Adipocyte Insulin Binding and Action in Moderately Obese NIDDM Patients After Dietary Control of Plasma Glucose: Reversal of Postbinding Abnormalities

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Studies of fat cells from patients with newly diagnosed, untreated non-insulin-dependent diabetes mellitus (NIDDM) have revealed severe abnormalities in insulin action on glucose transport and metabolism. To determine whether these defects can be reversed if good glycemic control is reached by dietary treatment, eight moderately obese NIDDM subjects were studied at diagnosis and again when the patients had been in good glycemic control induced by low-energy dieting for at least 2 mo (absence of glycosuria and fasting plasma glucose <7 mM). Average body weight decreased by 8 kg ($P < .05$). Fasting plasma glucose decreased from 11.5 ± 1.2 to 6.9 ± 0.9 mM, whereas fasting serum insulin concentrations were unchanged. Adipocyte insulin binding at tracer concentration (15 pM, 37°C) was not changed significantly (1.94 ± 0.52 to 2.05 ± 0.62% per 30 cm^2 surface area/ml). The basal (non-insulin-stimulated) glucose transport (tracer glucose concentration 5 μM) increased from 25 ± 12 to 44 ± 14 pmol · 90 min^{-1} · 10 cm^{-2} surface area ($P < .02$). The maximally insulin-stimulated glucose transport rate increased from 35 ± 20 to 78 ± 26 pmol/90 min ($P < .01$). The percentage insulin response above basal levels increased from 31 ± 40 to 89 ± 58% ($P < .01$). The insulin sensitivity (half-maximally stimulating insulin concentrations) was also improved ($P < .05$). Glucose conversion rates to total lipids increased 34 ± 62 and 65 ± 80% in basal cells and maximally insulin-stimulated cells, respectively ($.2 > P > .1$, $.1 > P > .05$). The percentage insulin response above basal level increased from 30 ± 24 to 67 ± 52% ($P < .05$). The percentage insulin response above basal level of glucose conversion to CO_2 also increased ($P < .05$). The results after diet treatment were not different from those of normal controls. We conclude that dietary treatment of moderately obese NIDDM patients that leads to good glycemic control results in reversal of the abnormalities observed in adipocytes of untreated NIDDM subjects. *Diabetes Care* 10:306–12, 1987

Non-insulin-dependent diabetes (NIDDM) is characterized by impairments in both insulin secretion and insulin action (1,2). In vivo studies of insulin action have displayed impaired insulin effect on hepatic glucose output as well as on peripheral glucose utilization (3,4). Studies of the only accessible target cell for insulin, the adipocyte, have shown multiple abnormalities in in vitro insulin binding and action in NIDDM subjects (5–8). In a recent study of newly diagnosed and untreated NIDDM patients, we found severe abnormalities in insulin action on adipocyte glucose transport and metabolism (9). Insulin treatment of NIDDM can diminish or normalize more of the in vivo and in vitro dysfunctions (10,11). From these studies, however, it is impossible to conclude whether the improved insulin action is caused by insulin treatment per se or by the amelioration of hyperglycemia.

We therefore examined whether hypoenergetic dieting of newly diagnosed NIDDM patients that leads to amelioration of hyperglycemia would lead to improved cellular insulin effects on glucose transport and metabolism.

MATERIALS AND METHODS

Patients. Eight obese NIDDM patients were studied at diagnosis; all met the National Diabetes Data Group criteria for diabetes mellitus (12). A glucagon test revealed the non-insulin-dependent nature of their disease (13). Pertinent clinical data are given in Tables 1 and 2. Informed consent

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was obtained in accordance with the Helsinki Declaration II. The patients were examined within the first 3 days of admission before any antidiabetic therapy was initiated. During the admission period, they ate the normal hospital diet for nondiabetic subjects (8000 ± 1200 kJ with 40% carbohydrate, 41% fat, and 19% protein). Eight normal subjects matched for age, sex, and body mass index (BMI) were also studied. Three days before the study they ate a diet similar to that of the diabetic subjects before the study.

Protocol. After a 10-h fast, a fat biopsy was taken at 0800 h with local anesthesia from the lateral gluteal region as previously described (14). On the same occasion a blood sample was obtained for estimation of chemical quantities in serum and for measurement of insulin binding to blood cells. Thirty minutes later, an oral glucose tolerance test was performed (ingestion of 75 g glucose during the initial 5 min).

During admission the patients were instructed by a trained dietitian in individual hypoenergetic diets with low content of fat and high content of carbohydrate, especially starch and fiber (5500 ± 900 kJ, 35% fat, 50% carbohydrate, and 15% protein). After discharge, the patients were followed regularly in the outpatient department. The therapeutic goals were fasting plasma glucose concentrations <7 mM and absence of glucosuria for at least 2 mo before reexamination. After a mean duration of 8 mo (range 5–10 mo) the patients were admitted into the hospital, and the study protocol was repeated.

Chemicals. Human albumin (Behringswerke, Marburg/Lahn, FRG), collagenase (213 U/mg *Clostridium histolyticum*, Worthington, Freehold, NJ), and D-U-[^{14}C]glucose (sp act 300 mCi/mmol, Radiochemical Centre, Amersham, UK) were purchased. A_{14}-[^{125}I]monoiodoinsulin (sp act 250 μCi/μg) was generously donated by the Novo Research Institute (Copenhagen) (15). Tissue and cells were suspended in HEPES buffer [100 mM in studies of monocyte (16) and erythrocyte (17) binding and 10 mM in studies of adipocytes (18)]. The pH was adjusted to 7.4 at 37°C in studies of fat cells and monocytes and adjusted to 7.8 at 37°C in erythrocyte studies.

Insulin-receptor binding studies. Adipose tissue (~10 g) was obtained by open biopsy from the upper quarter of the gluteal region after a square field had been anesthetized with an epidermal injection of 1% lidocaine without epinephrine. Details of fat cell isolation and determination of fat cell size and number were as previously described (14,18). Insulin binding to fat cells (~10^5 cells/ml of cell suspension) was measured in HEPES buffer at 37°C after incubation for 60 min with A_{14}-[^{125}I]monoiodoinsulin with or without increasing concentrations of unlabeled insulin. To compare insulin binding to fat cells and blood cells at the same temperature (insulin binding to blood cells must be measured at subphysiologic temperature to ensure steady-state specific binding), we also measured insulin binding at tracer insulin concentrations to fat cells at 15°C with a 120-min incubation period. Cell-associated radioactivity in the presence of 10 μM unlabeled insulin (nonspecific binding) averaged 4% of total binding at both 37 and 15°C. Specific insulin binding to adipocytes was expressed per 30 cm^2 surface area/ml.

Insulin-receptor binding to erythrocytes was determined as previously described (17) with the following modifications. After fractionation of the blood once on a Ficoll-Isopaque gradient, the erythrocytes were collected from the bottom of the tubes. The cells were resuspended 1:1 in 0.9% NaCl containing 50 mg/ml dextran 500. The tubes were inclined at 45° for 15 min at 37°C. The supernatant was then removed, thus reducing granulocyte contamination of the settled erythrocytes to <0.03/1000. After washing, the erythrocytes (at a vol fraction of 0.45) were incubated for 210 min at 15°C in 100 mM HEPES buffer with A_{14}-[^{125}I]monoiodoinsulin with or without native insulin (10 μM) (17). Nonspecific binding averaged 10% of total binding. Specific insulin binding was expressed per 5 × 10^9 cells/ml.

After blood fractionation, pure monocytes were separated from lymphocytes by exploiting their property of adhering to

TABLE 1
Clinical data of 8 patients with non-insulin-dependent diabetes mellitus (NIDDM) before and after dietary treatment and of 8 matched normal subjects

	NIDDM patients				Normal subjects		
No.	Sex	Age (yr)	BMI (kg/m²)*	Weight loss (kg)	Sex	Age (yr)	BMI (kg/m²)
1	F	28	43/37	20	F	32	38
2	F	64	32/30	5	F	63	30
3	F	65	29/29	0	F	61	30
4	M	62	27/26	3	M	58	26
5	M	43	27/26	4	M	44	26
6	M	50	27/24	9	F	45	25
7	M	49	36/34	5	M	46	35
8	M	67	28/23	15	M	63	26
Mean		53	31/29	8		51	29
SD		13	6/5	6		11	5

BMI, body mass index.
*Before/after dietary treatment.

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plastic surfaces at 37°C and detaching again at cold temperatures (19). In this way, homogeneous suspensions of monocytes were obtained. Monocytes were identified by morphological and cytochemical criteria, and insulin binding was performed as previously described (16). Monocytes (3 to 8 × 10^6 cells/ml) were incubated for 120 min in 100 mM HEPES buffer at 15°C with A_{14}-[^{125}I]monoiodoinsulin with or without native insulin (10 μM). Nonspecific binding was 21% of total binding. Specific binding was expressed per 5 × 10^6 pure monocytes/ml.

In vitro studies of insulin action. Glucose metabolism was measured by studies of the conversion of D-U-[^{14}C]glucose to ^{14}C-labeled total lipids and $^{14}CO_2$ as described previously (14). Isolated adipocytes were prepared in a 10-mM HEPES buffer containing 0.5 mM glucose (vol fraction 0.05). The cells were preincubated for 45 min at 37°C with or without insulin in increasing concentrations. Then, 0.4 μCi D-U-[^{14}C]glucose was added to each tube to a final concentration of 0.5 mM, and the incubation continued for 90 min. Sulfuric acid was added, and $^{14}CO_2$ was collected during the subsequent 60 min with phenethylamine as trapping agent. Then, a Dole extraction was performed (20), and a sample for liquid-scintillation counting was taken from the upper phase for estimation of lipid production (14).

Glucose transport was measured as the rate of lipogenesis after preincubation without glucose. D-U-[^{14}C]glucose was then added to a final concentration of 0.005 mM. As previously described (5,14), glucose transport is the rate-limiting step for glucose incorporation into total lipids at very low glucose concentrations.

TABLE 2
Biochemical data in 8 non-insulin-dependent diabetes mellitus (NIDDM) patients before and after dietary treatment and in 8 normal subjects

	NIDDM patients		
	Before treatment	After treatment	Normal subjects
Fasting plasma glucose (mM)	11.5 ± 1.2	6.9 ± 0.9*	5.4 ± 0.5
Fasting serum insulin (μU/ml)	19 ± 8	20 ± 10	14 ± 5
C-peptide (nM)			
Basal	0.88 ± 0.30		
Stimulated†	1.81 ± 0.60		
Fasting plasma ketone bodies (mM)	0.64 ± 0.38	0.15 ± 0.07*	0.19 ± 0.18
Fasting plasma FFA (mM)	0.49 ± 0.12	0.31 ± 0.10*	0.31 ± 0.09
Fat cell diameter (μm)	101 ± 8	96 ± 11*	102 ± 9

Values given as means ± SD. FFA, free fatty acids.
*$P < .01$ vs. NIDDM patients before treatment.
†Value 6 min after intravenous injection of 1 mg glucagon.

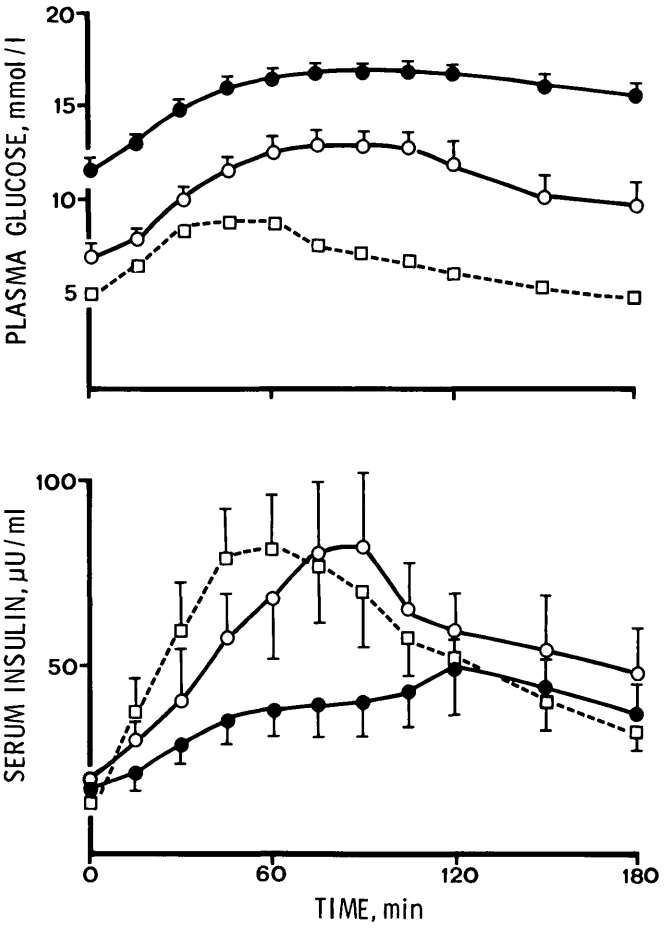

FIG. 1. Plasma glucose and serum insulin response (mean ± SE) to oral glucose (75 g) in 8 non-insulin-dependent diabetic patients before (●) and after (○) dietary treatment and in 8 normal controls (□).

Chemical quantities in serum and plasma. Plasma glucose was analyzed with a glucose dehydrogenase method (enzymatic kit, Merck, Darmstadt, FRG). Insulin in serum was measured by radioimmunoassay (21). Plasma acetoacetate and plasma 3-hydroxybutyrate were measured separately with the enzymatic micromethod (22). Plasma ketone bodies refer to the sum of the concentrations of these two metabolites. Plasma free fatty acids (FFAs; aliphatic carboxylate C_8 to C_{18}, nonesterified) were assayed according to the method of Itaya and Ui (23). Serum C-peptide was measured according to the method of Heding (24).

Statistical methods. Data in the text and tables are given as means ± SD; data in figures represent means ± SE. Significant differences between the intraindividual data pairs were assessed by Student's paired *t* test, whereas an unpaired Student's *t* test was used for comparisons between groups. Linear regression analysis was used in correlation studies with the least-squares method. Ketone bodies were log distributed and hence were log transformed before statistical analysis.

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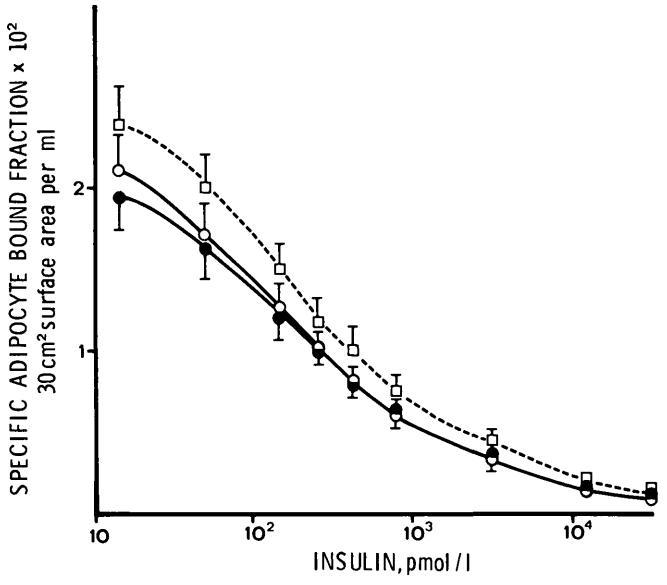

FIG. 2. Insulin binding to adipocytes from 8 newly diagnosed non-insulin-dependent diabetic patients before (●) and after (○) dietary treatment and from 8 normal controls (□). Adipocytes incubated with 15 pM ^{125}I-labeled insulin at 37°C for 1 h in absence or presence of unlabeled insulin in increasing concentrations (mean ± SE).

TABLE 3
Insulin binding to adipocytes, monocytes, and erythrocytes at 15°C in 8 patients with non-insulin-dependent diabetes (NIDDM) before and after dietary treatment and in 8 normal subjects

	NIDDM patients		
	Before treatment	After treatment	Normal controls
Adipocytes (30 cm²/ml)	3.10 ± 0.63	4.07 ± 1.28*	4.46 ± 1.47
Monocytes (5 × 10⁶/ml)	2.94 ± 1.02	2.78 ± 0.98	3.19 ± 0.78
Erythrocytes (5 × 10⁹/ml)	5.20 ± 1.13	4.50 ± 1.30	5.59 ± 1.64

Tracer insulin concentration 15 pM. Specific binding fractions × 10^2 (mean ± SD).
*$P < .05$ vs. NIDDM patients before treatment.

RESULTS

Clinical data of individual NIDDM patients and matched normal controls are given in Table 1. At the first presentation, the patients had significantly elevated fasting plasma glucose levels but were only slightly ketotic (Table 2). The non-insulin-dependent nature of their disease was obvious from the results of the glucagon test (Table 2). At the second examination, all the patients were well regulated, as judged by near-normalized fasting plasma glucose levels (Table 2). Fasting serum insulin levels were unchanged (Table 2). However, the insulin response to an oral glucose load was increased in all patients (Fig. 1). The area under the insulin response curve increased from 3585 ± 2400 to 6850 ± 5350 μU · min · ml^{-1} ($P < .01$). Plasma ketone bodies and plasma FFAs were normalized (Table 2). Mean adipocyte diameter was slightly decreased at the second examination ($.1 > P > .05$). Average weight loss was 8 ± 6 kg (Table 1).

Adipocyte insulin binding measured at 37°C was unchanged after treatment (Fig. 2). This was the case both when binding was expressed per surface area or per cell number. However, at 15°C, insulin binding to fat cell at tracer concentrations increased slightly but significantly when expressed per surface area (7 of 8 patients; Table 3; $P < .05$). When expressed per cell number, a modest and insignificant increase was observed. Monocyte and erythrocyte insulin binding was unchanged (Table 3). No correlations between individual binding values to different cell types were found.

Figure 3 depicts the insulin dose-response curves for glucose transport in adipocytes from the NIDDM patients before and after treatment and from the normal controls. Basal (non-insulin-stimulated) and maximally insulin-stimulated glucose transport rates increased in all NIDDM patients ($P < .01$). The percentage insulin responsiveness (percentage increase above basal levels) also increased significantly, from 42 ± 42 to 87 ± 58% ($P < .05$). Also, insulin sensitivity increased significantly, as shown by a leftward shift of the dose-response curve. [Half-maximally stimulating insulin concentration (ED_{50}) decreased in 6 subjects and was unchanged in 2 sub-

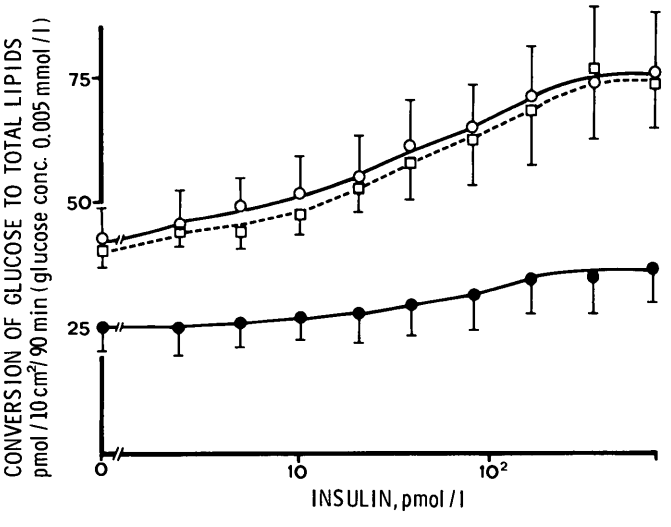

FIG. 3. Glucose transport rates in adipocytes from 8 non-insulin-dependent diabetic patients before (●) and after (○) dietary treatment and from 8 normal controls (□). Transport was measured as lipogenesis at tracer glucose concentrations (5 μM). Adipocytes preincubated in glucose-free HEPES buffer at 37°C with or without insulin in indicated concentrations for 45 min. Then, labeled glucose was added, and incubation was continued for 90 min (mean ± SE).

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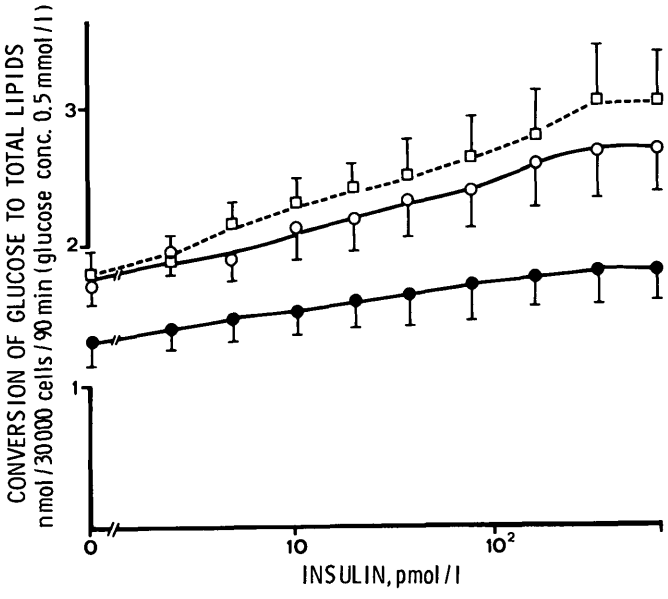

FIG. 4. Lipogenesis in adipocytes from 8 non-insulin-dependent diabetic patients before (●) and after (○) dietary treatment and from 8 normal controls (□). Lipogenesis was measured as described in Fig. 3 legend in HEPES buffer containing 0.5 mM glucose (mean ± SE).

jects, $P < .05$.] No correlation between changes in fasting plasma glucose levels and changes in basal or insulin-stimulated glucose transport rates or percentage insulin responsiveness was found. After treatment, glucose transport was similar to that of normal subjects (Fig. 3).

The insulin dose-response curves for adipocyte lipogenesis are shown in Fig. 4. Both basal and maximally insulin-stimulated lipogenesis rates increased moderately but insignificantly ($.2 > P > .1$ and $.1 > P > .05$, respectively) after dietary treatment of NIDDM patients. The percentage insulin responsiveness increased significantly from 30 ± 24 to 67 ± 58% ($P < .05$) after dietary treatment. Due to a very low percentage insulin response on adipoctye lipogenesis in three NIDDM patients before treatment, changes in insulin sensitivity could not be estimated in these subjects. The insulin sensitivity was increased in four and decreased in one NIDDM patient after diet treatment. Changes in lipogenesis rates were not correlated to changes in fasting plasma glucose. After treatment, adipocyte lipogenesis in NIDDM subjects was similar to that of normal controls (Fig. 4).

Similar results were obtained in the studies of glucose conversion to CO_2 (Fig. 5). The percentage response above basal levels increased from 7 ± 10 to 56 ± 48% ($P < .05$). After treatment, glucose conversion to lipids and CO_2 was similar to that of normal controls (Figs. 4 and 5).

DISCUSSION

Insulin-receptor binding. Insulin binding to adipocytes was not changed after diet treatment when measured at 37°C but was slightly yet significantly increased when measured at 15°C. These results correspond well to our previous findings in untreated NIDDM patients in which insulin binding to adipocytes was significantly decreased at 15°C but not at 37°C (9). Thus, the small decrease in insulin binding at low temperatures in untreated NIDDM patients seems to be easily reversible. The reason for the discrepancy between results of insulin binding at different temperatures may be differences in insulin and receptor processing. At 15°C, insulin is bound but not, or only to a very small extent, internalized, whereas at 37°C, insulin and receptors are internalized and recycled or degraded (25). Thus, at 37°C, differences in internalization, degradation, and/or recycling rates may be more important than changes in binding of insulin to surface receptors. Experiments at 15°C might therefore be more accurate assays of the receptor status itself, whereas studies at 37°C reflect the integrated binding, uptake, and handling of insulin in the cells and may thereby be a more physiologic parameter. Foley et al. (10) found a slight but significant increase in insulin binding to adipocytes at 37°C after 1 mo of insulin treatment, whereas Scarlett et al. (11) found a slight but insignificant increase at 24°C after 2 wk of insulin treatment. Published results regarding insulin binding to adipocytes from NIDDM patients are thus contradictory, which may partly be due to differences in treatment regimens. In our study, the increased binding at 15°C, although reaching significance, was small and probably not clinically relevant. Hence, it may be claimed that insulin binding to adipocytes is not essentially changed after amelioration of hyperglycemia, regardless of the treatment regimen.

Erythrocyte- and monocyte-receptor binding measured at 15°C did not change significantly after diet therapy, and no

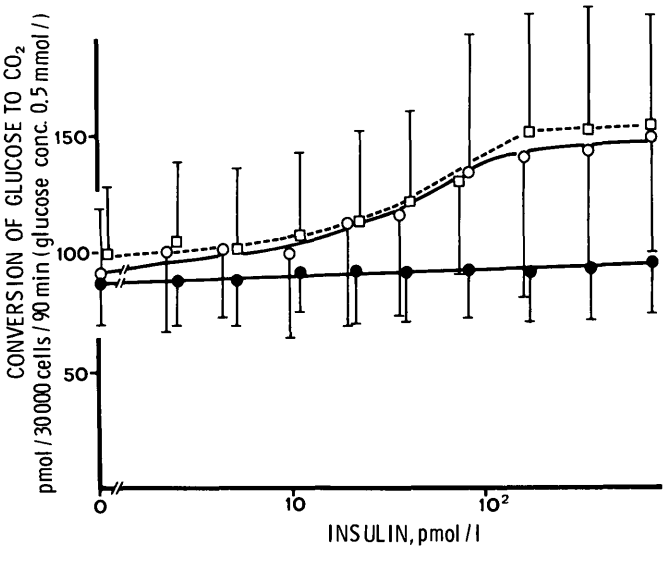

FIG. 5. CO_2 production in adipocytes from 8 non-insulin-dependent diabetic patients before (●) and after (○) dietary treatment and from 8 normal controls (□). CO_2 production was measured as described in Fig. 4 legend. CO_2 was collected with phenethylamine as trapping agent.

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correlations between individual binding values at tracer insulin concentration to different cell types were apparent. Thus, the change in adipocyte insulin binding at 15°C was not recognized by blood cell insulin binding. These findings add to those of other studies emphasizing that extrapolation of insulin-receptor status from one type of cell to another should be avoided (9,14,26,27).

Glucose transport. Our findings of increased basal and maximally insulin-stimulated glucose transport rates after control of hyperglycemia by diet treatment agree with the findings of Scarlett et al. (11) and Foley et al. (10) after control of hyperglycemia by insulin treatment. In addition, we found that both percentage insulin responsiveness and insulin sensitivity of adipocyte glucose transport increased when hyperglycemia was controlled by diet treatment for several months. These changes were not observed in the insulin-therapy studies. Note that, whereas percentage increases of the same magnitude of basal and insulin-stimulated transport rates reflect increased capacity of the transport system and not increased insulin action, the findings of increased maximal insulin responsiveness and insulin sensitivity demonstrate increased insulin action on adipocyte glucose transport.

The increase in basal and maximal glucose transport and in insulin action after diet therapy to levels similar to those of normal controls agrees with our previous findings in untreated NIDDM patients in which these variables were depressed compared with findings in normal controls (9). Thus, all dysfunctions of the non-insulin-stimulated and insulin-stimulated glucose transport system of adipocytes from NIDDM subjects seem to be reversed when hyperglycemia is controlled by dietary treatment, whereas only defects related to the capacity of the transport system and without relation to acute insulin exposition are changed when hyperglycemia is controlled by insulin treatment.

Foley et al. (10) and Scarlett et al. (11) found a significant correlation between the decline in fasting plasma glucose concentrations and the increase in maximally insulin-stimulated glucose transport rates. We failed to confirm such a relationship. This discrepancy is probably due to the great variability between patients in the former studies pertaining to initial fasting plasma glucose concentrations, including individuals with concentrations <7 mM (10), as opposed to the uniform decreases in fasting plasma glucose levels in our study. Thus, significant correlations will be difficult to detect.

Glucose metabolism. Total lipid and CO_2 production tended to increase in both basal and insulin-stimulated adipocytes after dietary treatment of NIDDM patients; maximal insulin responsiveness also increased significantly. Foley et al. (10) found that maximally insulin-stimulated lipogenesis was increased after insulin treatment of NIDDM subjects. However, no basal rates or dose-response curves were given in their study. In our previous study of untreated NIDDM patients, both absolute rates of basal and insulin-stimulated lipogenesis and maximal insulin responsiveness were impaired (9). Thus, all these abnormalities are reversed by diet-induced control of hyperglycemia. Unfortunately, data regarding the effect of insulin treatment on basal lipogenesis and insulin responsiveness on lipogenesis are not available in the study of Foley et al. (10).

Relationship to in vivo findings. The insulin secretion in response to an oral glucose load increased in all subjects to levels similar to those of the normal group. To what degree increased insulin secretion is responsible for improved glycemic status or whether this is caused primarily by amelioration of insulin resistance in peripheral tissues is still a matter for discussion (28). Alternatively, these phenomena may be secondary to improved glycemic status and to other factors associated with this.

Regardless of which theory is correct, note that in our study improved glucose tolerance and improved insulin secretion was the physiologic response to diet treatment, and serum insulin levels were within the limits of normal subjects. In the studies in which glycemic control was obtained by insulin treatment, the serum insulin levels were considerably higher (mean dose 110 ± 15 U/day).

We believe that the most important factor responsible for improved adipocyte glucose transport and metabolism is the amelioration of hyperglycemia and concomitant metabolic deterioration, regardless of the way this is achieved (i.e., insulin or diet treatment). However, whereas all defects observed in untreated NIDDM patients were reversed by controlling hyperglycemia with diet, insulin responsiveness and sensitivity were not affected by insulin treatment. The failure of insulin therapy to improve insulin responsiveness and sensitivity of adipoctyes from NIDDM patients may be due to adverse effects of the supraphysiologic serum insulin levels.

In studies of in vivo insulin action, Scarlett et al. (29) found that control of hyperglycemia by insulin ameliorates the decreased glucose utilization in peripheral tissues found in poorly controlled NIDDM patients. These authors have suggested that a relationship exists between these in vivo and in vitro findings such that the mechanism for changes in peripheral glucose utilization should be changes in glucose transport rates as measured in fat cells. This idea is based on the findings of significant positive correlations between alterations in fasting plasma glucose concentrations and alterations in maximally insulin-stimulated adipocyte glucose transport rates (5,8,10,29) and between alterations in maximal peripheral glucose utilization and maximally insulin-stimulated adipocyte glucose transport (8,11). However, glucose transport is not rate limiting for glucose processing in human adipocytes at physiologic and supraphysiologic glucose concentrations as shown by Kashiwagi et al. (5) and by us (14). Therefore, although great changes were found after treatment in the basal and insulin-stimulated glucose transport system in adipocytes, these changes cannot explain the improved glucose utilization of adipose tissue. The mechanism for this is the alterations in glucose conversion to lipids. In addition, only a small fraction of the peripheral glucose utilization is accounted for by adipose tissue, with the muscle tissue responsible for >90% of this. Thus, the use of in vitro adipocyte glucose transport as a model for in vivo glucose utilization is based on weak evidence. The finding of parallel changes in the two systems after treatment is probably be-

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cause both are secondary to the improved glycemic control, and the finding does not prove a direct relationship.

In conclusion, our results demonstrate that adipocytes from moderately obese NIDDM patients, in whom control of hyperglycemia is obtained by dietary intervention, exhibit improved basal and maximally insulin-stimulated glucose transport rates and improved insulin action on glucose transport and lipid and CO_2 production. In contrast, insulin binding is essentially unaltered. The improved adipocyte glucose processing is probably related to the amelioration of hyperglycemia and the concomitant metabolic deterioration.

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