six normal individuals in whom plasma glucose had been previously raised to levels typically encountered in ketoacidosis (above 600 mg/dl) by a combined infusion of glucose and somatostatin. The priming dose (6 U) and the continuous infusion rate (6 U/h) of insulin used in the present study are average doses employed in the "low-dose" insulin treatment of DKA.[15] The resulting rates of fall of plasma glucose in response to insulin

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infusion were used as a measure of insulin action on glucose disposal. In the normal volunteers, this estimate of tissue sensitivity to insulin was compared with that obtained with the euglycemic insulin clamp technique.[16]

METHODS

Chart review. Medical records of all patients presenting to the emergency department of the Yale-New Haven Hospital in ketoacidosis between January 1977 and September 1978 were reviewed. The records of 15 patients, treated with low-dose continuous intravenous insulin infusions (typically 6 U/h after a 6–10-U bolus) and fulfilling the following criteria, were analyzed in detail: (1) initial plasma glucose greater than 500 mg/dl; (2) plasma bicarbonate less than 15 meq/L, and an anion gap greater than 18 meq/L; (3) blood pH less than 7.30; and (4) plasma ketones present at greater than 1:2 dilution.

Table 1 summarizes the clinical and biochemical data obtained on these patients at the time of admission. The rate of decline of plasma glucose in all patients was measured from the recorded plasma glucose concentrations obtained between the commencement of insulin therapy and the initiation of a 5% dextrose infusion. Fluid and electrolyte (sodium, potassium, phosphorus, and bicarbonate) replacements were administered as deemed necessary by the physicians caring for the patients.

Study protocols. Six healthy adult volunteers (5 males, 1 female) with a mean age of 32 ± 2 yr and a mean weight of 70 ± 4 kg were studied. None were taking any medications and there was no primary family history of diabetes. All studies were carried out at 8 a.m. after a 12-h fast. A small polyethylene catheter was placed in a forearm vein for blood sampling; a second catheter was placed in the contralateral antecubital vein for glucose and hormone infusion. After measurement of basal plasma glucose and insulin, cyclic somatostatin (SRIF) (kindly provided by Dr. J. Rivier, Salk Institute, San Diego, California) was infused at a rate of 300 μg/h along with sufficient glucose (given as 20% dextrose with 0.45% saline) to raise the plasma glucose above 600 mg/dl. Once the plasma glucose exceeded 600 mg/dl (this required about 60 min), the glucose infusion was stopped but the SRIF infusion was continued, and regular insulin (Eli Lilly, Indianapolis, Indiana) was administered as a primed (6 U), continuous (6 U/h) infusion. Plasma glucose and insulin were then measured every 10 min. When the plasma glucose fell below 140 mg/dl, the insulin infusion was terminated. Before starting the SRIF, subjects voided and all subsequent urines were collected to quantitate urinary glucose loss. On another day, four of these subjects underwent a second study, with a protocol identical with that described above, except that no insulin was given. The fall in plasma glucose in these subjects was monitored for 2 h after stopping the glucose infusion. Five of the original six subjects also returned on a third occasion for a euglycemic insulin clamp study, as previously described.[16] In brief, plasma insulin concentration was acutely raised, and maintained at approximately 100 μU/ml by a primed-continuous (1 mU/min/kg body wt) insulin infusion for a period of 2 h. Plasma glucose was maintained constant at the basal level by measuring the plasma glucose concentration every 5 min and periodically adjusting a variable rate glucose infusion. Under the steady-state conditions of euglycemia that exist during the insulin clamp study, the amount of glucose taken up by all the body tissues equals the sum of the infused glucose and residual endogenous glucose production. We have previously shown that the insulin infusion rate employed in the present study (1 mU/min · kg) suppresses endogenous glucose production by 90–100% within 20 min.[17] Consequently, the rate of exogenous glucose infusion provides an estimate of the rate of glucose uptake by the body. The glucose clearance is calculated by dividing the mean rate of glucose uptake by the mean plasma glucose concentration.

In the control subjects studied during the falling glucose protocols, the fractional turnover of glucose (K) was estimated from the regression of the logarithm of plasma glucose concentration upon time. The slope of the line was determined using a least-squares fit.[18] Total glucose clearance (ml/min · kg body wt) was calculated as the product of K (min^{-1}) and the volume of distribution of glucose, which was assumed to be 25% of body wt,[19,20] or 250 ml/kg. The total rate of removal of glucose from the extracellular glucose pool was estimated from the product of the glucose distribution volume and the decrement in plasma glucose divided by the time over which the decrease in plasma glucose had occurred, or:

$$\text{Glucose removal (mg/min} \cdot \text{kg)} = \frac{(\text{glucose}_{(\text{initial})} - \text{glucose}_{(\text{final})})\ (\text{mg/ml}) \times 250\ \text{ml/kg}}{\text{time}_{(\text{final})} - \text{time}_{(\text{initial})}\ (\text{min})}$$

It must be emphasized that the fractional turnover of glucose and the glucose clearance and the rate of glucose removal, calculated as above, reflect the *net* loss of glucose from the extracellular glucose pool. In the control group, the hyperinsulinemia and hyperglycemia present during the falling glucose studies are sufficient to completely suppress endogenous glucose production.[17] Hence, net glucose clearance equals total glucose clearance, and net glucose removal equals total glucose removal from the extracellular glucose pool. In the ketoacidotic patients, however, endogenous glucose production may not be suppressed in spite of markedly elevated plasma insulin and glucose concen-

TABLE 1
Clinical and biochemical characteristics present on admission

	Mean ± SEM	Range
Age (yr)	44 ± 5	8–73
Weight (kg)	72 ± 12	27–125
Duration of diabetes (7 patients)* (yr)	16 ± 6	4–40
Maintenance insulin dose (U/day)	42 ± 7	25–80
Heart rate (beats/min)	111 ± 4	92–140
Blood pressure (mm Hg)	—	68/0–160/110
Mental status		
Alert (4/15)		
Lethargic (6/15)		
Obtunded-comatose (5/15)		
Plasma glucose (mg/dl)	949 ± 79	615–1688
Blood pH	7.17 ± 0.03	6.95–7.28
Serum HCO_3 (meq/L)	8 ± 0.8	4–13
Serum potassium (meq/L)	5.4 ± 0.4	1.9–7.0
Anion gap (meq/L)	33 ± 1.4	18–40
Blood urea nitrogen (mg/dl)	43 ± 4	15–68
Serum osmolarity (mosmol/L)	368 ± 14	331–431

* Eight patients were newly diagnosed diabetics.

trations. In this case, the net glucose removal, as calculated from the plasma glucose decline, underestimates total glucose removal by an amount equal to the residual endogenous glucose production or:

Net glucose removal = total glucose removal − endogenous glucose production

Total glucose removal in turn includes both tissue glucose uptake and urinary glucose excretion. Therefore, in the control subjects, tissue glucose uptake was calculated as the difference between total glucose removal from the extracellular glucose pool and urinary glucose loss. In these volunteers, tissue glucose clearance was then obtained as the ratio of tissue glucose uptake to the mean plasma glucose concentration during the period of glucose fall.

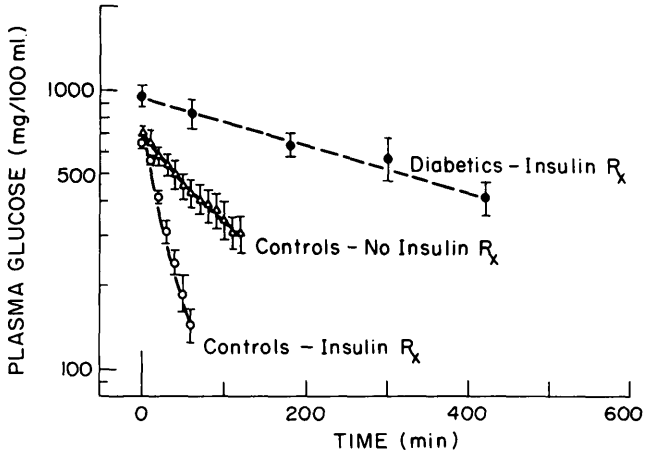
Glycosuria was not quantitated in the diabetic subjects; hence, total glucose removal cannot be partitioned to assess the separate contributions of tissue glucose removal and urinary glucose excretion to total glucose removal from the extracellular glucose pool. The dehydration and volume contraction present in the ketoacidotic patients may significantly reduce the glomerular filtration rate; hence, their rate of urinary glucose loss would be expected to be less than that of control subjects with a comparable degree of hyperglycemia. This effect could be partially responsible for any differences in total glucose removal observed between control and diabetic subjects. The confounding influence of differences in renal glucose handling can be minimized by comparing total glucose removal observed in the diabetic subjects with values for tissue glucose removal obtained in normal subjects. This is equivalent to assuming that urinary glucose losses in the diabetic subjects are nil. Using this comparison, any differences in glucose disposal observed between control and diabetic subjects must be regarded as a *minimum* estimate of the difference in insulin action.

All data are presented as the mean ± SEM. Comparisons between groups were performed using the unpaired *t* test.[18]

RESULTS

The fall in plasma glucose concentration in the 15 subjects with DKA after institution of insulin treatment is shown in Figure 1. The time course of the fall in plasma glucose was well approximated by a single exponential function (r = 0.986).

FIGURE 1. Time course of decline in plasma glucose in the ketoacidotic diabetic subjects (N = 15) and in normal volunteers (N = 6) after insulin treatment, and in normal volunteers not receiving exogenous insulin.



The mean fractional turnover of glucose (K) in these patients was 0.19 ± 0.02% min^{-1}. In the six normal individuals made hyperglycemic by infusion of glucose and somatostatin, the decline of plasma glucose after insulin treatment was much more rapid than in the ketoacidotic subjects (Figure 1). The mean fractional turnover of glucose in these subjects was 2.8 ± 0.3% min^{-1}, more than 10-fold greater than that of the diabetic patients ($P < 0.001$) (Figure 2). This difference is also reflected in the estimates of the half-time ($t^1/_2$) of the fall in plasma glucose, which was 6.1 ± 0.6 and 0.31 ± 0.03 h ($P < 0.001$) for the diabetic and control groups, respectively.

In the four control subjects whose plasma glucose was raised to 640 ± 25 mg/dl and then allowed to fall without administration of exogenous insulin, the rate of fall of plasma glucose was intermediate between the insulin-treated control group and the ketotic diabetics (Figure 1). The K in this group (0.68 ± 0.10% min^{-1}) was significantly greater than that in the ketotic diabetic group ($P < 0.001$).

The plasma insulin concentration in the insulin-treated controls averaged 311 ± 25 μU/ml over the 1 h required for their plasma glucose to fall below 140 mg/dl. In the control subjects not treated with insulin, the plasma insulin concentration averaged 21 ± 3 μU/ml over the 2 h after cessation of glucose infusion.

The initial plasma glucose concentration in the ketoacidotic patients, 948 ± 79 mg/dl tended to be higher than in controls ($P < 0.1$). However, in the six ketotic patients with an initial plasma glucose less than 800 mg/dl (mean 714 ± 26 mg/dl), the average K (0.21 ± 0.03% min^{-1}) and $t^1/_2$ (6.84 ± 2 h) values were not different from those in the nine ketotic patients with a plasma glucose concentration greater than 800 mg/dl at the time of admission (Figure 2).

Eight of the patients admitted in DKA had not received prior insulin therapy. In this subgroup, the fractional turnover rate of glucose was significantly lower (0.14 ± 0.02 versus 0.25 ± 0.01% min^{-1}, $P < 0.01$) than in patients who were on maintenance insulin therapy before hospitalization.

In the six insulin-treated control subjects, total glucose removal during the 60-min period of rapid decline in plasma glucose concentration averaged 16.9 ± 1.4 mg/min · kg

FIGURE 2. The fractional rate of fall of plasma glucose (K) after low-dose insulin in control subjects (N = 6), in the entire group of ketoacidotic diabetics (N = 15), and within three subgroups of DKA patients. These subgroups include: diabetics whose plasma glucose concentration, on admission, was either above (N = 9) or below (N = 6) 800 mg/dl, and patients who were on chronic insulin therapy at the time of development of the episode of DKA (N = 7).

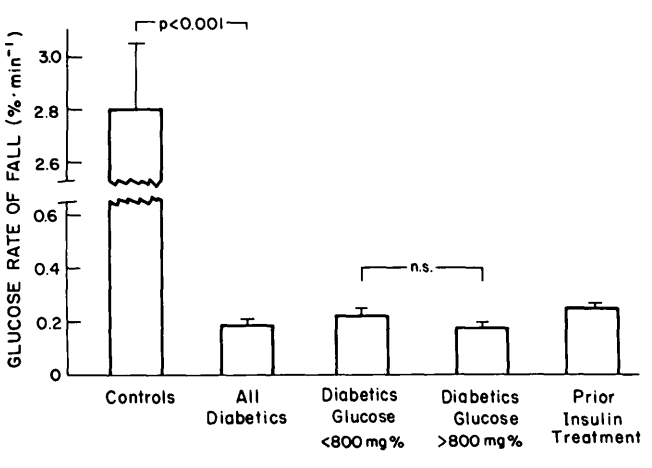


TABLE 2
Plasma glucose disposal in patients with DKA receiving insulin treatment, and in normal subjects rendered hyperglycemic, receiving or not receiving insulin treatment

	Total glucose removal (mg/min · kg)	Total glucose clearance (ml/min · kg)
Controls + insulin	16.9 ± 1.4	7.0 ± 0.7
Controls − insulin	7.6 ± 0.6†,‡	1.7 ± 0.3†,‡
DKA patients + insulin*	2.8 ± 0.2†	0.48 ± 0.05†

* In the DKA patients, glucose uptake and clearance are *net* measurements (see METHODS).
† $P < 0.001$ versus the controls + insulin.
‡ $P < 0.01$ versus the DKA patients.

(Table 2). This amount represented the sum of urinary glucose excretion (2.6 ± 0.3 mg/min · kg) and tissue glucose uptake (14.2 ± 1.4 mg/min · kg). Tissue glucose clearance, or the ratio of tissue glucose uptake to mean plasma glucose concentration, was calculated to be 5.8 ± 0.7 ml/min · kg. This value is very similar to that measured in the same subjects (5.9 ± 0.1 ml/min · kg) during the euglycemic insulin clamp study (mean plasma insulin = 125 μU/ml). In the four subjects rendered hyperglycemic who did not receive insulin, total glucose removal was significantly less than in the insulin-treated controls (7.6 ± 0.6 mg/min · kg, Table 2) and urinary glucose excretion (4.1 ± 0.7 mg/min · kg) accounted for more than 50% of the total glucose removal as a result of the prolonged hyperglycemia (Figure 1). In the DKA patients, net glucose removal and clearance during the decline in plasma glucose were both much lower than in either group of control subjects (Table 2).

DISCUSSION

The mean rate of fall of plasma glucose in the ketoacidotic diabetics during the first 5 h of insulin treatment was 80 ± 6 mg/dl/h. In several other studies of low-dose insulin treatment of DKA, the mean rate of fall of plasma glucose after insulin treatment has varied between 60 and 100 mg/dl/h.[15] Genuth has reported that continuous intravenous infusion of high doses of insulin (50 U/h) resulted in a decline in plasma glucose concentration of approximately 70 mg/dl/h.[21] Thus, the rate of decline in plasma glucose seen in our ketotic patients after insulin treatment is similar to that found by other investigators using either high- or low-dose insulin therapy. The observed time course of plasma glucose after insulin administration differed strikingly between the ketoacidotic subjects and the control subjects, in whom the mean rate of fall of plasma glucose exceeded 500 mg/dl/h. The ketoacidotic patients thus appeared to be severely resistant to the glucose-lowering action of insulin. A further appreciation of the degree of insulin insensitivity is gained from the much slower decline in plasma glucose seen in the ketotic patients compared with that found in hyperglycemic controls not given exogenous insulin (Figure 1). However, volume contraction might impair glycosuria in the DKA group and account for part of this difference. In the SRIF-treated controls, not given insulin, glycosuria averaged 4.1 ± 0.7 mg/min · kg, or 54% of the total rate of glucose disposal (7.6 ± 0.6 mg/min · kg), and tissue glucose uptake averaged 3.5 ± 0.3 mg/min · kg. Thus, despite a plasma insulin level of only approximately 20 μU/ml in these control subjects, tissue glucose uptake equaled or exceeded the combined tissue plus urinary glucose disposal in the diabetics (2.8 ± 0.2 mg/min · kg).

Since free plasma insulin measurements were not obtained in our diabetic subjects during insulin treatment, we cannot directly compare the plasma insulin levels achieved in response to insulin infusion in the two groups of subjects. However, seven of the treated diabetics had not received prior insulin treatment, and, therefore, should not have had insulin antibodies to complex with the infused insulin. Yet, in these subjects, the fractional glucose turnover was even slower than in the diabetics previously treated with insulin. In this regard, Asplin and Hartog[22] have measured free plasma insulin concentrations in patients during treatment of DKA with "low-dose" insulin infusions. They found that the plasma insulin response to insulin infusion in newly diagnosed diabetics was virtually identical to that seen in diabetics on chronic insulin treatment. Furthermore, when high-dose insulin infusion has been used in ketoacidosis yielding plasma insulin levels between 600 and 1000 μU/ml, the rate of decline of plasma glucose (70–100 mg/dl · h) was similar to that obtained in our patients treated with low-dose insulin.[5,21] Thus, it is unlikely that the slower rate of fall in plasma glucose in our diabetic patients was due to differences in the insulin levels achieved with the insulin treatment.

The insulin concentrations achieved in the systemic circulation with "low-dose" insulin infusion regimens have been reported in several studies to range between 50 and 200 μU/ml.[15] In recent studies of the dose-response relationship between plasma insulin concentration and glucose uptake in normal man,[23,24] the half-maximal stimulation of glucose uptake occurred at insulin concentrations between 80 and 120 μU/ml. Insulin stimulation of glucose uptake was saturated at plasma insulin concentrations between 300 and 500 μU/ml. If the dose-response relationship of insulin action on glucose metabolism is similar in normal and ketotic man, then the insulin concentrations achieved with insulin infusions between 5 and 10 U/h should provide near-maximal stimulation of glucose uptake.

In accord with this are results of several clinical studies of patients in DKA who received "high-dose" insulin infusions (approximately 50 U/h), resulting in plasma insulin levels above 1000 μU/ml.[5,21] Despite this extreme hyperinsulinemia, the rate of fall of plasma glucose was not significantly different from that observed with low-dose insulin treatment. Thus, the striking impairment in insulin-mediated glucose disposal, uniformly found in our patients with DKA, occurs in spite of insulin levels that maximize glucose uptake in normal subjects. Therefore, the clinical observation that low and high doses of insulin are equally effective in the treatment of DKA should not be interpreted as evidence that insulin resistance is not present in this condition.[5,6] To the contrary, in the light of the present results, the comparable efficacy of low- and high-dose insulin regimens indicates the presence of a state of extreme insulin resistance, which cannot be overcome by even very high insulin concentrations. A similar conclusion was suggested by Ginsberg,[25] who studied nine ketoacidotic diabetics using a modification of the quadruple infusion technique.[26] He found that the steady-state plasma glucose concentrations achieved with

insulin-glucose infusion soon after treatment of DKA were threefold higher than those measured in the same subjects restudied several weeks later.

Our observation that the fractional turnover of glucose (K) is depressed in virtually all the diabetic patients (range 0.05–0.29% min^{-1}) when compared with control subjects (range 1.95–3.7% min^{-1}) indicates that appreciable insulin resistance is present in virtually all ketoacidotic subjects. However, glycemia was corrected in these patients by low-dose insulin infusion. Ketoacidotic patients are occasionally encountered in whom low-dose insulin treatment fails to control glycemia while higher doses are eventually effective. In this small minority of patients the profound insulin resistance may represent an extreme extension of the insulin resistance seen in all ketoacidotic subjects or be attributable to the presence of insulin antibodies of sufficient titer and affinity to inactivate the infused insulin.

A further quantitative assessment of the degree of insulin resistance seen in the ketoacidotic patient can be derived from our estimates of plasma glucose clearance. In the controls, the rates of glucose clearance from plasma during both the falling glucose study (5.8 ± 0.7 ml/min · kg) and the euglycemic clamp study (5.9 ± 0.1 ml/min · kg) were about threefold enhanced over the values observed in the postabsorptive state (1.8–2.5 ml/min · kg).[17,23] This increase in glucose clearance is the expression of insulin's effect on glucose disposal. The corresponding measurement in the DKA patients, the net glucose clearance (0.5 ± 0.1 ml/min · kg), averaged less than 10% of the mean normal values. Furthermore, it should be noted that the net glucose clearance represents the sum of urinary and metabolic clearance, and therefore is an overestimation of insulin's effect on glucose disposal.

Pertinent to this, Owen et al. have recently measured the urinary clearance of glucose in a group of 10 ketoacidotic patients during rehydration before insulin administration.[27] In these patients, renal clearance of plasma glucose was approximately 0.25 ml/min · kg; this corresponds to roughly 50% of the net plasma glucose clearance measured in our group of patients. An appreciation of the magnitude of the impairment in plasma glucose clearance can be obtained if it is considered that in other known states of insulin resistance, such as type II diabetes,[26] uremia,[28] obesity,[29] or acromegaly,[30] glucose clearance has been reported to be decreased by 25–75%.

Whether the insulin resistance seen in ketoacidotic diabetics results from failure of insulin to suppress endogenous glucose production, from failure to stimulate glucose removal by peripheral tissues, or from a combination of these defects was not directly assessed in our studies. Some indication, however, can be derived from our data. The rate of glucose uptake in the controls (14.2 ± 1.4 mg/min · kg) was fivefold greater than in the ketoacidotic diabetics (2.8 ± 0.2 mg/min · kg). As indicated in METHODS, the net rate of glucose disposal in the diabetics may underestimate the acutal rate of tissue glucose removal to the extent that endogenous glucose production is not inhibited during insulin treatment. In previous studies, in which rates of endogenous glucose production were measured in insulin withdrawn, type I ketotic diabetics[31,32] reported values ranging from normal (2.0 mg/min · kg) to threefold elevated. Owen et al. have indeed reported a mean rate of splanchnic glucose production of 2.1 mg/min · kg in eight ketoacidotic diabetics studied with the hepatic vein catheter technique.[33] Even if it is assumed that hepatic glucose output was ongoing in our group of diabetics at a rate three times higher than basal (6 mg/min · kg), this could account for only 50% of the difference in glucose removal observed between normals and diabetics (14.2 − 2.8 = 11.4 mg/min · kg). This suggests that insulin-mediated glucose uptake by peripheral tissues must be severely impaired, and that this defect constitutes a quantitatively important contribution to the overall insulin resistance observed in our patients.

In summary, the results of the present study demonstrate that severe insulin resistance is present in virtually all ketoacidotic diabetics, and that impaired glucose disposal by peripheral tissues is one important site of this insulin resistance. The "successful" use of low-dose insulin regimens in the treatment of ketoacidosis is not the expression of normal tissue sensitivity to moderate hyperinsulinemia but of extreme resistance to insulin action, which is not overcome by further increasing the insulin dose.

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