Glycohemoglobin Levels Relate to the Response of Adipose Tissue Lipoprotein Lipase to Insulin/Glucose in Obese Non–Insulin-Dependent Diabetes Mellitus

Trudy J. Yost, Craig N. Sadur, and Robert H. Eckel

Adipose tissue lipoprotein lipase (ATLPL) is responsible for the provision of lipoprotein-derived fatty acids to adipocytes for storage as triglycerides. Fasting ATLPL has been shown to be decreased in non–insulin-dependent diabetes mellitus (NIDDM), an insulin-resistant state. Medically uncomplicated obesity, another state of relative insulin resistance, is associated with decreased stimulation of the enzyme in response to metabolic stimuli. It was therefore hypothesized that the increased insulin resistance of NIDDM would result in an even greater defect in the response of ATLPL to insulin/glucose. Gluteal adipose tissue biopsies were performed in 13 premenopausal obese women with NIDDM, before and after 6 hours of intravenous insulin and glucose. Metabolic data from these studies were then compared with those obtained from 26 nondiabetic obese women of similar age, weight, and fasting insulin concentration (obese controls [OBC]). As expected, fasting gluteal ATLPL activity was lower in the NIDDM group than in OBC (3.7 ± 0.9 *v* 11.1 ± 1.6 nmol free fatty acids [FFA]/min/10^6 cells, $P = .0003$). The change in ATLPL activity (ΔATLPL) in response to a 6-hour insulin/glucose infusion was not statistically different between the two groups (2.2 ± 1.1 *v* 4.7 ± 1.2, $P = .114$). However, in NIDDM subjects there was a strong positive relationship between ΔATLPL and glycohemoglobin (GHb) level ($r = .883$, $P = .0001$). Moreover, when obese NIDDM subjects were divided into those with GHb values in the lower half of the range (median, 10.5%) versus those with values in the upper half, the effect of glycemic control on ΔATLPL was highly significant (ΔATLPL, −0.6 ± 0.9 nmol FFA/min/10^6 cells *v* 4.6 ± 1.4, $P = .009$). Because FFA were suppressed less by insulin/glucose in obese NIDDM subjects, it may be that the increase in ATLPL in response to insulin/glucose seen in those subjects under poorer glycemic control serves to counteract NIDDM-related defects in insulin-mediated antilipolysis, and thereby serves to maintain adipocyte volume and overall adipose tissue mass.

LIPOPROTEIN LIPASE (LPL) is a hydrolytic enzyme that functions at the level of capillary endothelium to dissociate triglyceride esters from chylomicrons and very–low-density lipoproteins. In adipose tissue, this process provides fatty acids for reesterification and storage as adipocyte triglycerides.[1]

It is well established that non–insulin-dependent diabetes mellitus (NIDDM), an insulin-resistant state, is associated with decreased levels of adipose tissue LPL (ATLPL) in fasted subjects,[2,3] and that there is a high incidence of obesity in people with NIDDM.[4-7] In medically uncomplicated obesity, another state of relative insulin resistance, a defect in the stimulation of ATLPL activity in response to metabolic stimuli (eg, meals or intravenous insulin/glucose) has been demonstrated.[1,8] Although Pykälistö et al[9] have described a lack of change in ATLPL in response to meals in NIDDM, the effect of NIDDM on the change in ATLPL (ΔATLPL) in response to an insulin/glucose infusion has not yet been elucidated. Therefore, the goal of this study was to investigate the ΔATLPL that would occur in response to an insulin/glucose infusion in a group of obese women with NIDDM, and furthermore to examine the relationship of the change in the enzyme activity to glycemic control. Data from the obese NIDDM subjects were compared with those obtained from a cohort of nondiabetic obese women as control subjects (OBC).

SUBJECTS AND METHODS

Thirteen obese women with documented NIDDM were included in the study on the basis of the following criteria: aged 18 to 50 years; absence of cardiovascular, hepatic, pulmonary, renal, or oncologic disease; and, with the exception of sulfonylureas, no use of medication that could affect carbohydrate or lipid metabolism (ie, diuretics, β-blockers, glucocorticoids, or insulin). At the screening visit, serum electrolytes, liver and renal function, complete blood cell count, and thyroid-stimulating hormone were within normal ranges for all subjects. All subjects had NIDDM for at least 3 months before study and had been weight-stable for at least those 3 months. Nine subjects were on oral hypoglycemic agents at a stable dose; the other five NIDDM subjects were treated with diet therapy only. There were no differences in any of the measured parameters between NIDDM subjects on sulfonylureas and those treated with diet only. Metabolic data from the obese NIDDM study group were compared with data from 26 healthy female OBC of similar age, body weight, body mass index, and fasting serum insulin concentration. These women were recruited and studied under conditions identical to those for NIDDM subjects.

All studies were performed on the General Clinical Research Center (GCRC) at the University of Colorado Health Sciences Center after approval by the Colorado Multiple Institutional Review Board and subsequent provision of individual informed consent. Subjects consumed an isocaloric liquid formula diet (45% carbohydrate, 40% fat, and 15% protein) for 2 days as outpatients, and then fasted for 12 hours overnight on the inpatient metabolic ward. The following morning, each subject underwent a 6-hour insulin/glucose euglycemic clamp on the GCRC as previously described.[10] Fasting serum glucose concentration was measured that morning, but the protocol established 5.0 mmol/L (90 mg/dL) as the euglycemic goal for determining the variable glucose infusion needed during the study. Insulin was infused in an

From the Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado Health Sciences Center, Denver, CO.

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Present address: C.N.S., Kaiser Medical Office, Pleasanton, CA.

Address reprint requests to Robert H. Eckel, MD, University of Colorado Health Sciences Center, 4200 E Ninth Ave, B151, Denver, CO 80262.

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exponentially decreasing manner over the first 10 minutes, followed by a steady-state infusion of 861 nmol/m^2/min that was maintained for the duration of the 6-hour study. In NIDDM subjects, glucose infusion was not begun until the insulin infusate produced a decrease in serum glucose to approximately 5.0 mmol/L in each individual. Glucose infusion rate (GIR) was calculated as the mean value for the last 60 minutes of the 6-hour infusion study for all subjects (NIDDM and OBC).

Fasting blood samples were drawn on the morning of study for determination of serum glucose, total glycohemoglobin (GHb) (NIDDM only), insulin, free fatty acids (FFA), and plasma triglyceride levels. A gluteal adipose tissue biopsy was then performed in the fasted state for subsequent measurement of heparin-releasable LPL activity. A repeat adipose tissue biopsy was performed on the other side of the body at the 6-hour terminal time point of the infusion for determination of any ΔATLPL that had occurred in response to a 6-hour insulin/glucose infusion. The biopsy technique for retrieval of gluteal adipose tissue has been previously described.[11]

The assay for measurement of ATLPL activity has also been previously described.[12] In brief, the substrate was prepared with 5 mg unlabeled triolein (Sigma Chemical, St Louis, MO), 4 μCi (1-^{14}C)triolein (Amersham, Arlington Heights, IL), and 0.24 mg egg lecithin (Calbiochem, La Jolla, CA), all emulsified with 2 mol/L Tris hydrochloride buffer containing 10% fatty acid–free bovine serum albumin and normal human serum for a substrate volume of 4.0 mL. LPL was eluted from adipose tissue pieces (40 to 45 mg) into Krebs-Ringer phosphate buffer containing heparin 2.0 μg/mL (Upjohn, Kalamazoo, MI). After incubation of 0.1 mL eluted enzyme with 0.1 mL substrate for 45 minutes, enzyme activity was measured as hydrolyzed ^{14}C-labeled fatty acids and expressed as nanomoles FFA per minute per 10^6 cells.

Fat cells were obtained according to the method reported by Rodbell,[13] and adipocyte size was determined with a calibrated microscope using the method reported by DiGirolamo et al.[14] Serum insulin level was measured by radioimmunoassay.[15] Serum FFA levels were measured enzymatically with a colorimetric end point.[16] Plasma triglyceride levels were measured enzymatically.[17] Total GHb levels were measured by affinity chromatography (Glyc-Affin; Isolab, Akron, OH).

Data sets with normal distribution were analyzed using Student's *t* test and Pearson linear regression analysis. Data sets that were not normally distributed were analyzed using the Wilcoxon rank-sum test and Spearman-rank analysis. The general linear model was applied for two-way ANOVA (unbalanced design). Analyses that yielded probability levels no greater than .05 were considered statistically significant. Results are presented as the mean ± SEM.

RESULTS

Demographic data for the two groups are shown in Table 1. The two groups were similar in age, weight, body mass index (kilograms per square meter), and fasting serum insulin concentration. As expected, the mean fasting serum glucose concentration was higher for the NIDDM group than for the OBC group (9.2 ± 0.6 *v* 5.1 ± 0.1 mmol/L, $P = .0001$). Plasma triglyceride levels were also higher in the NIDDM group versus OBC (2.09 ± 0.27 *v* 1.41 ± 0.19 mmol/L, $P = .05$).

Figure 1 shows that fasting gluteal ATLPL was lower in the obese NIDDM group than in OBC (3.7 ± 1.0 *v* 11.1 ± 1.6 nmol FFA/min/10^6 cells, $P = .0003$). Although the ΔATLPL in response to a 6-hour insulin/glucose infusion in NIDDM subjects tended to be less than in OBC (ΔATLPL, 2.2 ± 1.1 *v* 4.7 ± 1.2 nmol FFA/min/10^6 cells), the difference did not reach statistical significance ($P = .144$). Neither the fasting level of ATLPL activity nor the ΔATLPL in response to insulin/glucose was correlated with the level of triglyceridemia in either group.

Table 1. Demographic Data and Fasting Laboratory Values for Obese NIDDM and OBC Groups

Characteristic	Obese NIDDM (n = 13)	OBC (n = 26)
Age (yr)	40 ± 3	37 ± 2
Weight (kg)	93.4 ± 4.6	91.1 ± 2.7
BMI (kg/m^2)	37.2 ± 1.5	34.0 ± 1.1
Glucose (mmol/L)	9.2 ± 0.6*	5.1 ± 0.1
Insulin (pmol/L)	278 ± 57	194 ± 34
Triglycerides (mmol/L)	2.09 ± 0.27†	1.41 ± 0.19
Cholesterol (mmol/L)	4.67 ± 0.22	5.05 ± 0.19
FFA (nmol/L)	838 ± 61	773 ± 51
Fat cell size (pL)	607 ± 59	620 ± 44
GIR (mmol/m^2/min)	8.8 ± 1.4*	17.0 ± 1.2
GHb (%)	10.7 ± 0.4	—

Abbreviations: BMI, body mass index; OBC, obese controls.
*$P = .0001$, †$P = .05$: *v* OBC.

Calculation of GIR during the course of an insulin/glucose euglycemic clamp is a measurement of relative insulin sensitivity. Accordingly, over the last 60 minutes of the infusion study, OBC in our present study had a mean GIR of 17.0 ± 1.2 mmol/m^2/min, while the more insulin-resistant obese NIDDM group had a lower GIR (8.8 ± 1.4, $P = .0001$). Because uncomplicated obesity and NIDDM are both states of relative insulin resistance and therefore represent a continuum of insulin sensitivity, relationships between GIR and fasting ATLPL and ΔATLPL were examined. There was a positive log-linear correlation between fasting ATLPL and GIR for all subjects combined ($N = 39$, $r = .441$, $P = .005$), but only a weak relationship between the two variables if 13 NIDDM subjects were considered alone ($r = .538$, $P = .057$). There was no correlation between GIR and ΔATLPL in either group or for all subjects combined. Not surprisingly, when all subjects were considered together, fasting serum glucose was inversely correlated with insulin sensitivity as measured by GIR ($r = -.623$, $P = .0001$).

Because glycemic control is an important metabolic

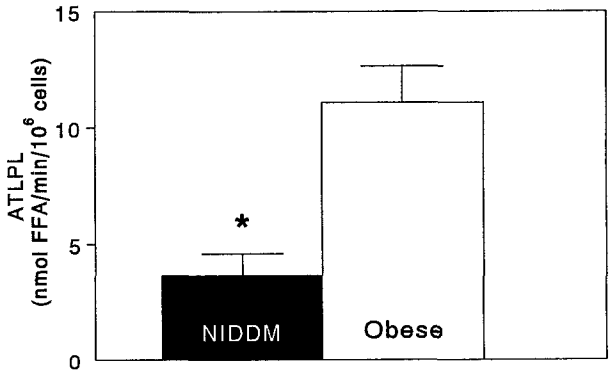

Fig 1. Fasting gluteal ATLPL activity in 13 obese subjects with NIDDM *v* 26 OBC (*$P = .0003$).

variable in NIDDM, relationships between ATLPL and total GHb for 13 NIDDM subjects were examined. There was no relationship between glycemic control and ATLPL activity measured in the fasted state. However, there was a strong positive relationship between GHb (percent) and ΔATLPL in response to insulin/glucose ($r = .883, P = .0001$; Fig 2), indicating that obese NIDDM subjects who were under worse glycemic control actually had greater increases in ATLPL following 6 hours of insulin/glucose than those who were under better control. When obese NIDDM subjects were divided into those with GHb levels in the lower half (n = 6) of the range (8.7% to 13.0%; median, 10.5%) versus those with levels in the upper half (n = 7), the effect of glycemic control on ΔATLPL was even more obvious ($P = .009$; Fig 3).

Decreases in serum FFA concentrations in OBC and the obese NIDDM group over the course of the 6-hour insulin/glucose infusion are illustrated in Fig 4. Despite FFA levels in the fasted state that were the same (Table 1), the antilipolytic effect of infused insulin/glucose was significantly greater in OBC than in the NIDDM group ($P = .0001$). FFA concentrations decreased with time in both groups ($P = .0001$). However, when comparisons were performed at a number of time intervals into the clamp, it was found that FFA levels were significantly higher in the NIDDM group (*v* OBC) throughout the insulin/glucose infusion ($P < .05$). There was no relationship between ΔATLPL and fasting levels of serum FFA or between ΔATLPL and ΔFFA (change in serum FFA from basal to 360 minutes) for either 13 obese NIDDM subjects considered alone or for all subjects considered together ($N = 39$).

DISCUSSION

Diabetes mellitus has been shown to be associated with a deficiency of fasting ATLPL by many investigators both in rodent models and in humans.[2] In general, the degree to which the enzyme activity is diminished has been related to the severity of the hyperglycemia. Studies in human subjects with NIDDM have shown that fasting hyperglycemia in the range of 8.3 to 16.5 mmol/L was associated with 40%

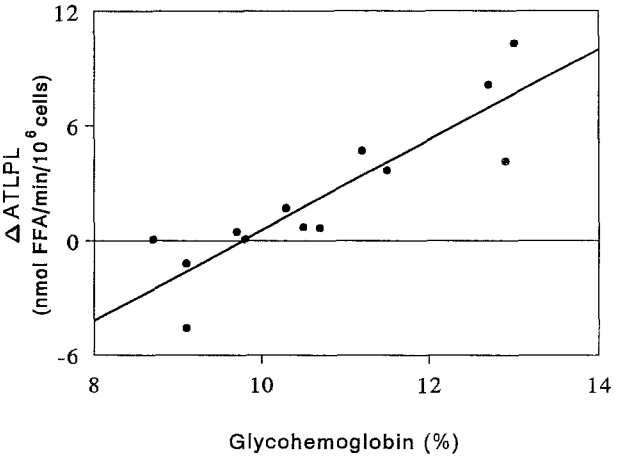

Fig 2. ΔATLPL in response to a 6-hour insulin/glucose infusion *v* total GHb in 13 obese NIDDM subjects ($r = .883, P = .0001$).

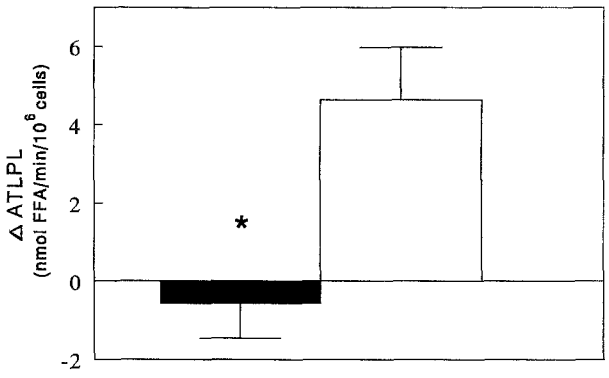

Fig 3. ΔATLPL in response to a 6-hour insulin/glucose infusion in 6 obese NIDDM subjects representing the lower half of total GHb levels for the group of 13 (range, 8.7% to 13.0%; median, 10.5%) *v* 7 obese NIDDM subjects with total GHb levels in the upper half ($P = .009$).

to 65% reductions in fasting gluteal ATLPL activity as compared with that in normal subjects.[18-21] These findings are supported by the present data, in which fasting ATLPL activity in NIDDM subjects with a mean fasting serum glucose of 8.9 ± 0.7 mmol/L (range, 5.2 to 13.1) was reduced by approximately 67% as compared with that in OBC. Obese subjects have even higher fasting levels of ATLPL than normal-weight subjects.[18,22-26] Therefore, a 67% decrease in ATLPL in fasted NIDDM subjects versus obese nondiabetic subjects represents a decrease similar to that previously reported.

The present study is unique in that it quantifies the change in the adipose tissue enzyme activity in response to a 6-hour insulin/glucose infusion in obese NIDDM subjects. The gluteal ΔATLPL that occurs in response to specific metabolic stimuli, eg, oral or intravenous glucose[27-29] or intravenous glucose and insulin,[1,25,30] has previously been shown to be diminished in obese subjects versus lean controls.[30] Thirteen subjects included in the present study not only were obese but also had NIDDM, a condition associated with even greater insulin resistance.[31] Pykä-

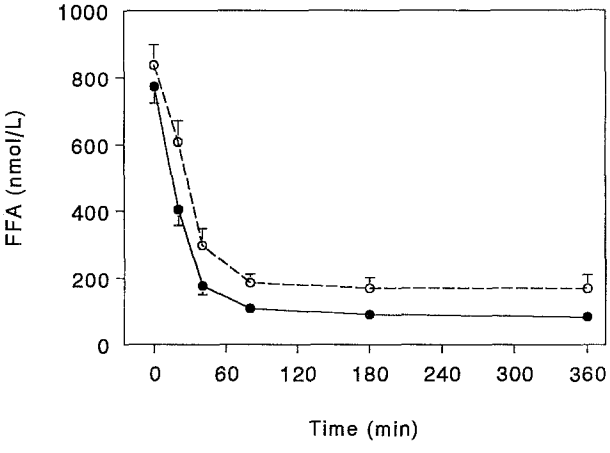

Fig 4. Decrease in serum FFA concentrations in 13 obese subjects with NIDDM (○) *v* 26 OBC (●) over the course of a 6-hour insulin/glucose infusion. Group: $df = 1, F = 21.36, P = .0001$; time: $df = 5, F = 99.72, P = .0001$.

listö et al[9] described a relationship between insulin deficiency and lack of stimulation of ATLPL with feeding in untreated hyperglycemic diabetic subjects. However, in the present study, the obese NIDDM group exhibited a mean ΔATLPL in response to insulin/glucose that was not statistically different from that measured in OBC.

Usually, ATLPL is increased by insulin in normal-weight subjects,[10] but in uncomplicated obesity the dose-response curve for ATLPL stimulation by insulin is shifted to the right.[1] As expected, GIR was even lower in obese subjects with NIDDM than in OBC. However, the increased insulin resistance of the obese NIDDM group was not associated with an exaggerated defect in the ΔATLPL seen in response to insulin/glucose.

Pollare et al[32] examined abdominal subcutaneous ATLPL measured in the fasted state and its relation to insulin resistance as determined by euglycemic clamp. They found no differences in fasting abdominal ATLPL between four groups representing a spectrum of insulin sensitivity: normal-weight control, obese normoinsulinemic, obese hyperinsulinemic, and obese diabetic. However, the response of abdominal ATLPL to insulin/glucose infusion (clamp) was not examined. In contrast to their study, the adipose tissue depot examined in the present study was the gluteal depot. Although it has been shown in nondiabetic obese women that fasting ATLPL and its regulation by insulin/glucose are largely similar between the abdominal and gluteal beds,[33] regional similarities/dissimilarities in metabolic regulation between these two adipose tissue beds in obese NIDDM subjects have not been described. As shown in Fig 1, fasting levels of the enzyme in gluteal adipose tissue were markedly different between the two groups. Moreover, Yost and Eckel[30] have shown that the fasting level of ATLPL activity is markedly higher in both adipose tissue regions (gluteal and abdominal) in nondiabetic obese subjects versus normal-weight subjects.

Pfeifer et al[34] have described "compensatory NIDDM," characterized by obesity, insulin resistance, and fasting plasma glucose levels less than 11.1 mmol/L (200 mg/dL). Affected individuals exhibit decreased first-phase insulin secretion, impaired carbohydrate utilization, and elevated plasma glucose concentrations. Under such conditions, basal hyperglycemia can be viewed as a compensatory mechanism for the restoration of normal carbohydrate production and utilization. The elevated plasma glucose compensates for impaired insulin secretion by maintaining insulin responsiveness to non–insulin-mediated glucose signals. In addition, Baron et al[35] showed that at basal serum glucose levels, rates of non–insulin-mediated glucose uptake in hyperglycemic NIDDM subjects were approximately two times those of euglycemic control subjects.

Because the hyperglycemia of NIDDM is associated with compensatory changes in carbohydrate metabolism, we wondered how relative glycemic control affected measurable parameters of adipose tissue metabolism, namely ATLPL activity. Surprisingly, NIDDM subjects under poorer glycemic control actually had a greater ΔATLPL in response to insulin/glucose than diabetic subjects under better control, with the relationship between GHb level and ΔATLPL being linear. This is not to imply that an even lower level of GHb will necessarily decrease the ΔATLPL that occurs in response to insulin. In nondiabetic, normal-weight subjects (who have even lower GHb levels), insulin infusion increases ATLPL activity.[10] However, as shown in Fig 3, obese NIDDM subjects with lower GHb values exhibited essentially no ΔATLPL in response to insulin/glucose, whereas those with higher GHb values demonstrated a significant positive response in the adipose tissue enzyme. One possible explanation for this interesting finding is that since fasting hyperglycemia (poor glycemic control) may be compensatory for the normalization of carbohydrate utilization and, in part, for the insulin secretory defect, the metabolic ΔATLPL in response to insulin/glucose may then also increase. Furthermore, an increase in glucose-dependent carbohydrate utilization may decrease the need for lipolysis products as fuel. Because adipose tissue lipolysis and ATLPL are reciprocally regulated,[1] this could also contribute to the restoration of ATLPL response to insulin/glucose to levels seen in subjects with obesity alone.

Most in vitro studies have demonstrated normal antilipolytic effects of insulin in adipocytes of subjects with obesity and NIDDM.[36-39] However, both normal[40,41] and impaired[42-45] suppression of FFA by insulin have been documented by in vivo studies. Groop et al[42] performed a study in nine lean NIDDM subjects and eight age- and weight-matched controls, the purpose of which was to determine whether the insulin resistance of NIDDM also involved alterations in FFA metabolism. They found that in the setting of a euglycemic clamp, plasma FFA concentration and the rate of plasma FFA turnover during graded hyperinsulinemia were significantly less in nondiabetic control subjects than in those with NIDDM. In a subsequent study in which Groop et al[43] again used the euglycemic clamp technique, it was documented that obesity with concomitant NIDDM was also associated with impaired maximal suppression of plasma FFA and rates of FFA turnover, FFA oxidation, and nonoxidative FFA disposal. Although FFA turnover rates were not measured in the present study, there was a significant impairment of the antilipolytic effect of insulin on serum FFA concentrations over the course of a 6-hour hyperinsulinemic clamp.

If in NIDDM the reduced maximal response of insulin on glucose uptake and oxidation in muscle is a primary defect, then perhaps maintaining an enhanced rate of FFA oxidation (through impaired antilipolysis and thus increased plasma FFA availability) is an adaptation that allows the energy demands of muscle to be met. Moreover, because the maintenance of body lipid stores is metabolically defended,[46] it may be that in the present study NIDDM subjects under worse glycemic control exhibited greater increases in ATLPL activity in response to insulin/glucose to counteract defects in insulin-mediated antilipolysis, thereby maintaining adipocyte volume and adipose tissue mass.

In summary, NIDDM with concomitant obesity is associ-

ated with reductions in fasting gluteal ATLPL activity as compared with that in OBC, but a similar degree of change was seen in the enzyme activity in response to an insulin/glucose infusion. However, the data presented here indicate that the degree of glycemic control in NIDDM, as measured by total GHb, is correlated with the ΔATLPL that occurs in response to insulin/glucose infusion, but in the opposite direction than might have been expected. Obese subjects with NIDDM who were under worse glycemic control actually exhibited a greater ΔATLPL in response to insulin/glucose, possibly related to improved carbohydrate utilization through the potentiation of non–insulin-mediated glucose uptake and/or the physiologic drive of the adipocyte to maintain cell volume, available energy stores, and adipose tissue mass. Moreover, obese NIDDM subjects exhibited impairment of the antilipolytic effect of insulin over the course of a 6-hour insulin/glucose euglycemic clamp as compared with OBC. Because the response of ATLPL to insulin/glucose is maintained in obese NIDDM subjects while antilipolysis remains impaired, it appears that the two metabolic phenomena may work together to maintain body weight while providing sufficient FFA for oxidative fuel.

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