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INSULIN RESISTANCE: A UNIVERSAL FINDING IN DIABETIC STATES

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Summary

The mechanisms contributing to the impairment in glucose metabolism in non-insulin-dependent diabetes mellitus, insulin-dependent diabetes mellitus, and diabetic ketoacidosis are summarized in Table 2. Impaired insulin secretion is charactistic of patients with IDD and DKA. In contrast, insulin secretion in NIDD may be normal, increased, or decreased. Peripheral tissue resistance to the action of insulin is present in all three diabetic conditions; it is moderate in NIDD and IDD and severe in DKA. Basal hepatic glucose production in NIDD and IDD can be either normal or increased, and correlates closely with the fasting plasma glucose concentration. In DKA, HGP is elevated. Suppression of HGP by insulin is normal in NIDD and IDD but severely impaired in DKA. Hepatic glucose uptake following oral glucose is decreased in NIDD; hepatic uptake of ingested glucose has not been examined in IDD and DKA.

In the present treatise we shall review the pathogenesis of the most common diabetic conditions: 1) non-insulin-dependent (Type II, maturity-onset) diabetes mellitus; 2) insulin-dependent (Type I, juvenile-onset) diabetes mellitus; and 3) diabetic ketoacidosis. Particular emphasis will be placed on the contribution of insulin resistance to the glucose intolerance observed in these three states. Both the site and mechanism(s) of the glucose intolerance will be discussed.

Table 1: Summary of plasma insulin response during oral (OGTT) and intravenous (IVGTT) glucose tolerance tests in diabetic subjects with fasting hyperglycemia. The early phase insulin response represents the initial 0-minute period during the IVGTT and the 0-60 minute period during the OGTT. N = normal; ↑ = increased; ↓ = decreased.

Reference	Plasma Insulin Response			Fasting Plasma Insulin Conc.	Fasting Glucose Conc. (mg %)	Type of Study	No. of Subject
	Early	Late	Total				
#1	↓	↓	↓	N	sl↑ (<110)	IVGTT	6
#2	↓	↓	↓	N	sl↑ (<120)	OGTT	19
#3	↓	↓	↓	N	sl↑*	IVGTT	8
#4	↓	↓	↓	N	>120	OGTT	183
#5	↓	↓	↓	N	135	OGTT & IVGTT	9
#6	↓	↓	↓	N	>140	OGTT	225
#7	↓	↓	↓	N	>150	OGTT	8
#8	↓	↓	↓	N	161	IVGTT	12
#9	↓	↓	↓	N	215	OGTT	10
#10	↓	↓	↓	N	217	OGTT	20
#11	↓	↓	↓	N	233	OGTT	11
#12	↓	↓	↓	N	↑*	IVGTT	19
#13	↓	↓	↓	N	↑*	OGTT	4
#14	↓	N	↓	N	↑*	IVGTT	15
#15	↓	N	↓	N	125	IVGTT	6
#16	↓	N	↓-N	N	180	OGTT	17
#17	-	-	↓	↑	235	OGTT	33
#18	↓	N-↑	N	N	129	IVGTT	5
#11	↓	↑	N	N	139	OGTT	9
#19	↓	N-↑	N	N	↑*	OGTT	17
#4	sl↓	N	N	N	110	OGTT	77
#20	N	N	N	N	146	OGTT	18
#21	N	N	N	↑	201	IVGTT	7
#9	N	N-↑	N	N	120	OGTT	10
#10	N	↑	N	N	115	OGTT	21
#22	N-↑	N-↑	N-↑	N	>140	OGTT	69
#23	-	-	N-↑	N	↑*	OGTT	9
#24	↑	↑	↑	N	>110	OGTT	8
#25	↑	↑	↑	N	140	OGTT	3
#26	↑	↑	↑	N-↑	148	OGTT	42
#27	↑	↑	↑	↑	153	OGTT	7
#28	↑	↑	↑	↑	↑*	OGTT	19

* = values not given.

I. Non-insulin-dependent diabetes mellitus (NIDDM)

A. Insulin Secretion. Considerable controversy exists concerning the role of insulin deficiency in the pathogenesis of non-insulin-dependent diabetes mellitus (1-29). Although many studies have demonstrated an impairment in insulin secretion (1-18), many reports have challenged this concept (9, 10, 20-28). A summary of the results from oral and intravenous glucose tolerance tests performed in normal weight NIDDM with varying degrees of fasting hyperglycemia is depicted in Table 1.

Most subjects with fasting hyperglycemia have been shown to have a defect in insulin secretion following both oral and intravenous glucose administration (Table 1). This impairment in insulin response is most marked during the early phase of the oral (0-60 minutes) and intravenous (0-10 minutes) tolerance test (1-19), but it is also evident during the later half (1-17). From reviewing the individual responses, it is also clear that with increasing severity of fasting hyperglycemia, there is a progressively greater impairment in both the early and late phases of insulin secretion. When the fasting plasma glucose concentration is in excess of 140 to 160 mg/dl, the plasma insulin response becomes quite flat. There are, however,

Table 2. Summary of the mechanisms contributing to the impairment in glucose metabolism in non-insulin-dependent diabetes mellitus, insulin-dependent diabetes mellitus, and diabetic ketoacidosis.

	Non-Insulin Dependent Diabetes Mellitus	Insulin-Dependent Diabetes Mellitus	Diabetic Ketoacidosis
Insulin Secretion	↓,N,↑	↓	↓
Insulin Resistance	MODERATE	MODERATE	SEVERE
Site of Insulin Resistance			
Peripheral Tissues	MODERATE	MODERATE	SEVERE
Liver			
Basal HGP	N,↑	N,↑	↑↑
Suppression of HGP	N	N	SEVERELY IMPAIRED
Hepatic Glucose Uptake (oral)	↓	?	?

several notable exceptions which indicate that factors other than diminished insulin secretion must contribute to the glucose intolerance in some maturity-onset diabetics. Thus, several groups (22, 24-28) have reported significant numbers of diabetic patients with fasting plasma glucose levels in the 140-160 mg % range in whom early, late, and total insulin responses are increased. In summary, most, but not all, non-insulin-dependent diabetics with fasting hyperglycemia are characterized by a deficient insulin response. However, this does not exclude the possibility of other coexisting defects in glucose homeostasis, i.e., abnormal hepatic glucose metabolism and peripheral tissue insensitivity to insulin. In fact, the finding of an elevated plasma insulin response in a significant percentage of NIDDM patients (22, 24-25) indicates the presence of insulin resistance as either a primary or, at least, a complicating feature of the diabetic state.

B. Insulin Resistance. Numerous investigators, employing a variety of techniques, including: the intravenous insulin tolerance test (29, 30), the combined intravenous insulin-oral glucose tolerance test (31), the forearm perfusion technique (32-34), the quadruple infusion protocol of Reaven (35-37), the somatostatin modification of Reaven's infusion protocol (38) and radioactive glucose isotope methods (39), have documented the presence of insulin resistance in NIDDM. Nonetheless, the presence of insulin resistance as an important pathogenetic factor in the development of NIDDM has not become widely accepted nor has the site(s) of the insulin resistance been defined.

Employing the insulin clamp technique (40) we have examined 38 normal weigth (IBW = 107 $\pm$ 2 %) NIDDM with a mean age of 57 $\pm$ 2 years (mean $\pm$ SEM). Thirty-three age (55 $\pm$ 2) and weight (IBW = 102 $\pm$ 1 %) matched subjects served as controls. None of the NIDDM were

taking any medications known to affect glucose tolerance. Tissue sensitivity to insulin was quantitated with the insulin clamp technique (40). Following a control period to allow for equilibration of ^{3}H-3-glucose, a prime-continuous (42,6 mU/m^2 surface area per min) infusion of crystalline porcine insulin was administered for two hours to achieve constant physiologic hyperinsulinemia. The plasma glucose concentration was maintained at basal. Preinfusion levels by determination of plasma glucose every 5 minutes and the periodic adjustment of a variable infusion of a 20 % glucose solution (40). Under these steady-state conditions of constant glycemia, the total amount of glucose taken up by all tissues of the body is equal to the sum of the exogenous glucose infusion rate and the rate of the endogenous (hepatic) glucose production. The rate of endogenous glucose production was calculated from the analysis of tritiated glucose kinetics (41).

Since hyperglycemia per se will enhance insulin-mediated glucose uptake by a mass action effect (42), in 11 of the 38 NIDD, following the initiation of the insulin infusion, the plasma glucose concentration was allowed to decrease to ~120 mg/dl before the exogenous glucose infusion was begun.

The mean fasting plasma glucose concentrations in the control and NIDD were 92±1 mg/dl and 150±9 mg/dl respectively. During the insulin clamp, the plasma glucose was held close to the basal level. In the 11 NIDD in whom the plasma glucose concentration was allowed to drop before initiating the exogenous glucose infusion, the mean steady-state glucose level during the clamp was 119±3 mg/dl. The fasting plasma insulin concentrations in the controls and NIDD were 13±1 μU/ml and 19±2 μU/ml, respectively ($P<0.005$). The steady-state insulin levels during the insulin clamp were 111±3 and 115±7 μU/ml.

During the insulin clamp, the total amount of glucose taken up by the body (20-120 min) in the 27 NIDD studied at their fasting glucose level, 4.57±0.31 mg/kg·min, was reduced by 28 % as compared to age-matched controls, 6.39±0.25 mg/kg·min, $P<0.01$ (Figure 1, left panel). The glucose clearance (total glucose metabolism ÷ plasma glucose concentration) was reduced to an even greater extent, 3.17±0.20 vs. 6.93±0.29 ml/kg·min, $P<0.001$ (Figure 2, left panel). In the 11 NIDD whose plasma glucose concentration was allowed to decrease to 119 mg/dl before starting the clamp study, the total amount of glucose metabolized, 3.32±0.36 mg/kg·min, was significantly less than in the NIDD studied at fasting hyperglycemic levels, $P<0.05$, or normals ($P<0.001$). Only one of the NIDD had a rate of glucose metabolism that was within the mean ±1 SEM observed in the control group (Figure 1). The glucose clearance in the NIDD studied at euglycemic levels, 2.83±0.31 ml/kg·min, was similar to that observed in NIDD studied at hyperglycemic levels (Figure 2). In the NIDD studied at hyperglycemic levels, the total amount of glucose metabolized during the insulin

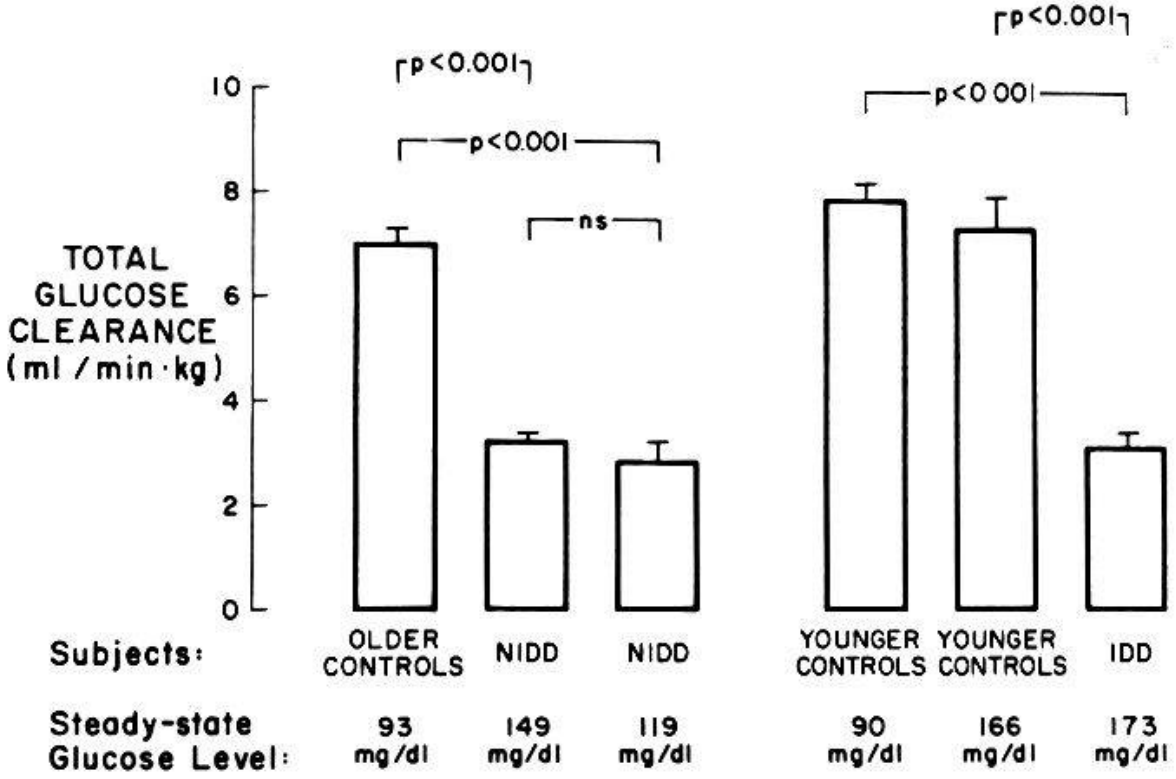

Fig. 1. Total glucose uptake in age-matched control subjects, non-insulin-dependent diabetics (NIDD), and insulin-dependent diabetics (IDD) during a 1 mU/min·kg insulin clamp. The mean steady-state plasma glucose levels during the clamp study for the various experimental groups are given at the bottom of the bars. Data are mean SEM. The p values refer to impaired t-test analysis.

clamp was positively correlated ($r=0.50$, $P<0.01$) with the fasting plasma glucose concentration. These results indicate the presence of moderate to severe insulin resistance in NIDDM. In addition, they suggest that fasting hyperglycemia is a compensatory mechanism that allows the diabetic cells to maintain a normal rate of glucose uptake, despite an impaired plasma insulin response.

In a general sense, the insulin resistance in NIDDM could result from one of three possible mechanisms: 1) augmented basal hepatic glucose production (HGP) which fails to suppress normally following hyperinsulinemia, 2) impaired splanchnic (hepatic plus intestinal tissues) glucose uptake, or 3) decreased glucose uptake by peripheral tissues.

In the NIDD, endogenous glucose production (2.50 ± 0.15 mg/min·kg) was slightly, though not significantly, greater than in the age-matched controls (2.18 ± 0.03, $0.1>p>0.05$) (Figure 3) and a strong direct correlation existed between fasting plasma glucose concentration and endogenous glucose production ($r=0.80$, $p<0.001$). In contrast, the fasting glucose clearance was only weakly related to fasting plasma glucose in an inverse fashion ($r=0.31$, $0.1>p>0.05$). During the clamp, hepatic glucose production in the control subjects declined to 0.43 ± 0.05

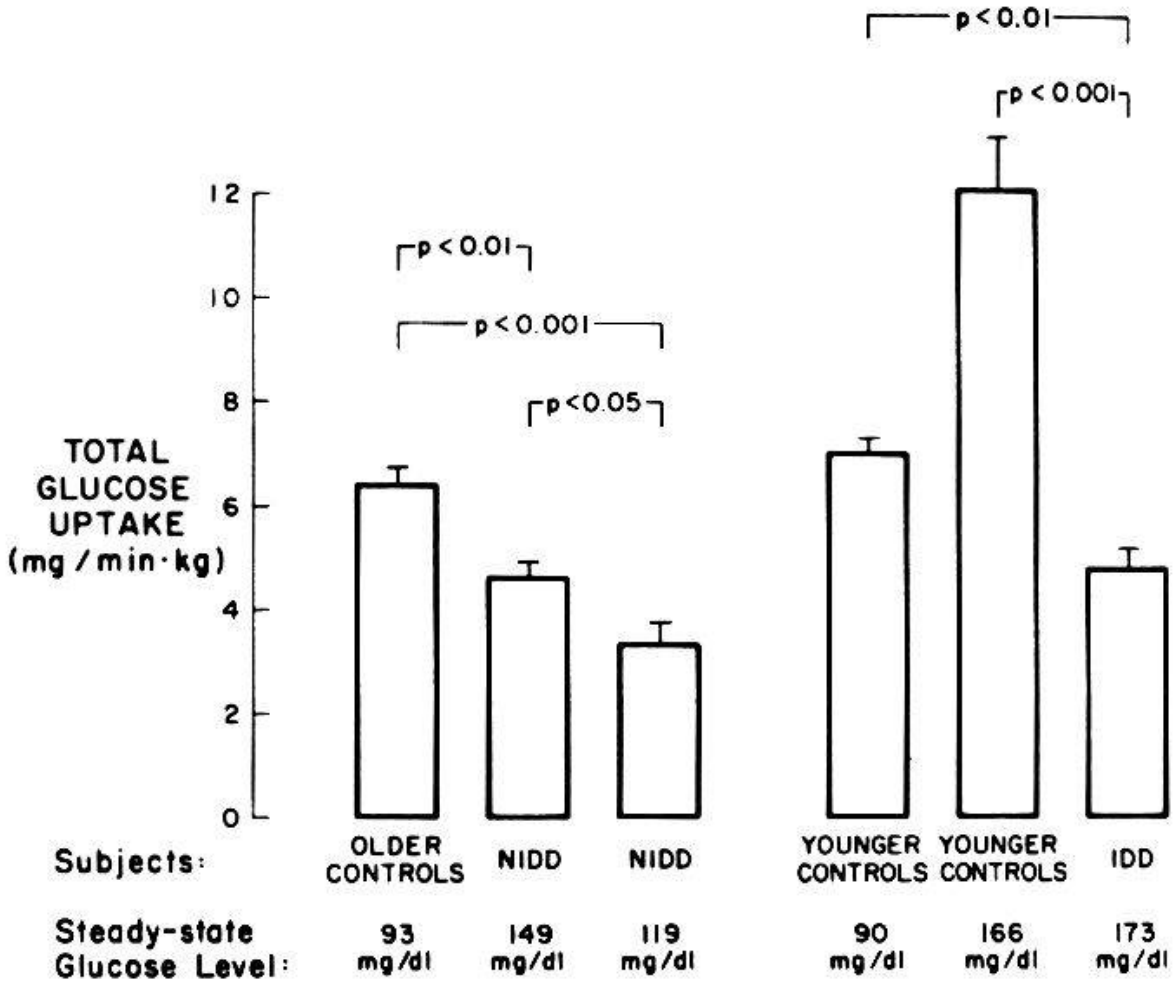

Fig. 2. Total plasma glucose clearance (total glucose uptake : steady-state plasma glucose concentration) in the various experimental groups. All indications are as in Figure 1.

mg/min·kg within 20 min. Over the second hour of the clamp study, hepatic glucose production was suppressed by >95 % (to 0.08±0.02 mg/min·kg). In the NIDD the time-course as well as the absolute degree of inhibition of hepatic glucose production were similar to those of the respective control group (Figure 3). These results indicate that increased production of glucose during the postabsorptive state is the major determinant of fasting hyperglycemia. It should be emphasized that the increase in basal hepatic glucose production occurred in the presence of elevated fasting levels of insulin and glucose, both of which are known to suppress HGP (43). Despite the increase in basal HGP, suppression of hepatic glucose production in response to hyperinsulinemia is normal (Figure 3). Thus, the insulin resistance documented during the insulin clamp studies can not be attributed to impaired suppression of HGP. We have previously shown that even under extreme degrees of hyperglycemia (400 mg/dl) and hyperinsulinemia (900 μU/ml), the splanchnic bed removes only 5-10 % of an intravenous glucose load (44). Therefore, it seems unlikely that impaired splanchnic glucose uptake

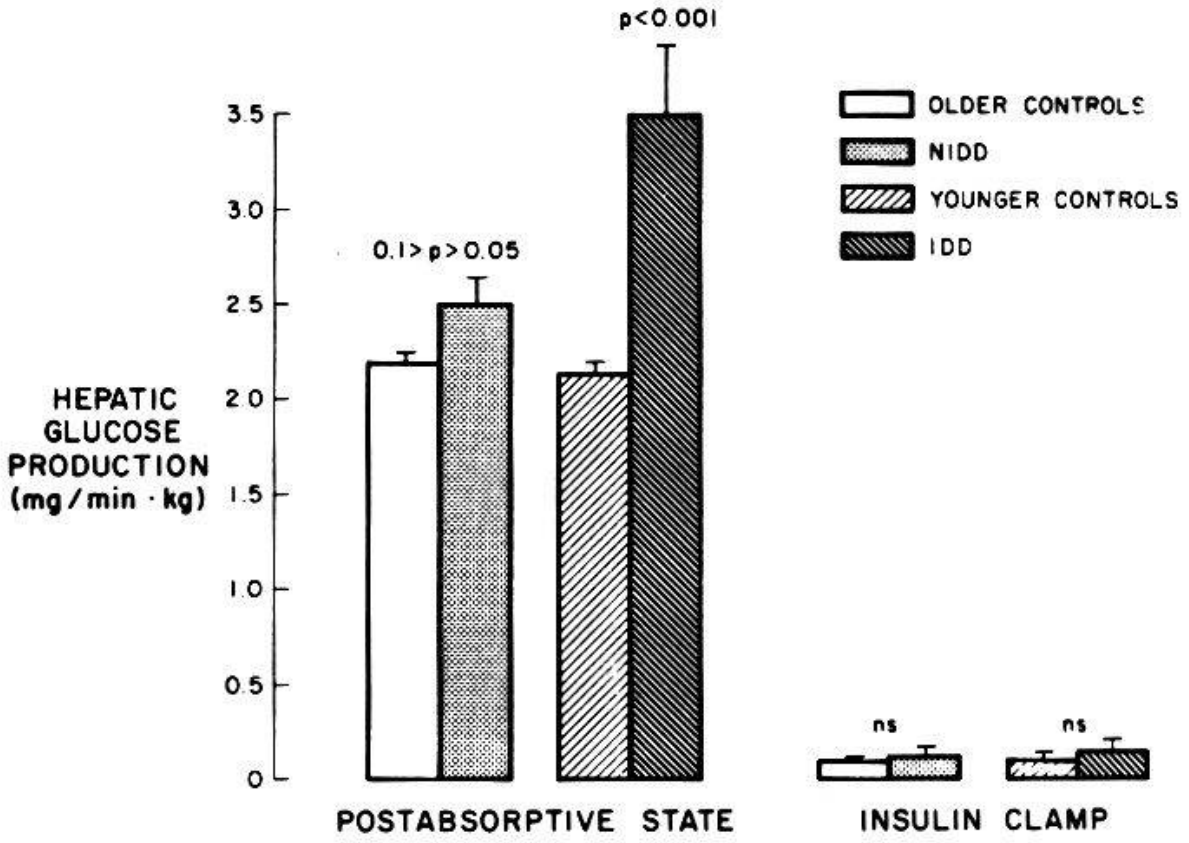

Fig. 3. Hepatic glucose production in the postabsorptive state and during the 2nd hour of a 1 mU/min·kg insulin clamp in non-insulin-dependent diabetics (NIDD), insulin-dependent diabetics (IDD), and their respective, age-matched controls. Data are means SEM. The p values refer to impaired t-test analysis.

could account for the insulin resistance observed in NIDDM individuals. Recently, we have confirmed this assumption by performing insulin clamp studies in combination with hepatic venous catheterization (DeFronzo, Gunnarson and Wahren, unpublished observations). Insulin-mediated glucose metabolism, 4.37±0.45, was significantly diminished compared to controls ($P<0.01$) but splanchnic glucose uptake (0.24 mg/kg·min) was not significantly different from controls. These results indicate that the site of insulin resistance must reside in peripheral tissues, most likely muscle. In fact, we have recently confirmed this by direct femoral venous catheterization to quantitate leg glucose exchange. In these studies, leg glucose uptake was decreased by 30-40 % compared to controls and this decrease closely paralleled the decrease in total body glucose metabolism.

In summary, the results of the insulin clamp studies indicate that insulin resistance is a universal finding in NIDDM and that the primary site of insulin resistance resides in peripheral tissues, most notably muscle. It should be noted that all of the above studies employed intravenous insulin/glucose administration. As discussed earlier, under such conditions, the

splanchnic region takes up only a small percentage of the infused glucose load. In contrast, when glucose is administered orally, 60 % of the ingested load is disposed of by the liver (2, 44-46). Thus, the route of the glucose administration (i.e., oral versus intravenous) is an important determinant of splanchnic glucose metabolism. Felig et al have shown that net glucose retention within the splanchnic region is markedly impaired in NIDDM following oral glucose ingestion (27). These results suggest that the diabetic may lack those putative mechanism (i.e., hormonal, neural, other) whereby oral glucose enhances liver glucose uptake independently of (or synergistically with) the effect of hyperinsulinemia and hyperglycemia (47, 48).

II. Insulin-dependent Diabetes Mellitus

As discussed in the preceeding section, insulin resistance has become a well established feature of non-insulin-dependent diabetes mellitus. However, few studies have examined whether or not insulin resistance is also present in insulin-dependent, Type I (juvenile-onset) diabetes mellitus. Himsworth and Kerr (49) were amongst the first to suggest that insulin action might be impaired in insulin-dependent diabetics (IDD). Using a combined insulin-glucose tolerance test they found that, although most insulin-dependent diabetics whose disease started early in life were insulin sensitive, a significant percentage manifested resistance to the action of insulin. Employing the same insulin-glucose tolerance test, Martin and Stocks found that 22 of 43 insulin-dependent diabetics were insulin resistant (50). Ginsberg (51), using the quadruple infusion (propranolol, epinephrine, glucose and insulin) technique to measure tissue sensitivity to insulin, found normal sensitivity in six insulin-dependent diabetics. However, a wide range was observed with three of the six diabetics being well above the mean of the controls and 3 well below the mean control value. Harano et al (38), employing the somatostatin modification of the quadruple infusion technique, demonstrated significant insulin resistance in five of five insulin-dependent diabetics studied. Taken as a whole the above studies would suggest that a significant percentage of IDD demonstrate insulin resistance. However, it is a common clinical teaching that in the absence of insulin antibodies, tissue sensitivity to insulin is normal in IDD and insulin-dependent diabetes is not listed as a cause of insulin resistance (52).

To examine whether or not insulin resistance was present in IDD, we studied 11 normal weight (IBW = 101$\pm$4%), young (34$\pm$3 years) Type I diabetics with the insulin clamp technique. The duration of diabetes in the insulin-dependent group was 10$\pm$3 years, and their daily requirement of NPH insulin was 34$\pm$3 units. Seven of the 11 had a prior history of diabetic ketoacidosis. Thirty-six healthy volunteers, matched for age (36$\pm$1 years) and ideal body weight

(102±1%) served as the control population. Since hyperglycemia is known to enhance glucose metabolism by a mass action effect (42), five of the control subjects were restudied with a combined hyperglycemic-insulin clamp to simulate the mean plasma glucose and insulin levels observed in the diabetic group.

The fasting plasma glucose concentration in the diabetics, 173±24 mg/dl, was approximately two-fold higher than in the controls, 91±1 mg/dl ($p<0.001$). During the period of hyperinsulinemia the glucose concentration was maintained at 173±24 mg/dl in the diabetic group. In the 36 control subjects clamped at euglycemic levels, the fasting plasma glucose concentration was maintained at 90±1 mg/dl. In the five control subjects who were clamped at hyperglycemic levels, the fasting plasma glucose concentration (89±2 mg/dl) was maintained at 166±2 mg %. The fasting plasma insulin concentration in the control group, 14±1 μU/ml, was raised and maintained at 107±3 μU/ml. In the five controls studied with the combined hyperglycemic-insulin clamp, the steady-state plasma insulin concentration was 107±4 μU/ml. The fasting and steady-state plasma free-insulin levels in the eleven diabetics averaged 9 ±1 and 91±5 μU/ml respectively.

In the IDD, the total amount of glucose metabolized (20-120 min), 4.77±0.48 mg/kg·min, was significantly reduced, by 32 %, compared to controls, 7.03±0.22 mg/kg·min, $P<0.01$ (Figure 1, right panel). The degree of impairment in glucose metabolism in the IDD is even more striking when compared to the control subjects who were studied at comparable degrees of hyperglycemia and hyperinsulinemia (12.14±0.96 mg/kg·min, $P<0.01$). The rate of insulin-mediated glucose metabolism was not significantly different between IDD and NIDD. The rate of glucose clearance in the IDD, 3.08±0.29 ml/kg·min, was markedly reduced compared to controls, 7.83±0.25 ml/kg·min, $P<0.001$ (Figure 2, right panel), but was not significantly different from the NIDD (3.17±0.20). The total rate of glucose metabolism was positively correlated ($r=0.61$, $P<0.05$) with the fasting plasma glucose concentration. In contrast, the glucose clearance was inversely ($r=0.80$, $P<0.001$) correlated with the fasting plasma glucose. In the IDD, basal hepatic glucose production (3.51±0.34 mg/min·kg) was markedly increased ($P<0.001$) as compared to age-matched controls (2.13±0.04) (Figure 3). Fasting glucose clearance was lower than normal (2.03±0.12 vs 2.35±0.04 ml/min·kg, $p<0.001$). Fasting plasma glucose levels displayed a positive correlation with the rates of glucose production ($r=0.87$, p 0.001), and a negative correlation with the rates of glucose clearance ($r=0.72$, $p<0.001$). During the period of hyperinsulinemia (insulin clamp) there was a nearly complete suppression of HGP in both IDD and controls (Figure 3). These results are qualitatively very similar to those from NIDD and indicate the presence of significant resistance to the action of insulin.

Several points are worthy of emphasis when comparing the two groups of diabetics. Firstly, the rates of endogenous glucose production tended to be higher in the NIDD and were definitely increased in the IDD (Figure 3). In fact, in virtually every diabetic subject, whether insulin-independent or insulin-dependent, with fasting plasma glucose levels higher than 180 mg/dl, endogenous glucose release was elevated in absolute terms. Moreover, even "normal" rates of glucose production were inappropriately high for the associated degree of hyperglycemia. In previous studies, we have shown that in normal subjects hyperglycemia effectively suppresses hepatic glucose production even in the presence of low insulin levels (43). In the diabetics in this study, fasting plasma insulin concentrations were raised (NIDD) or only slightly reduced (IDD) compared to normal. In summary, it seems possible to conclude that in diabetic subjects the liver is resistant to the restraining action of insulin and/or hyperglycemia on basal glucose release. Frank over-production of glucose may result, especially when the resistance is severe or is associated with some degree of hypoinsulinemia (as is the case of IDD patients).

The second similarity is that the plasma glucose clearance in the fasting state was reduced in both NIDD and IDD. Here, it should be noted that in those diabetics with fasting plasma glucose concentrations higher than 180 mg/dl, the renal threshold for glucose was presumably exceeded, and significant glycosuria was present. Since urinary glucose losses were not quantitated in the present study, the calculated rates of plasma glucose clearance overestimate tissue glucose clearance by an amount equal to urinary glucose clearance. Consequently, the actual rates of tissue glucose clearance would be even lower than calculated. Thus, in NIDD and IDD alike, significant insulin resistance was present in the peripheral tissues in the basal state. It is of interest that the basal rates of glucose uptake (=rates of glucose production, Figure 3) were not reduced, since the lower glucose clearance rates were associated with raised plasma glucose levels. Fasting hyperglycemia therefore appears to serve a compensatory function in driving glucose into cells which have a reduced specific capacity to take up glucose. Although it is implicit in the definition of insulin resistance that only insulin-dependent tissues (principally muscle and fat) are responsible for the impaired efficiency of glucose uptake, it cannot be excluded that the insulin-independent tissues (brain, red blood cells, renal medulla, and intestine) may also clear plasma glucose at reduced rates. Finally, in the IDD fasting hypoinsulinemia, although slight, may also contribute to the observed defect in basal glucose clearance, just as it does to the glucose overproduction.

Thirdly, during the insulin clamp, total glucose uptake was decreased by 30 % in the NIDD, and by 32 % in the IDD (Fig. 1) despite their higher plasma glucose levels (150 and 173 mg/dl, vs. 90 mg/dl in the controls). The magnitude of this defect is fully appreciated when

glucose uptake is "corrected" for the plasma glucose concentration, i.e., by calculating the glucose clearance. Again, both the NIDD and the IDD showed a marked reduction in glucose clearance, and the similarity of this change in the two groups of patients is striking (61 % vs. 54 %).

Fourthly, during the insulin clamp, hepatic glucose production was inhibited in both the NIDD and the IDD to the same extent as in normals. The present experiments do not answer the question of whether suppression of hepatic glucose production in diabetics might be impaired with smaller elevations in plasma insulin concentration. Nevertheless, the present results do demonstrate that whatever deficit there might be in the ability of the diabetic liver to shut off glucose release in response to insulin, this can be overcome by higher insulin levels (~100 μU/ml). The physiologic relevance of this observation is that, following the ingestion of a glucose load, portal vein plasma insulin levels rise about 100 μU/ml, and stay high for a considerable length of time (53). Therefore, unless the insulin response to glucose administration is severely deficient (as in IDD patients), failure of the liver to inhibit glucose release in response to glucose ingestion is not likely to be a major contributory factor to postprandial hyperglycemia.

III. Diabetic ketoacidosis

While it is generally accepted that insulinopenia is the primary pathogenetic factor in the development of diabetic ketoacidosis, the contribution of insulin resistance is less certain. Recent studies demonstrating comparable efficacy of low and high dose insulin regimens (54-56) have led many investigators to conclude that insulin resistance is not present in patients with diabetic ketoacidosis (DKA). However, it should be noted that these so-called "low dose" regimens (i.e., 6-10 unit bolus plus 6-10 units per hour intravenously) actually result in plasma insulin levels that maximally stimulate glucose metabolism in normal man. Therefore, it might not be surprising if higher doses of insulin failed to stimulate glucose uptake any further above that observed with "low dose" insulin therapy. Since DKA is characterized by severe metabolic acidemia and elevated plasma concentrations of free fatty acids, catecholamines, growth hormone, cortisol and glucagon (all of which are known to antagonize the action of insulin), it would be surprising if insulin sensitivity were not found to be impaired in ketoacidotic patients.

To examine whether or not insulin resistance is present in DKA, we compared the rate of fall of plasma glucose following a primed-continuous insulin infusion in 15 ketoacidotic diabetics and in a group of 6 normal individuals in whom plasma glucose had been previously raised to levels typically encountered in ketoacidosis (above 600 mg/100 ml) by a combined infusion

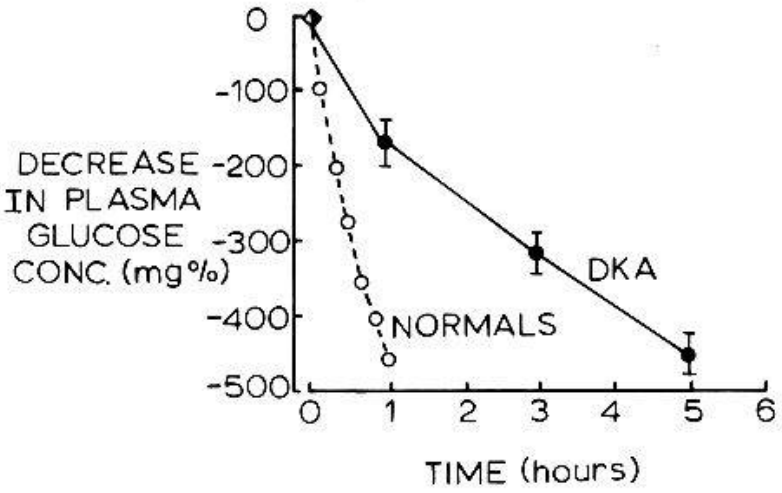

Fig. 4. Time course of decline in plasma glucose in the ketoacidotic diabetic subjects (N= 15) and in normal volunteers (N=6) following insulin treatment.

of glucose and somatostatin. The priming dose (6 units) and the continuous infusion rate (6 units/hour) of insulin used in the present study are average doses employed in the "low-dose" insulin treatment of DKA. All of the diabetics fulfilled the following criteria: a) initial plasma glucose greater than 500 mg % (mean = 949±79 mg %), b) plasma bicarbonate less than 15 meq/L (mean = 8±1 meq/L) and an anion gap greater than 18 meq/L (mean = 33±1 meq/L), c) blood pH less than 7.30 (mean = 7.17±0.03), and d) plasma ketones present at greater than 1 : 4 dilution.

The rate of fall in plasma glucose concentration in the 15 DKA subjects following initiation of insulin treatment is shown in Figure 4. The mean fractional turnover of glucose (k) in these patients was 0.19±0.02 % min^{-1}. In the 6 normal individuals who were made hyperglycemic by infusion of glucose and somatostatin, the rate decline of plasma glucose following insulin was much more rapid than in the ketoacidotic subjects (Figure 4). The mean fractional turnover of glucose in these subjects was more than 10-fold greater than in the diabetic patients (2.8±0.3 % min^{-1}, $p<0.001$). This difference was also reflected by the half time ($t\frac{1}{2}$) of the fall in plasma glucose concentration, which averaged 6.1±0.6 and 0.31±0.03 hours ($p<0.001$) for the diabetic and control groups, respectively.

To examine the site of insulin resistance and to quantitate the severity of impairment in insulin action, we have performed insulin clamp studies in patients admitted with diabetic ketoacidosis. A typical example is shown in Figure 5. Immediately upon admission, subjects were given a prime-continuous infusion of ^{3}H-3-glucose to measure rates of glucose appearance and disappearance. Subjects were also hydrated with ½ normal or normal saline as indicated and received sufficient sodium bicarbonate to maintain their plasma bicarbonate concentra-

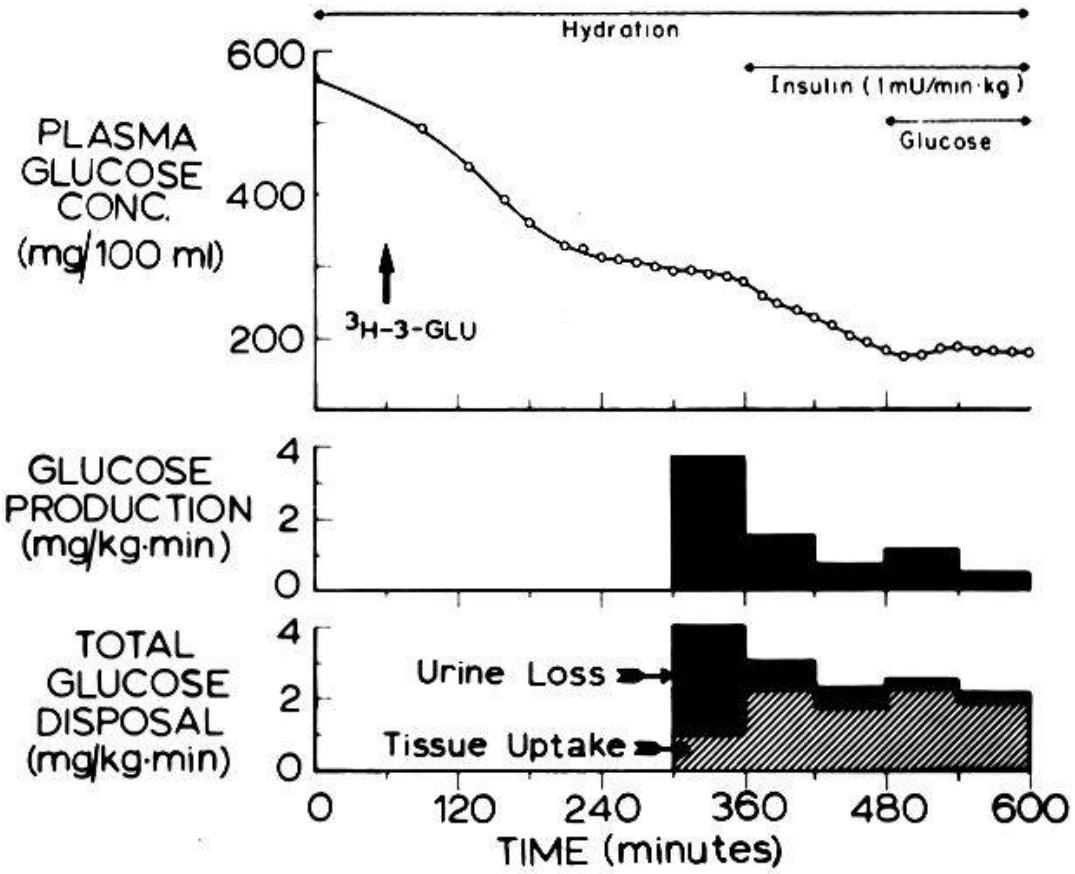

Fig. 5. Treatment of diabetic ketoacidosis with hydration followed by insulin. See text for a more detailed discussion.

tion between 10-15 meq/L. Three to four hours after initiating the ^{3}H-3-glucose infusion, a prime-continuous insulin infusion (1 mU/kg·min) was begun to raise the plasma insulin concentration by approximately 100 μU/ml (Figure 5). When the plasma glucose concentration had declined to 180 mg %, a variable glucose infusion was initiated and the plasma glucose concentration was clamped at 180 mg %. Urinary glucose losses were quantitated throughout. The total rate of glucose disposal was calculated from kinetic analysis of the tritiated glucose turnover. The tissue uptake of glucose was derived by subtracting the urinary glucose losses from the total rate of glucose disappearance. The rate of endogenous glucose production was calculated from the changes in tritiated glucose specific activity as previously described (41) The results of a representative patient are shown in Figure 5.

With hydration alone the plasma glucose concentration fell from 570 mg % to approximately 300 mg %. Basal hepatic (endogenous) glucose production was increased about 80 %, 3.64 mg/kg.min. Tissue uptake of glucose was only 0.96 mg/kg·min. In normal controls hepatic glucose production in the basal state equals the rate of glucose disposal by the entire body and is approximately 2.0-2.2 mg/kg· min. Thus, both impaired tissue uptake of glucose and ex-

cessive HGP contribute to the fasting hyperglycemia in patients with DKA. Following 4 hours of insulinization, tissue glucose uptake rose to only 2.23 mg/kg·min. This rate of glucose metabolism is similar to that observed in normal individuals under basal conditions, i.e., a plasma insulin concentration of 10-15 μU/ml. Thus, the peripheral tissues of DKA patients are severely resistant to the action of insulin. The ability of insulin to suppress HGP is also markedly impaired in DKA. Even after 4 hours of physiologic hyperinsulinemia (~100 μU/ml), HGP still was 0.4-0.5 mg/kg·min. In a normal individual a similar degree of hyperglycemia would cause a nearly complete (0.1-0.2 mg/kg·min) suppression of HGP within 30 minutes (see Figure 3). Thus, diabetic ketoacidosis is characterized by both peripheral and hepatic resistance to the action of insulin.

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