Hyperglycemia Decreases Glucose Uptake in Type I Diabetes

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SUMMARY

It has recently been postulated that hyperglycemia per se may contribute to insulin resistance in diabetes. To examine this possibility directly, we measured glucose uptake after 24 h of hyperglycemia (281 ± 16 mg/dl) and normoglycemia (99 ± 6 mg/dl) in 10 type I (insulin-dependent) diabetic patients (age 33 ± 3 yr, relative body wt 102 ± 3%) treated with continuous subcutaneous insulin infusion. Hyperglycemia was induced by an intravenous glucose infusion, whereas saline was administered during the control day. During both studies the patient received a similar diet and insulin dose. After hyper- and normoglycemia, a primed continuous infusion of insulin (40 mU · m^{-2} · min^{-1}) was started, and plasma glucose was adjusted to and maintained at 142 ± 2 and 140 ± 2 mg/dl, respectively, during 60–160 min of insulin infusion. The rate of glucose uptake after hyperglycemia averaged 8.3 ± 1.1 mg · kg^{-1} · min^{-1}, which was lower than the rate after the normoglycemic period (10.1 ± 1.2 mg · kg^{-1} · min^{-1}, $P < .001$). In conclusion, short-term hyperglycemia reduces glucose uptake in type I diabetic patients. Thus, part of the glucose or insulin resistance in these patients may be caused by hyperglycemia per se. *Diabetes* 36:892–96, 1987

Insulin resistance is commonly observed in type I (insulin-dependent) diabetes mellitus (1,2). However, the exact causes of insulin resistance in these patients are still poorly understood, because various metabolic alterations coexist, making it difficult to prove causalities. Perhaps the most commonly encountered abnormalities that have been linked to insulin resistance in type I diabetes include insulin deficiency, hyperinsulinemia, and poor glycemic control. Insulin deficiency is associated with insulin resistance, but a possible causal relationship between insulin deficiency and insulin resistance is obscured by accompanying poor glycemic control (3,4). Correction of insulin deficiency by insulin therapy improves insulin action in type I diabetic patients (4), but again the concomitant improvement in metabolic control also could contribute to the improvement in insulin action. In long-term diabetes, peripheral hyperinsulinemia has been suggested to decrease insulin action (5). However, because hyperinsulinemia is combined with hyperglycemia in diabetic patients, the role of hyperinsulinemia as a cause of insulin resistance is difficult to assess.

In a recent cross-sectional study addressing the relationship between various clinical parameters and insulin action in type I diabetic patients, we found a significant inverse relationship between the degree of glycemic control and insulin action (2,6). This association was independent of body weight, insulin dose, and residual C-peptide secretion, suggesting that hyperglycemia or some associated metabolic alteration might be a cause of insulin resistance in these patients. In this study, we examined directly whether hyperglycemia per se decreases glucose uptake during insulin stimulation. We studied a group of type I diabetic patients treated with continuous subcutaneous insulin infusion (CSII). Glucose uptake was measured twice in each patient: after 24 h of hyperglycemia and after 24 h of normoglycemia. Diet and insulin dose were kept constant on both occasions.

SUBJECTS AND METHODS

SUBJECTS

Ten type I diabetic men [age 33 ± 3 yr, relative body wt (7) 102 ± 3% (mean ± SE)] were studied. The mean duration of diabetes was 13 ± 2 yr. Basal C-peptide levels were undetectable (<0.10 μg/L, $n = 4$) or low (0.17 ± 0.03 μg/L, $n = 6$) (normal range 1.0–2.0 μg/L). All patients had been treated with CSII therapy for at least 1 mo before the study. The patients used a portable, battery-driven infusion pump (model AS6C, Auto-Syringe, Hooksett, NH, or Nordisk

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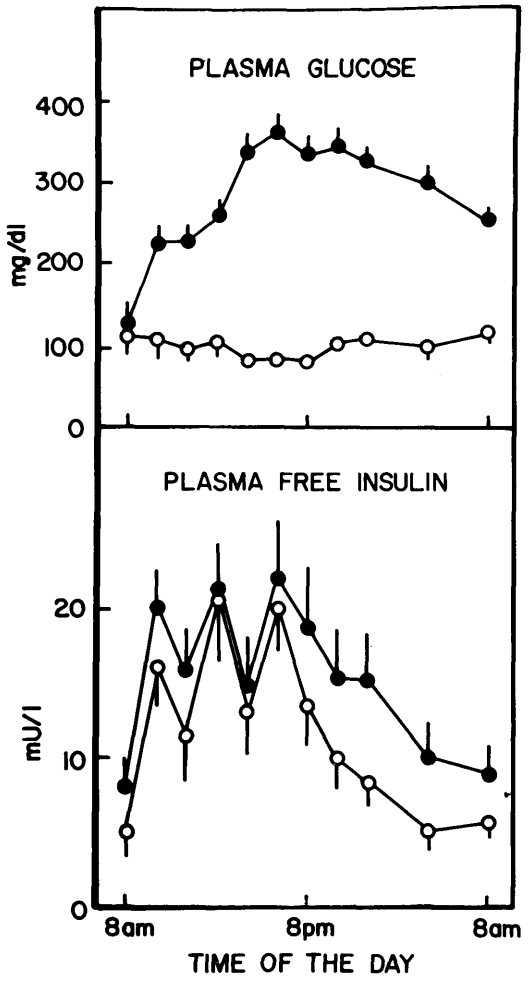

FIG. 1. Plasma glucose and free-insulin levels during hyperglycemic (●) and normoglycemic (○) 24-h periods.

Infuser, Gentofte, Denmark) for insulin (Actrapid, Novo, Copenhagen, Denmark) administration. Six of the 10 patients had insulin antibodies [9–31% (8)], whereas in four patients the insulin-antibody level was within the normal range (<2.5%). Preceding both studies, the patients were equally and well controlled, as reflected by their near-normal fasting plasma glucose (Fig. 1) and glycosylated hemoglobin (HbA_1) (Table 1) levels. Three patients had background retinopathy, but none had signs of neuropathy or nephropathy. The purpose, nature, and potential risks of the study were explained to all subjects before consent to participate was obtained. The experimental protocol was approved by the Ethical Committee of the Helsinki University Hospital.

EXPERIMENTAL DESIGN

Insulin action was measured twice in each patient: after 24 h of hyper- and normoglycemia, respectively. The studies were performed in a random order with a 1-wk interval. During the whole study period, the patients had their usual diets, containing 30 kcal/kg, with 50% carbohydrate, 30–35% fat, and 15–20% protein, and served as breakfast, lunch, supper, and three snacks. No changes were made in insulin administration during the study. The mean daily insulin dose averaged 34.8 ± 4.5 U/day; of this, 55% was given as a constant-rate basal infusion, and 14, 13, 14, and 4% were given before breakfast, lunch, supper, and snacks, respectively.

On the morning of the hyperglycemic study, two catheters were inserted into forearm veins, one for infusion of 10% glucose and another for blood sampling. The sampling catheter was kept patent by infusing 0.9% saline. The rate of the glucose infusion was adjusted to elevate and maintain plasma glucose at ~280 mg/dl. During the normoglycemic 24-h period, the patients received a saline infusion. Blood samples were taken every 2 h during both studies to determine plasma glucose and free-insulin levels.

INSULIN ACTION

After 24 h of either hyper- or normoglycemia, a primed continuous intravenous insulin infusion was started at 0800 h (9). The rate of the constant-rate insulin infusion was 40 mU · m^{-2} · min^{-1}. When the patients were studied after the hyperglycemic period, plasma glucose was first allowed to decline to 140 mg/dl, and thereafter a variable-rate glucose infusion was started to maintain plasma glucose at this level until 160 min had elapsed from the start of the insulin infusion. After the normoglycemic 24-h period, plasma glucose was kept at ~140 mg/dl throughout the 160 min. Adjustments in the glucose infusion rate were made based on plasma glucose values obtained from arterialized venous blood as previously described (2,4,9). Blood was also withdrawn to determine serum free insulin (at 0, 30, 60, 80, 100, 120, 140, and 160 min), C-peptide, glucagon, cortisol, and growth hormone (0 and 60 min), as well as serum triglyceride and HbA_1 (at 0 min) levels.

ANALYTICAL PROCEDURES

Serum free-insulin concentrations were determined by radioimmunoassay with the Phadeseph insulin radioimmunoassay kit (Pharmacia, Uppsala, Sweden) after precipitation with polyethylene glycol (10). The blood samples for free insulin were kept on ice and centrifuged within 1–2 h. The resultant serum was stored at −20°C until assay. After thawing, the serum was immediately extracted with cold 25% polyethylene glycol (1:1, vol:vol) as described by Gennaro and Van Norman (11). Serum C-peptide was determined

TABLE 1
Individual rates of glucose uptake after 24 h of normo- and hyperglycemia

Patient	Rate of glucose uptake (mg · kg^{-1} · min^{-1})	
	After normoglycemia	After hyperglycemia
1	15.04	11.69
2	14.24	12.97
3	14.14	11.51
4	13.04	12.43
5	8.72	6.85
6	8.72	5.96
7	7.77	5.16
8	6.79	5.44
9	6.68	5.36
10	5.50	5.90
Mean ± SE	10.06 ± 0.57	8.32 ± 1.15*

*$P < .001$ vs. normoglycemia.

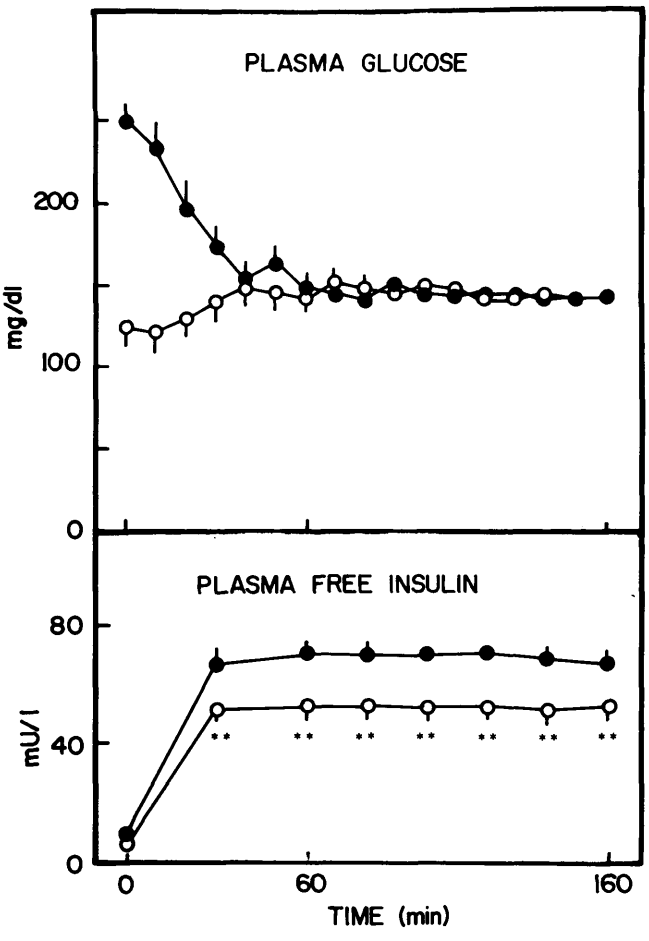

FIG. 2. Plasma glucose and free-insulin levels during measurement of glucose uptake in morning after hyperglycemia (●) and normoglycemia (○). Rate of glucose uptake was determined during 60–160 min. **$P < .01$ vs. hyperglycemia.

according to Kuzuya et al. (12). Serum glucagon (13), growth hormone (14), and cortisol (15) were measured by radioimmunoassay, triglycerides by autoanalyzer (16), and HbA_1 by microcolumn chromatography (17). All data are presented as means ± SE. Statistical comparisons between the hyper- and normoglycemic studies were performed by paired *t* test analysis.

RESULTS

DIURNAL GLUCOSE AND INSULIN LEVELS

Infusion of glucose for 24 h resulted in a mean plasma glucose level of 281 ± 6 mg/dl, which was 2.8-fold higher (Fig. 1) than during the normoglycemic 24-h period (99 ± 6 mg/dl). Plasma free-insulin levels averaged 16 ± 3 and 12 ± 2 μU/ml (NS) during hyper- and normoglycemia, respectively. Plasma insulin profiles were not significantly different during the 2 days (Fig. 1), although a slight tendency toward higher insulin levels was observed during the hyperglycemic night ($P < .1$ for hyper- vs. normoglycemic night at midnight and 0400 h).

INSULIN ACTION

Glucose and insulin levels. Fasting plasma free-insulin levels were 8.9 ± 2.3 and 5.7 ± 1.1 μU/ml (NS) on the morning after hyper- and normoglycemia. During insulin infusion, the plasma free-insulin level rose to significantly higher levels after hyperglycemia (69 ± 3 μU/ml) than after normoglycemia (53 ± 4 μU/ml, $P < .01$; Fig. 2). During measurement of the glucose uptake rate (60–160 min), plasma free-insulin level reached steady state in both studies (Fig. 2). During the last 100 min of insulin infusion, plasma glucose levels averaged 142 ± 2 and 140 ± 2 mg/dl with coefficients of variation of 6 ± 1 and 6 ± 1% in the hyper- and normoglycemic studies, respectively.

Glucose uptake. After 24 h of normoglycemia, the rate of glucose uptake during the 60- to 160-min period averaged 10.1 ± 1.2 mg · kg^{-1} · min^{-1}. After hyperglycemia, the rate of glucose uptake was lower ($P < .001$) than during normoglycemia (Fig. 3; Table 1). To compensate for the difference in plasma steady-state free-insulin levels, we divided the rate of glucose uptake (M) by the ambient plasma free-insulin level (I). The M/I was 37 ± 6% lower ($P < .001$) after hyperglycemia (12.3 ± 1.7 mg · kg^{-1} · min^{-1} per μU/ml × 100) than after normoglycemia (20.6 ± 2.9 mg · kg^{-1} · min^{-1} per μU/ml × 100).

HORMONES AND METABOLITES

Basal levels of serum C-peptide, growth hormone, glucagon, cortisol, and triglyceride were comparable after hyper- and normoglycemia, or when determined at 1 h from the start of insulin infusion (Table 2).

DISCUSSION

In type I diabetic patients, both insulin deficiency and peripheral hyperinsulinemia have been implicated as pathogenetic factors in the development of insulin resistance (2–5). However, an improvement in insulin action has been observed in these patients during CSII therapy in the face of both diminished (18) and unchanged (19,20) insulin requirements, indicating that factors other than insulin deficiency were responsible for enhanced insulin action. Although during CSII therapy a decrease in the level of insulin-antagonistic hormones has been found (21), this was not the case in the study of Beck-Nielsen et al. (20), who measured

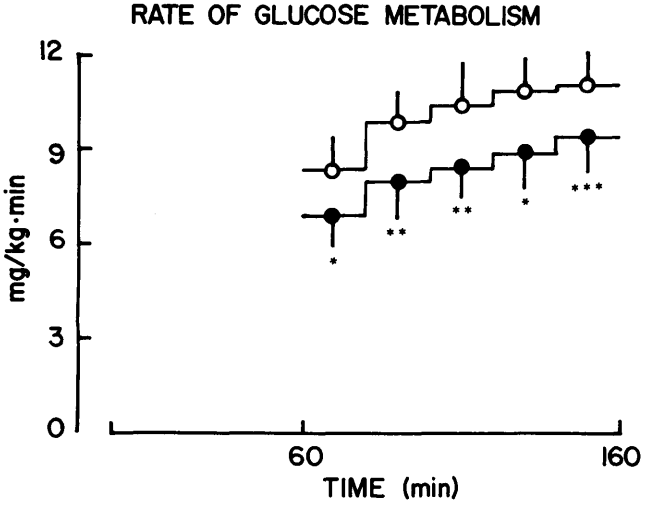

FIG. 3. Rate of glucose metabolism after hyperglycemia (●) and normoglycemia (○). *$P < .05$, **$P < .01$, ***$P < .001$ vs. normoglycemia.

TABLE 2
Effects of 24 h of hyper- and normoglycemia at baseline and 60 min after start of insulin infusion

	Hyperglycemia		Normoglycemia	
	0 min	60 min	0 min	60 min
HbA_1 (%)	9.4 ± 0.3		9.4 ± 0.4	
C-peptide (μg/L)	0.17 ± 0.02	0.14 ± 0.01	0.16 ± 0.02	0.15 ± 0.01
Triglyceride (mM)	0.80 ± 0.09		0.83 ± 0.09	
Growth hormone (μg/L)	0.9 ± 0.2	4.5 ± 2.0	1.0 ± 0.4	2.3 ± 1.2
Cortisol (nM)	452 ± 6	365 ± 40*	452 ± 9	299 ± 16*
Glucagon (ng/L)	198 ± 8	156 ± 19	138 ± 9	128 ± 13

*$P < .05$ vs. 0 min.

both insulin action and insulin antagonists before and 6 mo after CSII therapy. The only consistent change in the studies showing enhanced insulin action during CSII therapy was an improvement of glycemic control (18–20). Revers et al. (22), who found normal insulin action in five well-controlled type I diabetic patients but insulin resistance in five poorly controlled patients, also suggested that some connection might exist between glycemic control and insulin action. In this study we directly measured the influence of preceding hyperglycemia on glucose uptake. A 24-h period of hyperglycemia reduced glucose uptake significantly. This result supports the conclusions drawn from the above studies (18–20,22) and raises the possibility that a causal relationship exists between hyperglycemia and reduced glucose uptake in type I diabetes. However, the etiology of insulin resistance in type I diabetic patients may be multifactorial, and the possible contribution of other factors such as insulin deficiency (3,4), hyperinsulinemia (5,23,24), insulin antibodies (25), or increased secretion of insulin-antagonistic hormones (26) could also be involved. To attribute the reduction in glucose uptake after hyperglycemia to differences in insulin action, the data critically depend on the condition that the mass-action effect of glucose at 140 mg/dl is the same whether glucose is increased or decreased to this level.

In this study, glucose uptake was measured during hyperglycemia and hyperinsulinemia. Under these conditions, total glucose uptake represents the sum of glucose uptake stimulated by insulin and the mass-action effect of glucose (27). In type I diabetic patients, both insulin-mediated and insulin-independent (28) glucose uptake are diminished. Therefore, the observed reduction in glucose uptake after the hyperglycemic day could reflect either glucose or insulin resistance.

The mechanism by which hyperglycemia decreased glucose uptake in this study is intriguing. A fall in plasma glucose even within the hyperglycemic range provokes hypoglycemic symptoms and release of insulin antagonists in some patients (29). In this study, plasma glucose was allowed to fall to 140 mg/dl after the hyperglycemic period to measure glucose uptake under identical conditions as after the normoglycemic period. None of the patients had hypoglycemic symptoms during the studies, and the changes in growth hormone, cortisol, and glucagon levels after hyper- and normoglycemia were similar. We did not follow catecholamine levels during the studies. However, in the study of DeFronzo et al. (29), who lowered plasma glucose by an insulin infusion similar to that in this study, growth hormone release occurred more often than epinephrine or norepinephrine release, and the counterregulatory response did not consist solely of an increase in catecholamines in any of the subjects. Also, our patients were well controlled and treated with CSII, which would be expected to reset the glucostat to a lower rather than higher level (30). Thus, it is unlikely that the decrease in glucose uptake after hyperglycemia was due to insulin-antagonistic hormones.

In normal subjects under conditions similar to these in this study, the splanchnic tissues take up ~10–20% of the infused glucose (31), and thus, extrahepatic tissues are quantitatively dominating for glucose uptake. During hyperglycemia and hyperinsulinemia, most of the glucose is stored, presumably as muscle glycogen (32,33). Studies addressing in vivo glucose uptake and muscle glycogen content suggest that these parameters may be inversely related. After glycogen-depleting exercise, Bogardus et al. (34) found an increase in whole-body glucose uptake and muscle glycogen synthase activity, whereas Mott et al. (33) found reduced insulin action for glucose storage and a reduced glycogen synthase activity after overnutrition. In this study, one possible explanation for the decrease in glucose uptake after hyperglycemia could be a decrease in glycogen synthase activity due to an increase in muscle glycogen during the 24-h glucose infusion. However, this possibility remains speculative, because we did not measure glycogen synthase activity. A second factor contributing to the decrease in glucose uptake could be a glucose-induced decrease in glucose transporters (35).

Steady-state plasma free-insulin levels were significantly higher after the hyperglycemic than the normoglycemic period. Because the insulin infusion rates were identical, elevated insulin levels indicate decreased insulin clearance after hyperglycemia. In this study the plasma glucose levels were comparable when plasma insulin levels were measured. Therefore, unless the preceding hyperglycemia had some persisting effect on insulin clearance, hyperglycemia per se (36,37) cannot satisfactorily explain the difference in plasma free-insulin levels. A more likely explanation is that the abilities of tissues to take up glucose and insulin are linked to each other. Cross-sectional data from Pima Indians indicate that the steady-state plasma free-insulin level that is achieved during a 40-mU · m^{-2} · min^{-1} insulin infusion is inversely related to the rate of glucose uptake and that this relationship is independent of body fat content (C. Bogardus, unpublished data). Also, defects in insulin internalization were recently found in insulin-resistant type II diabetic patients (38), suggesting that reduced insulin action and the ability of tissues to take up insulin may be related.

In conclusion, short-term hyperglycemia decreases glucose uptake in type I diabetic patients. The clinical implications of this observation are obvious. First, the deleterious effect of hyperglycemia per se on glucose uptake may contribute to the development of insulin (or glucose) resistance in various hyperglycemic states and/or aggravate insulin resistance due to other causes. Second, an improvement in glycemic control should be considered a contributing factor to the enhanced glucose uptake observed during therapeutic interventions, e.g., diet (39), oral antidiabetic drugs (40–42), and CSII (18–20).

REFERENCES

1. DeFronzo RA, Hendler R, Simonson D: Insulin resistance is a prominent feature of insulin-dependent diabetes. *Diabetes* 31:795–801, 1982
2. Yki-Jarvinen H, Koivisto VA: Natural course of insulin resistance in type 1 diabetes. *N Engl J Med* 315:224–30, 1986
3. Barrett EJ, DeFronzo RA, Bevilacqua S, Ferrannini E: Insulin resistance in diabetic ketoacidosis. *Diabetes* 31:923–28, 1982
4. Yki-Jarvinen H, Koivisto VA: Insulin sensitivity in newly-diagnosed type 1 diabetics following ketoacidosis and after a 3 month insulin therapy. *J Clin Endocrinol Metab* 59:371–78, 1984
5. Pedersen O, Hjøllund E: Insulin receptor binding to fat and blood cells and insulin action in fat cells from insulin-dependent diabetics. *Diabetes* 31:706–15, 1982
6. Yki-Jarvinen H, Helve E, Koivisto V: Poor glycemic control: a cause of insulin resistance in long-term type I diabetes (Abstract)? *Diabetes* 34:46A, 1985
7. Metropolitan Life Insurance Company: Desirable weights for adults. *Metropolitan Life Insurance Co Stat Bull* 40:624, 1959
8. Gerbitz KD, Kemmler W: Method for rapid quantitation and characterization of insulin antibodies. *Clin Chem* 24:890–94, 1978
9. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method of quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–24, 1979
10. Desbuquois B, Aurbach GD: Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. *J Clin Endocrinol* 33:732–38, 1971
11. Gennaro WD, Van Norman JD: Quantitation of free, total and antibody-bound insulin in insulin-treated diabetics. *Clin Chem* 21:873–79, 1975
12. Kuzuya H, Blix PM, Horwitz DL, Steiner DF, Rubenstein AH: Determination of free and total insulin and C-peptide in insulin-treated diabetics. *Diabetes* 26:22–29, 1977
13. Heding LG: Radioimmunological determination of pancreatic and gut glucagon in plasma. *Diabetologia* 7:10–18, 1975
14. Kirkham KE, Hunter WM: *Radioimmunoassay Methods*. Edinburgh, Livingstone, 1971
15. Rolleri E, Zannino M, Orlandini S, Malvano R: Direct radioimmunoassay of plasma cortisol. *Clin Chim Acta* 66:319–25, 1976
16. Mosinger F: Photometric adaptation of Dole's microdetermination of free fatty acids. *J Lipid Res* 6:157–59, 1965
17. Welch SG, Boucher BJ: A rapid micro-scale method for the measurement of haemoglobin $A_{1(a+b+c)}$. *Diabetologia* 14:209–11, 1978
18. Yki-Jarvinen H, Koivisto VA: Continuous subcutaneous insulin infusion therapy decreases insulin resistance in type I diabetes. *J Clin Endocrinol Metab* 58:659–66, 1984
19. Lager I, Lonnroth P, von Schenk H, Smith U: Reversal of insulin resistance in type I diabetes with continuous subcutaneous insulin infusion. *Br Med J* 287:1661–64, 1983
20. Beck-Nielsen H, Richelsen B, Hasling C, Nielsen OH, Heding L, Sørensen NS: Improved in vivo insulin effect during continuous subcutaneous insulin infusion in patients with IDDM. *Diabetes* 33:832–38, 1984
21. Tamborlane WV, Sherwin RS, Koivisto V, Hendler R, Genel M, Felig P: Normalization of the growth hormone and catecholamine response to exercise in juvenile-onset diabetic subjects treated with a portable insulin infusion pump. *Diabetes* 28:785–88, 1979
22. Revers RR, Kolterman OG, Scarlett JA, Gray RS, Olefsky JM: Lack of in vivo insulin resistance in controlled insulin-dependent, type I, diabetic patients. *J Clin Endocrinol Metab* 58:353–58, 1984
23. Rizza RA, Gerich JE, Haymond MW, Westland RE, Hall LD, Clemens AH, Service FJ: Control of blood sugar in insulin-dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion, and intensified conventional insulin therapy. *N Engl J Med* 303:1313–18, 1980
24. Rizza RA, Mandarino LJ, Genest J, Baker BA, Gerich JE: Production of insulin resistance by hyperinsulinemia in man. *Diabetologia* 28:70–75, 1985
25. Van Haeften T, Heiling V, Gerich J: Moderate titer insulin antibodies impair postprandial glucose tolerance (Abstract). *Diabetes* 35:3A, 1986
26. Campbell PJ, Bolli GB, Cryer PE, Gerich JE: Pathogenesis of dawn-phenomenon in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 312:1473–79, 1985
27. Verdonk CA, Rizza RA, Gerich JE: Effects of plasma glucose concentration on glucose utilization and glucose clearance in normal man. *Diabetes* 30:535–37, 1981
28. DeFronzo RA, Simonson DC, DelPrato S: Glucose resistance in diabetes: evidence for impaired insulin-independent glucose uptake. *Diabetes Res Clin Pract* 1 (Suppl. 1):S128, 1985
29. DeFronzo RA, Hendler R, Christensen N: Stimulation of counterregulatory hormonal response in diabetic man by a fall in glucose concentration. *Diabetes* 29:125–31, 1980
30. Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS: Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with type 1 diabetes. *Ann Intern Med* 103:184–90, 1985
31. DeFronzo RA, Ferrannini E, Hendler R, Felig P, Wahren J: Regulation of splanchnic and peripheral glucose uptake by insulin and hyperglycemia in man. *Diabetes* 32:35–45, 1983
32. Bogardus C, Lillioja S, Stone K, Mott D: Correlation between muscle glycogen synthase activity and in vivo insulin action in man. *J Clin Invest* 73:1185–90, 1984
33. Mott DM, Lillioja S, Bogardus C: Overnutrition induced decrease in insulin action for glucose storage: in vivo and in vitro in man. *Metabolism* 35:160–65, 1986
34. Bogardus C, Thuillez P, Ravussin E, Narigma M, Azhar S: Effect of muscle glycogen depletion on in vivo insulin action in man. *J Clin Invest* 72:1605–10, 1983
35. Van Putten JP, Krans HMJ: Glucose as a regulator of insulin-sensitive hexose uptake in 3T3 adipocytes. *J Biol Chem* 260:7996–8001, 1985
36. Kaplan N, Madison LL: Effects of endogenous insulin secretion on the magnitude of hepatic binding of labeled insulin during a single transhepatic circulation in human subjects (Abstract). *Clin Res* 7:248, 1959
37. Tranberg K-G, Thorell J: Variation in the disappearance of unlabeled insulin from plasma: studies with portal and peripheral infusions. *Diabetes* 28:846–51, 1979
38. Trischitta V, Gullo D, Squatrito S, Pezzino V, Goldfine ID, Vigneri R: Insulin internalization into monocytes is decreased in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 62:522–28, 1986
39. Kolterman OG, Greenfield M, Reaven GM, Saekow M, Olefsky JM: Effect of a high carbohydrate diet on insulin binding to adipocytes and on insulin action in vivo in man. *Diabetes* 28:731–36, 1979
40. Mandarino LJ, Gerich JE: Prolonged sulfonylurea administration decreases insulin resistance and increases insulin secretion in non-insulin-dependent diabetes mellitus: evidence for improved insulin action at a postreceptor site in hepatic as well as extrahepatic tissues. *Diabetes Care* 7 (Suppl. 1):89–99, 1984
41. Simonson DC, Ferrannini E, Bevilacqua S, Smith D, Barrett E, Carlson R, DeFronzo RA: Mechanism of improvement in glucose metabolism after chronic glyburide therapy. *Diabetes* 33:838–45, 1984
42. Kolterman OG, Gray RS, Shapiro G, Scarlett JA, Griffin J, Olefsky JM: The acute and chronic effects of sulfonylurea therapy in type II diabetic subjects. *Diabetes* 33:346–54, 1984