Change in Skeletal Muscle Lipoprotein Lipase Activity in Response to Insulin/Glucose in Non–Insulin-Dependent Diabetes Mellitus

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Skeletal muscle lipoprotein lipase (SMLPL) provides fatty acids to myocytes for lipoprotein triglyceride oxidation. In human obesity, an insulin-resistant state, SMLPL levels measured in the fasted state are either decreased or unchanged as compared with levels in normal-weight controls. However, insulin/glucose infusion increases SMLPL activity in obese individuals, whereas in normal-weight subjects the activity is decreased. One of the goals of this study was to determine the impact of obesity with concomitant non–insulin-dependent diabetes mellitus (NIDDM) on fasting SMLPL and on the change in SMLPL activity (ΔMLPL) in response to an insulin/glucose infusion. Because NIDDM is often a more insulin-resistant state, it was hypothesized that SMLPL activity would be further increased by insulin/glucose in subjects who were obese and had NIDDM. Measurements of SMLPL were made from biopsies of vastus lateralis skeletal muscle taken before and after a 6-hour insulin/glucose infusion in the setting of a euglycemic clamp. Thirteen nondiabetic obese women (OBC) and six nondiabetic normal-weight women (NWC) were used as control subjects. SMLPL levels measured in the fasted state were significantly lower in obese NIDDM subjects as compared with either control group. Relative insulin action was determined by calculation of the mean glucose infusion rate (GIR) required to sustain euglycemia over the last 60 minutes of the infusion. For all three groups combined, representing a continuum of insulin sensitivity, there was a positive correlation between GIR and fasting SMLPL. As described earlier, in the NWC group SMLPL activity decreased significantly after 6 hours of insulin/glucose, and in the OBC group SMLPL increased after insulin/glucose. In contrast, SMLPL activity did not change after insulin/glucose infusion in obese NIDDM subjects. Overall, these data indicate that although insulin action seems to be important in determining the level of SMLPL activity measured in the fasted state in human subjects, it is not the major contributor to the change in SMLPL activity that occurs in response to an insulin/glucose infusion.

LIPOPROTEIN LIPASE (LPL) is an enzyme that resides on the capillary walls of many tissues, including adipose tissue and cardiac and skeletal muscle. In adipose tissue, LPL provides lipoprotein triglyceride-derived fatty acids that are taken up, reesterified, and stored as triglycerides in the adipocyte.[1] Although LPL in skeletal muscle (SMLPL) is the same protein as that in adipose tissue,[2] the lipase has a different role in muscle, ie, to provide triglyceride fatty acids directly or indirectly to myocytes for oxidation.[3] The unique functions of adipose tissue LPL and SMLPL in fatty acid fuel partitioning are evidenced by divergent tissue-specific responses of the lipase to insulin/glucose. In normal-weight individuals, it has been shown that a 6-hour infusion of insulin/glucose (at maintained euglycemia) results in stimulation of adipose tissue LPL activity and either a decrease or no change in SMLPL activity.[4] These divergent tissue-specific LPL responses to insulin/glucose may serve to direct lipoprotein triglyceride-derived fatty acids away from muscle to adipose tissue for storage.

In obesity, an insulin-resistant state, the normal suppressive action of insulin/glucose on SMLPL is not seen, and SMLPL activity actually increases after an insulin/glucose infusion.[5,6] The purpose of this study was to determine if SMLPL was further altered in obesity with concomitant non–insulin-dependent diabetes mellitus (NIDDM), an even more insulin-resistant state. It was hypothesized that an even greater increase in SMLPL activity in response to an insulin/glucose infusion in obese NIDDM (compared with that seen in obesity alone) would suggest that insulin action was a major contributor to metabolic changes in LPL activity seen in skeletal muscle. The relationships of fasting SMLPL and the change in the enzyme activity in response to insulin/glucose versus lipoproteins, free fatty acids (FFA), and anthropometry in obese NIDDM subjects, obese controls, and normal-weight individuals were also examined.

SUBJECTS AND METHODS

Seven obese women with documented NIDDM, 13 nondiabetic obese women (OBC), and six normal-weight women (NWC) were included in the study on the basis of the following criteria: aged 18 to 50 years and premenopausal; 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 count, and thyroid-stimulating hormone were within normal ranges for all subjects. All NIDDM subjects had diabetes for at least 3 months before study. Six of seven NIDDM subjects were on oral hypoglycemic agents at a stable dose, and the other was treated with diet therapy only. There was one Hispanic woman in the NIDDM group; all others were white. There was no difference in results obtained for the Hispanic subject and results for the other NIDDM subjects.

All studies were performed at 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,

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Submitted May 25, 1994; accepted September 21, 1994.

Supported by National Institutes of Health (NIH) Grant No. DK-26356 and NIH General Clinical Research Center Grant No. RR-00051.

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0026-0495/95/4406-0017$03.00/0

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 at the GCRC as previously described.[7] In obese NIDDM subjects, oral hypoglycemic agents (where applicable) were administered approximately 1 hour before initiation of blood sampling on the morning of study. The fasting serum glucose concentration was measured that morning. Regardless of the level of fasting glycemia, 5.0 mmol/L (90 mg/dL) was the euglycemic goal for determining the variable glucose infusion needed during the study. Insulin was infused in an exponentially decreasing manner over the first 10 minutes as a bolus, followed by a steady-state infusion rate of 287 nmol/m^2/min, which was maintained for the duration of the 6-hour study. In each diabetic individual, the glucose infusion was not begun until the insulin infusate produced a decrease in serum glucose to approximately 5.0 mmol/L. The glucose infusion rate (GIR) was calculated as the mean value over the last 60 minutes of the infusion study for all subjects.

Fasting blood samples were drawn on the morning of study for determination of serum glucose, cholesterol, HDL cholesterol (HDL-C), insulin, FFA, and plasma triglyceride levels. A skeletal muscle biopsy from the vastus lateralis was then performed in the fasted state for measurement of heparin-releasable LPL (HR-LPL) activity. A second skeletal muscle biopsy was performed on the other leg after 6 hours of insulin/glucose infusion. The biopsy technique for retrieval of skeletal muscle tissue has been previously described.[4] There was no apparent difference between muscle tissue retrieved from obese subjects (OBC or NIDDM) and that retrieved from NWC. The site of biopsy (vastus lateralis) was the same in all subjects, and all adipose tissue was easily dissected and removed from the muscle tissue pieces obtained. For confirmation of the latter, muscle samples from two obese subjects were sectioned and examined histologically, and there was no adipose tissue contamination.

The assay for measurement of SMLPL activity has also been previously described.[4] 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 muscle tissue pieces (40 to 50 mg) into Krebs-Ringer phosphate buffer containing 15 μg/mL heparin (Upjohn, Kalamazoo, MI). After incubation of 0.1 mL eluted enzyme with 0.1 mL substrate for 45 minutes, the reaction was stopped by addition of an organic mixture containing chloroform/methanol/heptane (1.25:1.41:1.00), and fatty acids were extracted with a bicarbonate buffer (pH 10). After mixing and centrifugation, an aliquot of the top layer containing extracted fatty acids was counted in a beta scintillation counter (Beckman Instruments, Fullerton, CA). Enzyme activity was expressed as nanomoles FFA released per minute per gram of tissue. The lipase assay was standardized each time using an aliquot from the same pool of human postheparin plasma.

Serum insulin level was measured by radioimmunoassay.[8] Serum FFA levels were measured enzymatically with a colorimetric end point.[9] Plasma triglyceride levels were measured enzymatically,[10] as was serum total cholesterol.[11] HDL-C was quantified enzymatically after separation using the method reported by Warnick et al.[12]

Differences between groups were determined using one-way ANOVA with subsequent pairwise multiple comparisons using the Bonferroni *t* test method. Pearson product-moment and Spearman rank-order correlation procedures were applied to determine correlation coefficients between variables. Student's *t* test was applied to analyze paired data within the same group (eg, basal SMLPL *v* 6-hour SMLPL) and to analyze differences between variables that existed for only two groups (eg, waist to hip ratio). A probability level $\leq .05$ was considered statistically significant. Results are presented as the mean ± 1 SEM in the text and Table 1.

RESULTS

Table 1 lists anthropometric data for each group and mean fasting blood values measured on the morning of the euglycemic clamp study. The mean age in the diabetic group was greater than in either of the control groups. Obese NIDDM subjects and OBC were similar in body weight and body mass index ([BMI] kilograms per square meter). As expected, weight and BMI were significantly greater in NIDDM subjects and OBC than in NWC. Percent body fat was not different between OBC and the obese NIDDM group (43.8% ± 1.9% *v* 43.3% ± 2.1%). The waist to hip ratio was greater in the obese NIDDM group than in OBC (0.87 ± 0.04 *v* 0.77 ± 0.02, $P = .025$). Percent body fat and waist to hip ratio data were not available for NWC.

Fasting triglycerides were higher in the NIDDM group than in OBC or NWC, but were not different in OBC versus NWC (Table 1). Fasting serum FFA concentrations were similar between NIDDM subjects and OBC, and were not significantly different in NIDDM subjects versus NWC. Fasting serum insulin levels were significantly higher in the NIDDM group as compared with OBC and NWC, and were also higher in OBC versus NWC. As expected, fasting glucose levels were higher in NIDDM subjects as compared with OBC and NWC, but mean fasting glucose values were similar in OBC and NWC. There were no differences between groups in fasting plasma cholesterol levels, but HDL-C was significantly lower in the NIDDM group as compared with NWC (0.92 ± 0.07 *v* 1.48 ± 0.08 mmol/L, $P < .001$). HDL-C levels in OBC (1.15 ± 0.06) were also lower than in NWC ($P = .007$).

Glucose disposal measured during an insulin/glucose clamp primarily reflects muscle glucose uptake, and in normal-weight subjects muscle glucose uptake has been shown to be negatively correlated with the insulin-mediated decrease in SMLPL.[13] Differences in insulin action between the two control groups and the obese NIDDM group were determined by calculation of the mean GIR required to sustain euglycemia over the last 60 minutes of the infusion.

Table 1. Anthropometric Data and Fasting Serum/Plasma Values for NWC, OBC, and NIDDM Subjects

	NWC (n = 6)	OBC (n = 13)	NIDDM (n = 7)
Age (yr)	32 ± 3†	34 ± 2‡	43 ± 2
Weight (kg)	54.6 ± 2.6*†	93.5 ± 3.2	96.4 ± 5.8
BMI (kg/m^2)	19.8 ± 0.6*†	34.3 ± 1.0	35.1 ± 1.2
Triglycerides (mmol/L)	0.89 ± 0.13†	1.37 ± 0.17‡	2.38 ± 0.37
FFA (μmol/L)	709 ± 59	958 ± 40	923 ± 132
Insulin (pmol/L)	31 ± 3*†	57 ± 9‡	112 ± 14
Glucose (mmol/L)	5.1 ± 0.1†	5.0 ± 0.1‡	11.8 ± 1.7
Glycohemoglobin (%)	—	—	11.5 ± 1.2

*NWC *v* OBC, $P < .05$.
†NWC *v* NIDDM, $P < .05$.
‡OBC *v* NIDDM, $P < .05$.

GIR in NWC was substantial at 18.0 ± 1.1 mmol/m^2/min, and significantly greater than in the more insulin-resistant OBC (12.5 ± 0.7, $P < .001$). The obese NIDDM group, as a consequence of even greater insulin resistance, demonstrated a GIR of 4.6 ± 1.3, which was significantly less than that seen in OBC ($P < .001$) or NWC ($P < .001$).

The level of SMLPL measured in the fasted state (Fig 1, time 0) in NWC was similar to that measured in OBC but significantly greater than in NIDDM subjects ($P < .001$). Fasting SMLPL activity in the NIDDM group was also significantly less than in OBC ($P < .001$). Although in NIDDM subjects there was a negative correlation between fasting SMLPL and fasting serum insulin concentration ($r = -.877, P = .010$), this relationship was not seen for any of the other groups. However, when all subjects were considered, there was a significant inverse correlation between fasting SMLPL and fasting insulin concentration ($N = 26$, $r = -.598$, $P = .001$). Despite the relationship with fasting insulin, there was no correlation between fasting SMLPL activity and the level of glycohemoglobin measured in obese NIDDM subjects. (Glycohemoglobin levels were not measured for subjects in the two nondiabetic control groups.) When subjects in all three groups were considered together as a continuum of insulin sensitivity, there was a strong correlation between fasting SMLPL and GIR ($r = .658, P = .0003, N = 26$; Fig 2).

SMLPL activity decreased from basal in response to a 6-hour insulin/glucose infusion in NWC ($P = .023$, data previously reported[4]), whereas in OBC, SMLPL was significantly increased at the 6-hour terminus of the infusion as compared with basal ($P = .001$) (Fig 1). In contrast, in the obese NIDDM group, SMLPL was unchanged after 6 hours of insulin/glucose infusion. The change in SMLPL with insulin/glucose infusion was significantly different in OBC (mean increase) versus NWC (mean decrease; $P < .001$). The lack of change in SMLPL activity seen in the NIDDM group after 6 hours of insulin/glucose was different from the decrease seen in SMLPL in NWC ($P = .002$). However, there was no difference in ΔSMLPL between OBC and obese NIDDM subjects.

The only variable measured that was found to relate to ΔSMLPL was BMI. In OBC, the relationship between the two variables was positive ($r = .591$, $P = .034$). Moreover, when NWC and OBC were combined, the correlation was even stronger ($r = .816$, $P = .0001$). When obese NIDDM subjects were considered alone, there was no relationship between ΔSMLPL and BMI, nor was one seen in NWC.

DISCUSSION

Decreased LPL activity in adipose tissue has been repeatedly identified in fasted human subjects with NIDDM.[14-17] However, few studies to date have also examined the effect of NIDDM on SMLPL, and then only in the fasted state. Taskinen et al[18] reported that in both men and women with NIDDM, the fasting activity of HR-SMLPL was similar to that measured in nondiabetic subjects. In a study of obese NIDDM subjects before, during, and 3 months after weight reduction, Vessby et al[15] showed that fasting HR-SMLPL decreased during weight loss. After maintenance of the weight-reduced state, enzyme activities returned to baseline. Data from nondiabetic controls were not included in the study. Most recently, Pollare et al[19]

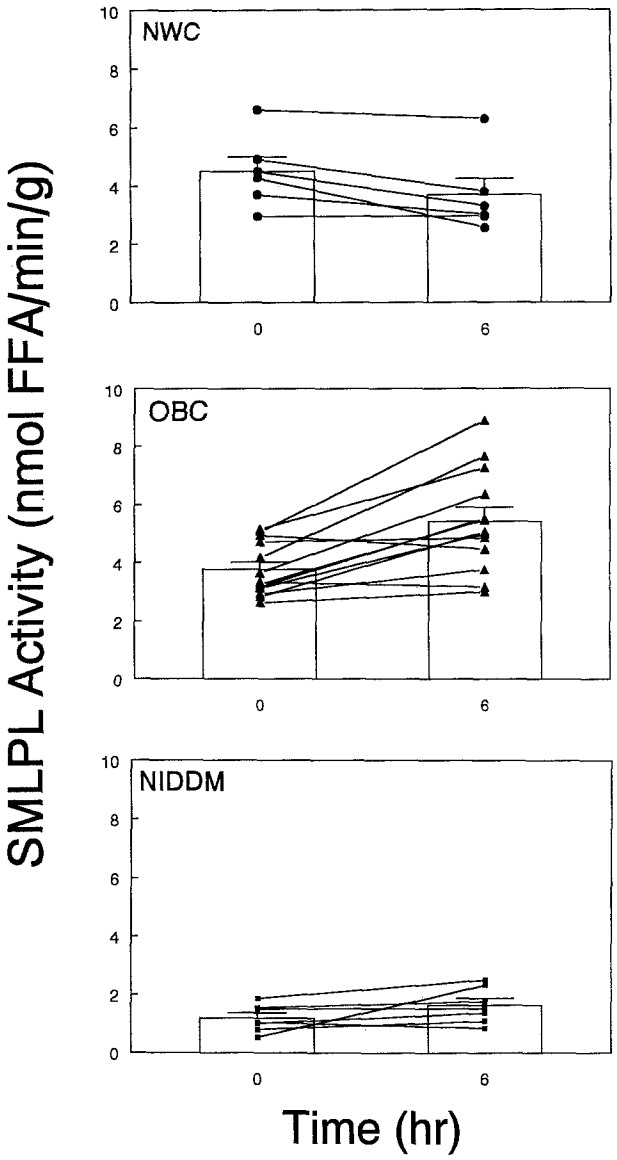

Fig 1. SMLPL activity measured at time 0 (fasting) and at the 6-hour terminus of an insulin/glucose infusion in 6 NWC, 13 OBC, and 7 obese NIDDM subjects. As shown by the bar graphs representing time 0, the activity of SMLPL in the fasted state in NWC was similar to that in OBC (4.5 ± 0.5 *v* 3.8 ± 0.3 nmol FFA/min/g, P = NS) but significantly greater than in the obese NIDDM group (4.5 ± 0.5 *v* 1.2 ± 0.2, $P < .001$). At time 0, OBC also had SMLPL levels that were significantly greater than in the NIDDM group ($P < .001$). In NWC, there was a significant decrease in SMLPL after 6 hours of insulin/glucose (ΔSMLPL = −0.8 ± 0.3 nmol FFA/min/g, $P = .023$), whereas OBC exhibited a significant increase in SMLPL (Δ = 1.7 ± 0.4, $P = .001$). In contrast, there was little or no change in SMLPL after 6 hours of insulin/glucose in NIDDM subjects (Δ = 0.3 ± 0.1, P = NS). When multiple group comparisons were made for the change in SMLPL activity in response to insulin/glucose, NWC differed from OBC ($P < .001$) and obese NIDDM subjects ($P = .002$).

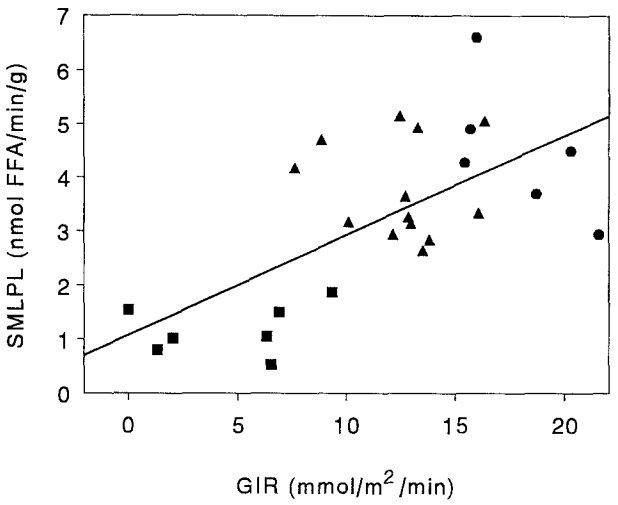

Fig 2. SMLPL measured in the fasted state *v* GIR over the last 60 minutes of insulin/glucose euglycemic clamp in 3 groups combined (N = 26, *r* = .658, *P* = .0003). (■) NIDDM; (▲) OBC; (●) NWC.

found that fasting HR-SMLPL activity was not lower in untreated NIDDM subjects than in OBC. In contrast, the data presented here indicate that SMLPL activity measured in the fasted state is much lower in treated obese NIDDM subjects than in OBC of similar weight or NWC.

The seven obese NIDDM subjects included in this study were believed to be representative of the most "usual" clinical picture of this form of diabetes mellitus, ie, middle-aged adults who are overweight, mildly hypertriglyceridemic, and moderately hyperglycemic and hyperinsulinemic. The modest level of hypertriglyceridemia (211 ± 33 mg/dL; range, 114 to 369) in this group is a common component of the clinical pathology of NIDDM. The modest degree of hypertriglyceridemia has not been shown to have an impact on SMLPL nor on its regulation in fasted subjects. The NIDDM group was 9 years older than the OBC; however, this difference has no proven impact on SMLPL or its regulation by insulin/glucose, or other perturbations such as exercise or feeding. Overall, there is no evidence that triglyceride levels or age contributed to the results.

In the study reported by Taskinen et al,[18] when NIDDM subjects were divided into less hyperglycemic (fasting serum glucose < 7.0 mmol/L) and more hyperglycemic (> 7.0 mmol/L) groups, SMLPL was 34% lower in the more hyperglycemic subjects. Although we found no relationship between fasting SMLPL and the level of glycohemoglobin or fasting serum glucose in NIDDM subjects in our study, there was a significant inverse correlation between SMLPL and fasting serum insulin concentration. Because NIDDM subjects were not insulin-treated, this suggests that the fasting level of SMLPL in NIDDM is in part determined by insulin sensitivity.

It was therefore not surprising in the overall study population that SMLPL in fasted subjects (N = 26) correlated with GIR. Pollare et al[19] found such a relationship across four groups of subjects with varying degrees of insulin sensitivity/insulin resistance. They also found an inverse correlation between SMLPL and fasting insulin concentration in their combined study population, supportive of the similar significant correlation for the N of 26 reported here. Interestingly, Lithell et al[20] also reported an inverse correlation between fasting SMLPL and fasting serum insulin concentration, but in glucose-tolerant 48-year-old men. Overall, these data would seem to support the hypothesis that muscle lipase in the fasted state is impacted strongly by factors related to overall glucose metabolism.

This is the first study to examine the impact of obesity with concomitant NIDDM on the metabolic change in SMLPL activity in response to an insulin/glucose infusion. Because humans spend the majority of their existence in the postprandial state, we believe that the change in LPL activity in response to metabolic stimuli is more important in fuel partitioning than the level of the enzyme measured in the fasted state. In the study presented here, the change in SMLPL activity in response to insulin/glucose in obese subjects with NIDDM was intermediate between that seen in NWC (in whom SMLPL activity decreased) and OBC (in whom SMLPL activity increased). It has previously been shown that medically uncomplicated obesity is associated with an increase in SMLPL in response to insulin/glucose, a change that is in the opposite direction from that seen in NWC.[5,6] Because of the documented increase in SMLPL in response to insulin/glucose in OBC, it was predicted that obese subjects with the additional insulin resistance of NIDDM might exhibit an even greater increase in the muscle enzyme in response to an insulin/glucose infusion. However, despite more insulin resistance, the change in SMLPL in response to insulin/glucose in obese NIDDM subjects was actually blunted as compared with that measured in OBC. This suggests that in NIDDM, insulin resistance is less important in predicting the SMLPL response to insulin/glucose; other factors must therefore be involved.

Because SMLPL is only one pathway by which the fatty acid fuel requirements of skeletal muscle can be met, perhaps the differences in the response of SMLPL to insulin/glucose in obese NIDDM subjects and OBC relate to changes in FFA metabolism. Groop et al[21] used the euglycemic clamp technique to show that NIDDM was associated with impaired maximal suppression of plasma FFA and rates of FFA turnover. The increased lipolytic rates in NIDDM subjects as compared with OBC and NWC may mean that much of the fatty acid fuel requirements of the muscle are being met by FFA rather than by lipoprotein-derived fatty acids. However, in OBC the oxidative fuel needs of the muscle might not be adequately met by FFA. Therefore, an insulin/glucose-mediated increase in SMLPL could be important.

In summary, SMLPL in fasted obese NIDDM subjects is reduced, an abnormality related to fasting insulinemia. When subjects in all three groups were considered together, GIR (as a continuous variable) was found to be related to the level of SMLPL measured in the fasted state. In OBC SMLPL activity increased after 6 hours of insulin/glucose, but in the obese NIDDM group the change in

SMLPL in response to a 6-hour insulin/glucose infusion was blunted. Although insulin action seems to be important in determining the level of SMLPL activity measured in the fasted state in human subjects, it is not the major contributor to the change in SMLPL activity that occurs in response to a 6-hour insulin/glucose infusion in obese subjects with NIDDM.

ACKNOWLEDGMENT

We would like to thank the nurses, laboratory technicians, and dietary personnel of the GCRC at the University of Colorado Health Sciences Center for their valuable assistance in performing this protocol. Computation assistance was provided by the DEC/Ultrix computer system (Digital Equipment Corp, Maynard, MA) funded under the GCRC grant.

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