Comparison of Insulin-mediated and Glucose-mediated Glucose Disposal in Patients with Insulin-dependent Diabetes Mellitus and in Nondiabetic Subjects

I. L. HANSEN, P. E. CRYER, AND R. A. RIZZA

SUMMARY

To determine whether glucose-mediated as well as insulin-mediated regulation of glucose utilization and glucose production is impaired in patients with insulin-dependent diabetes mellitus (IDDM), six nonobese, diabetic patients and seven age-, sex-, and weight-matched nondiabetic subjects were studied. Despite slightly higher free insulin concentrations in the diabetic patients than in the nondiabetic subjects during 0.2 mU/kg · min (22 ± 3 versus 15 ± 2 μU/ml) and 1.0 mU/kg · min (98 ± 10 versus 75 μU/ml) insulin infusions, glucose utilization at plasma glucose concentrations of 95, 135, and 175 mg/dl was lower in the diabetic patients than in the nondiabetic subjects. The increment in glucose utilization per increment in plasma glucose (i.e., slope) in the diabetic and nondiabetic subjects, respectively, did not differ significantly during either the 0.2 (1.7 ± 1.3 versus 1.4 ± 0.5 dl/kg · min) or 1.0 (4.4 ± 1.1 versus 6.2 ± 1.0 dl/kg · min) mU/kg · min insulin infusions, although they tended to be higher in the nondiabetic subjects during the latter infusion.

Thus, although stimulation of glucose utilization by insulin is impaired in patients with IDDM, the ability of an increase in glucose concentration to increase glucose utilization does not appear to differ from that present in nondiabetic subjects, at insulin concentrations in the low physiologic range. Whether differences exist in the high physiologic range remains to be determined. DIABETES 1985; 34:751–55.

In nondiabetic man, glucose utilization is influenced both by changes in insulin and glucose concentration.[1–3] Several recent reports have suggested that patients with insulin-dependent diabetes mellitus (IDDM) have a decreased increment in glucose utilization per increment in insulin concentration implying insulin resistance.[4–6] The current studies were undertaken to determine whether the increment in glucose utilization per increment in plasma glucose concentration is also decreased. To do so, insulin-mediated effects on glucose utilization were assessed by comparing rates of glucose utilization in diabetic and nondiabetic subjects under conditions in which insulin and glucose concentrations were held constant. Glucose-mediated effects were assessed by measuring the increments in glucose utilization per increment in plasma glucose concentration when plasma insulin concentrations were held constant.

MATERIALS AND METHODS

Subjects. Informed, written consent was obtained from six patients with IDDM and seven healthy adult volunteers of comparable age (29 ± 2 versus 32 ± 4 yr), sex (4 F, 2 M versus 5 F, 2 M), and obesity (BMI 23 ± 1 versus 22 ± 1 kg/m^2). Insulin dependency was documented in five of the diabetic patients by means of a lack of change in C-peptide concentration after either intravenous (i.v.) injection of 1 mg of glucagon (N = 3) or ingestion of Sustacal (Mead-Johnson Nutritional Division, Evansville, Indiana) (N = 2). The sixth patient had a history of ketoacidosis and onset of diabetes at age 7 yr. At the initiation of the study, glycosylated hemoglobin concentration averaged 12.2 ± 1.3% (range 8.8–17.4%) and total insulin dose averaged 44 ± 6 U/day.

Experimental design. Subjects were studied on separate occasions at least 2 wk apart. Menstruating women were studied at monthly intervals. All protocols were begun between 7:30 a.m. and 8:00 a.m. after a 10–12-h overnight fast. Diabetic patients received no intermediate-acting insulin during the 24 h before study. A primed-continuous infusion of 2-^{3}H-glucose was initiated at time 0 for isotopic determination of glucose utilization and production rates. Glucose labeled in the second position was employed to avoid potential confounding effects of uptake and rerelease of labeled glucose by the liver under conditions of hyperglycemia and hyper-

From the Endocrine Research Unit, Department of Medicine, Mayo Clinic, Rochester, Minnesota (I.L.H., R.A.R.); and the Washington University School of Medicine, St. Louis, Missouri (P.E.C.).
Address reprint requests to R. A. Rizza, M.D., Endocrine Research Unit, Department of Medicine, Mayo Clinic, Rochester, Minnesota 55905.
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TABLE 1
Plasma glucose and insulin concentrations during 95, 135, and 175 mg/dl glucose clamps during infusions of insulin at rates of 0.2 and 1.0 mU · kg^{-1} · min^{-1}

	Plasma glucose (mg/dl)			Insulin (μU/ml)				
	Basal	Clamp	Coefficient of variation (%)	Basal	mU/kg/min (0.2)	Coefficient of variation (%)	mU/kg/min (1.0)	Coefficient of variation (%)
Diabetic	180 ± 31	96 ± 3	6.7 ± 2.2	19 ± 4	23 ± 4	14.2 ± 2.6	93 ± 12	12.5 ± 2.6
	249 ± 18	134 ± 2	3.7 ± 0.9	17 ± 4	21 ± 2	16.2 ± 1.8	92 ± 12	11.3 ± 1.0
	244 ± 67	174 ± 4	4.5 ± 0.7	18 ± 4	22 ± 4	14.0 ± 1.2	108 ± 8	14.9 ± 1.8
Nondiabetic	90 ± 3	95 ± 2	5.7 ± 0.8	9 ± 2	14 ± 2	13.3 ± 1.9	75 ± 5	12.5 ± 2.5
	90 ± 2	135 ± 2	4.2 ± 0.8	9 ± 2	15 ± 2	14.0 ± 2.0	78 ± 6	14.2 ± 2.8
	95 ± 5	173 ± 2	4.2 ± 0.4	8 ± 2	16 ± 2	22.8 ± 4.5	73 ± 3	13.2 ± 2.2

insulinemia.[7] Although 2-^{3}H-glucose has been reported to overestimate actual glucose utilization in animals by approximately 10–20%, the percent overestimate appears to remain constant during hyperinsulinemia and hyperglycemia.[8] Somatostatin (250 μg/h, Beckman Instruments, Palo Alto, California) was infused in both diabetic and nondiabetic subjects from 0 to 360 min to inhibit endogenous insulin release. Insulin (Iletin II pork insulin, Eli Lilly and Company, Indianapolis, Indiana) was infused at a rate of 0.2 mU/kg/min from 0 to 240 min and at 1.0 mU/kg/min from 240 to 360 min. Plasma glucose concentration was clamped at either 95, 135, or 175 mg/dl in all nondiabetic subjects and in four diabetic patients using a variable infusion of 50% glucose as previously described.[1] In two of the diabetic patients, plasma glucose concentrations were clamped at 95 and 135 mg/dl only.

Hormone and substrate determinations. Arterialized venous blood samples were obtained at 10-min intervals for determination of plasma glucose (YSI Glucose Analyzer, Yellow Springs Instruments, Yellow Springs, Ohio) and at 30-min intervals for the determination of hormone concentrations. Free insulin was measured according to a modification of the method of Nakayawa et al.[9] in which 35% polyethylene glycol was used to precipitate potential insulin antibodies. Free C-peptide was measured as described by Heding et al.[10] Cortisol was measured using a kit from Serono (Braintree, Massachusetts) utilizing magnetic separation of the antibody bound complexes. Plasma glucagon, growth hormone, epinephrine, norepinephrine, and glucose specific activities were measured as previously described.[11] Glucagon concentrations could not be accurately determined in one diabetic patient presumably due to an interfering factor.

Calculations. Rates of glucose utilization and endogenous production were calculated during the final 30 min of each insulin infusion as previously described.[1] Data in the text and figures are presented as mean ± SEM. The nonpaired *t*-test was used for comparison between groups. Slope was determined by linear regression analysis. A P-value of <0.05 was considered significant.

RESULTS

Plasma glucose and insulin concentrations. Before the study, the plasma glucose concentrations in the diabetic patients were significantly greater than those in the nondiabetic subjects (220 ± 24 versus 92 ± 3 mg/dl, $P < 0.05$). After initiation of the 0.2 mU · kg^{-1} · min^{-1} insulin infusion, plasma glucose concentrations were allowed to decrease in the diabetic patients and were increased in the nondiabetic subjects during the initial 120–150 min. Thereafter, plasma glucose concentrations were maintained equivalent in the diabetic and nondiabetic subjects (Table 1).

Before initiation of the insulin infusion, plasma insulin concentrations were slightly but significantly greater in the diabetic patients than in the nondiabetic subjects (17 ± 4 versus 9 ± 2 μU/ml, $P < 0.05$). Plasma insulin concentrations remained slightly greater in the diabetic patients than in the nondiabetic subjects during each of the clamps at both insulin infusion rates (22 ± 3 versus 15 ± 2 and 98 ± 10 versus 75 ± 4 μU/ml) although these differences did not reach statistical significance (Table 1).

C-peptide, glucagon, growth hormone, cortisol, epinephrine, and norepinephrine concentrations (Figure 1). Plasma C-peptide concentrations before initiation of the insulin and somatostatin infusions were significantly lower in the diabetic patients than in the nondiabetic subjects (0.2 versus 1.1 ng/ml, $P < 0.05$). During the somatostatin and insulin infusions, C-peptide concentrations were comparable between groups and at each level of glycemia; C-peptide concentrations decreased in the nondiabetic ($P < 0.0005$) but not in the diabetic subjects. Plasma glucagon, growth hormone, cortisol, epinephrine, and norepinephrine concentrations were not significantly different in diabetic and nondiabetic subjects either before or after the insulin and somatostatin infusion. Plasma glucagon and cortisol concentrations decreased significantly from baseline in the nondiabetic and diabetic subjects ($P < 0.05$) after initiation of the somatostatin and insulin infusions. A decrease in norepinephrine concentrations from baseline ($P < 0.02$) was observed in the diabetic patients at plasma glucose concentrations of 95 and 135 mg/dl but no change was observed in nondiabetic subjects. No consistent change in epinephrine or growth hormone concentrations from baseline was observed in either group.

Glucose utilization and production rates (Figure 2). Glucose utilization during the final 30 min of each insulin infusion was significantly ($P < 0.05$) lower in the diabetic patients than in the nondiabetic subjects at both the 0.2 and 1.0 mU · kg^{-1} · min^{-1} insulin infusion during the 95 mg/dl (3.0 ± 0.3 versus 3.9 ± 0.3 and 7.7 ± 0.6 versus 9.5 ± 0.6 mg · kg^{-1} · min^{-1}, respectively) and 135 mg/dl (3.2 ± 0.2 versus 4.8 ± 0.6 and 9.4 ± 0.6 versus 13.2 ± 1.0 mg · kg^{-1} · min^{-1}, respectively) glucose clamps. During the 175 mg/dl glucose clamp, the glucose utilization rates were also lower

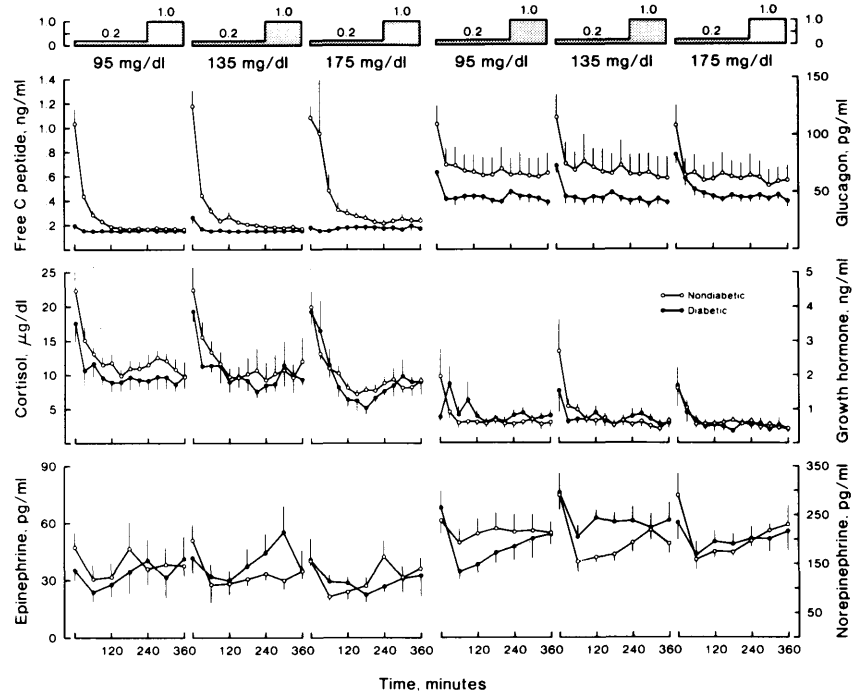

FIGURE 1. Glucose utilization rates and plasma glucose concentrations in diabetic and nondiabetic subjects during infusion of insulin at rates of 0.2 and 1.0 mU · kg^{-1} · min^{-1}.

at both the 0.2 and 1.0 mU · kg^{-1} · min^{-1} insulin infusion (4.3 ± 1 versus 5.1 ± 0.2 and 11.5 ± 0.8 versus 14.6 ± 0.7 mg · kg^{-1} · min^{-1}, respectively) but this difference reached significance only during the 1.0 mU · kg^{-1} · min^{-1} infusion.

Glucose utilization increased significantly ($P < 0.05$) in the nondiabetic subjects when the plasma glucose concentration was increased from 95 to 175 mg/dl during both the 0.2 mU · kg^{-1} · min^{-1} (3.9 ± 0.3 versus 5.1 ± 0.7 mg · kg^{-1} · min^{-1}) and the 1.0 mU · kg^{-1} · min^{-1} (9.4 ± 0.6 versus 14.6 ± 0.7 mg · kg^{-1} · min^{-1}) insulin infusion rates. Glucose utilization also increased in the diabetic patients with increasing glucose concentrations (3.0 ± 0.3 versus 4.3 ± 1.0, 7.7 ± 0.6 versus 11.5 ± 0.8 mg · kg^{-1} · min^{-1}, respectively during 0.2 and 1.0 mU · kg^{-1} · min^{-1} insulin infusions) although the increase was only significant at the higher infusion rate.

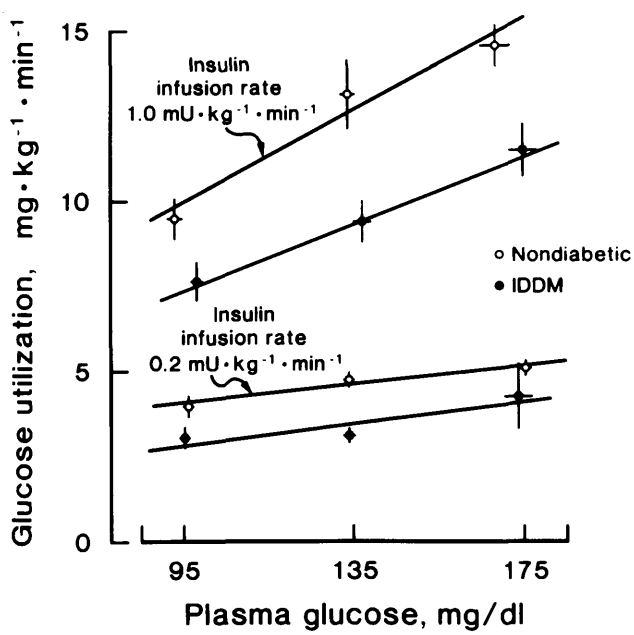

FIGURE 2. C-peptide and counterregulatory hormonal responses in diabetic and nondiabetic subjects during 95, 135, and 175 mg/dl glucose clamps at insulin infusion rates of 0.2 and 1.0 mU/kg/min.

The increase in glucose utilization per increase in plasma glucose (i.e., slope) did not differ significantly between diabetic and nondiabetic subjects during either the 0.2 mU · kg^{-1} · min^{-1} (1.7 ± 1.3 versus 1.4 ± 0.5 × 10^{-2} dl/kg · min) or the 1.0 mU · kg^{-1} · min^{-1} (4.4 ± 1.1 versus 6.2 ± 1.0 × 10^{-2} dl/kg · min) insulin infusions. However, since the prevailing insulin concentration can influence the relationship between change in glucose utilization and change in plasma glucose concentration[3,12] and since the insulin concentrations were slightly higher in the diabetic than nondiabetic subjects, the slopes were reassessed using the glucose utilization rates calculated to be present in the normal subjects at insulin concentrations equivalent to those observed in the diabetic patients (22 and 98 μU/ml). The slopes thus calculated were slightly lower in the diabetic than nondiabetic subjects during both the 0.2 mU/kg · min (1.65 ± 1.29 versus 1.88 ± 0.46 dl/kg · min) and 1.0 mU/kg · min (4.43 ± 1.13 versus 8.99 ± 2.2 dl/kg · min) insulin infusions. Neither of these differences reached statistical significance ($P > 0.98$ and 0.1, respectively).

Rates of glucose production during the 0.2 mU · kg^{-1} · min^{-1} insulin infusion did not differ significantly in the diabetic and nondiabetic subjects during either the 95 (1.2 ± 0.4 versus 0.7 ± 0.4 mg · kg^{-1} · min^{-1}), 135 (0.9 ± 0.2 versus 1.2 ± 0.1 mg · kg^{-1} · min^{-1}), or 175 mg/dl (0.8 ± 0.2 versus 0.7 ± 0.1 mg · kg^{-1} · min^{-1}) glucose clamps, respectively. Glucose production was completely suppressed in both groups during the 1 mU · kg^{-1} · min^{-1} insulin infusion.

DISCUSSION

The current studies indicate that, although at a given glucose concentration stimulation of glucose uptake by insulin is impaired in patients with IDDM, the ability of an increase in glucose concentration to stimulate glucose uptake does not differ significantly in diabetic and nondiabetic subjects.

The present studies confirm recent reports that patients with IDDM are insulin resistant.[4–6] These reports have not met universal acceptance due to uncertainties introduced by differences in insulin and glucose concentrations between diabetic and nondiabetic subjects and the possible effect of insulin antibodies in delaying achievement of "steady-state" insulin concentration. These factors do not appear to account for the decreased response to insulin observed in the current studies. Plasma insulin concentrations reached steady state within 30 min of initiation of the insulin infusion and, if anything, were slightly higher in the diabetic patients than in the nondiabetic subjects. Plasma glucose concentrations did not differ in the diabetic and nondiabetic subjects, thereby obviating the need for calculation of glucose clearance, the use of which has met with considerable controversy.[2,3] The decrease in glucose utilization in the diabetic patients cannot be ascribed to differences in counterregulatory hormone concentrations, since plasma growth hormone, cortisol, epinephrine, norepinephrine, and glucagon concentrations were equivalent in the diabetic and nondiabetic subjects throughout the study. The current studies cannot determine whether the impairment in insulin action was due to the patients' relatively poor glycemic control or resulted from a defect intrinsic to the diabetic state.

The current results also are consistent with reports that insulin-induced suppression of glucose production is normal in patients with IDDM.[4,5] Since the insulin concentrations employed in those studies were above the concentration required to produce maximal suppression of glucose production in nondiabetic subjects, a difference in insulin sensitivity may have been overlooked.[1] Although current studies also failed to demonstrate impaired suppression of glucose production using insulin concentrations (15–25 μU/ml) well within the physiologic range, these results should also be interpreted with caution. If impaired suppression of glucose production by insulin in diabetic patients is due to inappropriate elevation of glucagon concentration,[13] then differences between diabetic and nondiabetic subjects may not have been detected, since glucagon secretion was comparably decreased in both the diabetic and nondiabetic subjects by the somatostatin infusion.

Somewhat surprisingly, a pattern of increased suppression of glucose production with increasing glucose concentrations was not observed in the diabetic or nondiabetic subjects. This observation is similar to that reported by Proietto et al. in diabetic patients[14] but in contrast to the report by Sacca et al.[15] Although a direct inhibitory effect of glucose on glucose production is well-documented in vitro,[16] few in vivo studies have examined this question in nondiabetic subjects independent of changes in circulating insulin concentrations. It is likely, however, that in the current study, since glucose production was already markedly suppressed at a glucose concentration of 95 mg/dl during the combined insulin and somatostatin infusion, further suppression with increasing glucose concentrations may have been difficult to detect. In addition, lack of apparent suppression of glucose production with increasing glucose concentration may have been caused by futile cycling of the isotope.[17]

In contrast to the decreased ability of insulin to stimulate glucose utilization in patients with IDDM, the current studies indicate that the increase in glucose utilization per increase in plasma glucose concentration did not differ significantly in patients with IDDM and nondiabetic subjects. This conclusion, however, has to be tempered by the possible influence of the differences in insulin concentration in the diabetic and nondiabetic subjects. Consistent with previous reports,[3,13] the current experiments demonstrate that the change in glucose utilization per change in plasma glucose concentration increased as plasma insulin concentration increased (i.e., the slope in the nondiabetic subjects increased from 1.4 to 6.2, $P < 0.01$, when the insulin infusion rate was increased from 0.2 to 1.0 mU/kg · min). We, therefore, calculated the slopes in the nondiabetic subjects at insulin concentrations equivalent to those observed in the diabetic subjects (i.e., 22 and 98 μU/ml) assuming that glucose utilization increases as a linear function of plasma insulin concentration. The differences in slope between diabetic and nondiabetic subjects remained minimal at the lower insulin concentrations (1.65 ± 1.29 versus 1.88 ± 0.46), but were more marked at the higher insulin concentrations (4.43 ± 1.1 versus 8.99 ± 2.2 dl/kg · min). Neither difference reached statistical significance. The calculation of the slope during the 1.0 mU/kg · min insulin infusion should be viewed with caution, however, since glucose utilization begins to plateau at this rate. The above calculation, therefore, may have overestimated the actual slope in the nondiabetic subjects.[1]

The lack of difference between diabetic subjects at the highest insulin infusion rate also could be due to saturation of glucose transporter sites in the nondiabetic subjects. We believe that this explanation is unlikely, since the slope of glucose utilization with change in glucose concentration in diabetic and nondiabetic subjects was not significantly different when the data were analyzed either as change in glucose from 95 to 135 mg/dl or when all three glucose levels were included. However, this possibility cannot be excluded, since we did not determine whether glucose utilization would continue to increase linearly in the nondiabetic subjects with increasing glucose concentrations. Thus, the current study strongly suggests that the ability of glucose to enhance glucose utilization is equivalent in diabetic and nondiabetic subjects at insulin concentrations within the lower physiologic range. The possibility still remains that glucose mediation of glucose utilization may be impaired in diabetic patients at insulin concentrations within the high physiologic range.

The effects of glucose on glucose utilization observed in the current study differed somewhat from those recently reported by Proietto et al.[14] Although these authors documented a decrease in insulin action in patients with IDDM, they noted a smaller increment in glucose utilization per increase in plasma glucose concentration in the diabetic patients. The results of this study, however, are difficult to interpret, since the insulin infusion rates utilized differed between the diabetic and nondiabetic subjects as did the increments in glucose and levels at which the glucose concentrations were clamped. Furthermore, the nondiabetic subjects were infused with somatostatin but the diabetic patients were not.

The lack of somatostatin infusion in both groups may result in inhibition of secretion of growth hormone in one group but not in the other group, therefore potentially leading to differences in glucose transport between groups.[18]

The observation that insulin-induced, but not glucose-induced, stimulation of glucose utilization is decreased in patients with IDDM is intriguing in light of the recent reports that insulin stimulates glucose uptake by a rapid, reversible translocation of glucose transport units from a large intracellular pool to the plasma membrane.[19] The presence of a normal increment in glucose uptake per increment in glucose concentration implies normal function of each transport unit, whereas the impaired response to insulin suggests a decrease in number of active transport units. The postulate is consistent with the demonstration by Karnieli et al. that insulin resistance of the rat adipose cell in streptozocin-induced diabetes mellitus is due to depletion of intracellular glucose transport systems.[20]

In conclusion, the current studies suggest that while IDDM patients have an impaired response to insulin, their compensatory increase in glucose utilization in response to hyperglycemia at insulin concentrations generally present during exogenous insulin therapy does not differ significantly from that observed in nondiabetic subjects.

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