The Response of Plasma Triglyceride, Cholesterol, and Lipoprotein Lipase to Treatment in Non-insulin-dependent Diabetic Subjects Without Familial Hypertriglyceridemia

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SUMMARY

The effects of treatment on plasma total triglyceride, total cholesterol, and plasma postheparin lipase activities have not been evaluated in non-insulin-dependent diabetic (NIDD) subjects without a coexisting familial lipid disorder. In 49 untreated NIDD subjects, there was a linear relationship between glycosylated hemoglobin (GHb) and triglyceride ($r = 0.35$, $P < 0.02$). This correlation was improved after adjusting for the effects of obesity by a partial correlation analysis. After therapy, there was a significant relationship between the change in GHb and the change in triglyceride.

To determine whether changes in lipid removal from plasma may contribute to the decrease in plasma lipid concentrations during treatment, the plasma postheparin lipoprotein lipase and hepatic lipase activities were evaluated in a subgroup ($N = 8$) of these NIDD subjects before and after 1 and 3 mo of therapy. Plasma postheparin hepatic lipase activity in the NIDD subjects was not different from that observed in six normal control subjects and did not change during therapy. In contrast, plasma postheparin lipoprotein lipase activity was lower in the untreated NIDD subjects than in the control subjects. Analysis of the two phases (early and late) of the postheparin lipoprotein lipase activity in plasma showed that the abnormal early phase in untreated NIDD corrected to normal values in less than a month, but the late phase was not corrected until the 3-mo measurement. These findings suggest that some NIDD subjects have a defect in heparin releasable lipoprotein lipase activity, which is reversed with improved glycemic control. This defect in lipoprotein lipase could contribute to the elevation in plasma triglyceride concentration by limiting triglyceride removal from plasma. DIABETES 32:525–531, June 1983.

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Plasma triglyceride concentration is elevated in both non-insulin-dependent diabetic (NIDD) and insulin-dependent diabetic (IDD) subjects.[1–7] Both decreased triglyceride removal and/or increased triglyceride production have been incriminated in the etiology of elevated triglyceride concentration in subjects with diabetes mellitus.[8–10] In untreated IDD subjects with or without familial hypertriglyceridemia, there is a decrease in both triglyceride removal and a total plasma postheparin plasma lipolytic activity.[4,6,11,12] Similarly, in untreated symptomatic NIDD subjects who also have a familial type of hypertriglyceridemia, there is a decrease in triglyceride removal associated with abnormalities in lipoprotein lipase (LPL) activity.[13] However, in NIDD subjects without a concomitant familial hypertriglyceridemia, it is not clear whether or not plasma postheparin lipolytic activity is decreased or normal.[4]

With inititation of antihyperglycemic therapy, there is a decrease in plasma triglyceride concentration in both IDD[6,7,14] and NIDD subjects.[1,15] In addition, antihyperglycemic therapy improves total plasma postheparin lipolytic activity in IDD subjects with or without familial hypertriglyceridemia[4,6,11,12] and NIDD subjects with familial hypertriglyceridemia.[13] However, the effect of antihyperglycemic therapy on plasma postheparin lipolytic activity has not been evaluated in NIDD subjects without familial hypertriglyceridemia.

METHODS AND MATERIALS

Subjects. Forty-nine non-insulin-dependent diabetic subjects (NIDD) were included in these studies; 46 were male and 3 were postmenopausal females who were not on estrogen therapy. None of these subjects had evidence of a familial lipid disorder. The method of evaluating the family pedigree has been previously described.[12,16,17] None of the subjects had ever been treated for diabetes for the preceding 84 mo. With the exception of one subject who was on a fixed dose of aspirin for arthritis, none of the patients were

on any medications at the time of the studies. None had clinical evidence of thyroid disease, ethanol abuse, or evidence of diabetic nephropathy.

Six normal adult male subjects were also studied. Their physical and biochemical characteristics are shown in Table 3.

Procedures. All studies were performed after an overnight fast; no cigarette smoking was allowed on the day of the studies. All subjects were eating an ad libitum diet prior to and during the studies. Subjects were instructed to withhold their morning dose of insulin, placebo, or sulfonylurea until after the studies were completed.

All 49 untreated NIDD subjects were evaluated before any antihyperglycemic therapy. Eight of these subjects were not evaluated again. Twelve of the remaining 41 NIDD subjects were treated with variable dose conventional insulin therapy. Twenty-two of the subjects were treated with variable-dose sulfonylurea therapy (chlorpropamide N = 17, tolbutamide N = 5). Seven of the subjects were placed on a placebo. Twenty-nine (insulin N = 12, sulfonylurea N = 12, placebo N = 5) subjects were evaluated after 1 mo of treatment, and all 41 NIDD subjects were reevaluated after 3 mo of treatment. On each occasion, the subject was weighed and venous blood was obtained for measurement of plasma glucose, triglyceride, cholesterol, and glycosylated hemoglobin.

Six normal individuals and eight diabetic subjects had plasma postheparin lipoprotein lipase and hepatic lipase activity measured. The eight diabetic subjects were studied while untreated and after 1 and 3 mo of therapy with either insulin (N = 4) or sulfonylureas (N = 4). One subject was not studied after 1 mo of therapy, but was restudied after 3 mo of therapy. Heparin was administered to produce maximal response in total plasma postheparin lipolytic activity.[12] Since there is evidence of two phases of release of total plasma postheparin lipolytic activity,[12,18] an early phase (mean of the 10-, 30-, and 60-min values) and a late phase (mean of the 210- and 240-min values) was calculated for each subject for analysis of the data.

Analytical methods. Plasma glucose was determined with the AutoAnalyzer glucose oxidase method (Technicon Instrument Corp., Tarrytown, New York). Total glycosylated hemoglobin was determined by either the column method[19] or by the colorimetric method.[20] Total plasma triglyceride and cholesterol concentrations were determined by the Lipid Research Clinic techniques.[21]

Plasma postheparin lipoprotein lipase and hepatic lipase activities were determined by a modification of previously reported assays.[4,18,22] The antibody to human plasma postheparin hepatic lipase was kindly provided by Drs. J. Huttunen, C. Ehnholm, and E. Nikkilä of Helsinki, Finland. All samples from a particular subject were measured in a single assay.

Statistical analyses used included Student's paired *t* test and nonpaired *t* test, covariance of analysis with regression, and partial correlation coefficient analysis.

RESULTS

Effects of antihyperglycemic treatment. Table 1 summarizes the effect of treatment in the insulin, sulfonylurea, and placebo-treated groups of NIDD subjects. Comparisons be-

TABLE 1
Physical and biochemical characteristics of NIDD subjects

	N	Age (yr)	Duration (mo)	Percent of ideal body weight		Fasting plasma glucose (mg/dl)		Glycosylated hemoglobin (% total Hb)		Fasting plasma triglyceride (mg/dl)		Fasting plasma cholesterol (mg/dl)	
				UNR_x	3 mo	UNR_x	3 mo	UNR_x	3 mo	UNR_x	3 mo	UNR_x	3 mo
All treated NIDDs	34	53 ± 2	34 ± 6	126 ± 4	131 ± 4*	245 ± 11	168 ± 9*	14.0 ± 0.5	11.4 ± 0.4*	212 ± 28	139 ± 16†	217 ± 10	197 ± 6§
Insulin-treated	12	43 ± 4	30 ± 10	111 ± 6	119 ± 5†	274 ± 17	199 ± 20†	15.7 ± 1.1	13.2 ± 0.9	169 ± 58	94 ± 15	228 ± 24	197 ± 8
Sulfonylurea-treated	22	59 ± 1	36 ± 8	134 ± 5	138 ± 5‡	229 ± 13	150 ± 6*	13.1 ± 0.5	10.3 ± 0.3*	235 ± 29	163 ± 21*	211 ± 8	198 ± 8§
Placebo-treated NIDDs	7	57 ± 2	43 ± 17	135 ± 11	135 ± 10	214 ± 22	226 ± 28	12.3 ± 1.0	12.1 ± 1.0	167 ± 23	154 ± 19	220 ± 23	224 ± 18
Untreated NIDDs	8	54 ± 4	49 ± 18	132 ± 13		217 ± 24		12.3 ± 1.0		200 ± 86		206 ± 26	
All NIDDs before treatment	49	54 ± 2	38 ± 6	128 ± 4		236 ± 9		13.5 ± 0.4		204 ± 24		216 ± 8	

All values are $\bar{X}$ ± SEM. Abbreviations: UNR_x = untreated; 3 mo = 3 months of treatment; NIDD = non-insulin-dependent diabetic.
*$P < 0.001$ UNR_x versus 3 mo.
†$P < 0.005$ UNR_x versus 3 mo.
‡$P < 0.01$ UNR_x versus 3 mo.
§$P < 0.05$ UNR_x versus 3 mo.

tween the insulin and sulfonylurea-treated patients were not made since the physical and biochemical characteristics of the patient determined the mode of treatment.

After 1 mo of therapy, 29 of the NIDD subjects were re-evaluated. The NIDD subjects treated with either insulin or sulfonylurea had a decrease in both fasting plasma glucose (FPG) concentration ($\Delta = -43 \pm 12$ mg/dl, $P < 0.002$) and glycosylated hemoglobin (GHb; $\Delta = -1.8 \pm 0.4\%$, $P < 0.001$). Despite an increase in percent ideal body weight (%IBW; $\Delta = +3 \pm 1\%$, $P < 0.005$), there was a significant decrease in fasting plasma triglyceride concentration for the group of treated patients ($\Delta = -65 \pm 32$ mg/dl, $P < 0.05$). Fasting plasma cholesterol also decreased ($\Delta = -20 \pm 11$ mg/dl), but this fall was not statistically significant. In contrast to these results, the subjects who received placebo (N = 5) did not have a significant change in FPG ($\Delta = -13 \pm 9$ mg/dl), GHb ($\Delta = -0.8 \pm 0.4\%$), %IBW ($\Delta = 0 \pm 2\%$), fasting plasma triglyceride ($\Delta = -20 \pm 16$ mg/dl) or cholesterol concentration ($\Delta = -3 \pm 19$ mg/dl).

After 3 mo of therapy, 41 NIDD subjects were evaluated (Table 1). The NIDD subjects treated with either insulin or sulfonylureas had a decrease in FPG and GHb (both $P < 0.001$). Despite significant weight gain, there was still a decrease in both fasting plasma triglyceride ($P < 0.005$) and cholesterol concentration ($P < 0.05$). In contrast, subjects who received placebo (N = 7) demonstrated no significant change in any of the measurements (Table 1).

In 49 untreated NIDD subjects, there was a significant linear relationship between the degree of hyperglycemia and triglyceride and cholesterol concentrations (Table 2). There was also a significant relationship between %IBW and triglyceride and cholesterol concentrations. The relationship between the degree of hyperglycemia and triglyceride and cholesterol level improved after adjustment for the effects of obesity. Thus, those untreated NIDD subjects with the highest GHb and FPG levels had the highest plasma triglyceride and cholesterol concentrations, particularly after the effects of obesity were eliminated.

Twenty-nine patients were evaluated before and after 1 mo of treatment with insulin, sulfonylureas, or placebo; and a total of 41 subjects were evaluated before and after 3 mo of therapy. Since a significant linear relationship between the untreated measurement and the change in the measurement after 3 mo of therapy could be demonstrated in the 34 subjects that were treated with insulin or sulfonylureas for GHb ($r = -0.67$, $P < 0.001$), fasting plasma triglyceride ($r = -0.83$, $P < 0.001$) and fasting plasma cholesterol ($r = -0.79$, $P < 0.001$) both absolute change and percent change from baseline were considered. A significant linear relationship was demonstrated between the change from untreated values of GHb and the change both of triglyceride and of cholesterol concentration. These relationships were maintained after the effects of a change in %IBW was eliminated by partial correlation analysis and when percentages were used (Table 2). Figure 1 shows the relationship between the percentage of changes of GHb and both triglyceride and cholesterol concentrations. Thus, the subjects with the greatest glycemic response to treatment also had the greatest

TABLE 2
Correlation coefficient for the relationships between physical and biochemical parameters and plasma lipid levels before and after antihyperglycemic therapy

	Triglyceride		Cholesterol	
	Unadjusted value	Adjusted* for %IBW	Unadjusted value	Adjusted* for %IBW
Untreated NIDD (N = 49)				
GHb	0.35§	0.42#	0.45¶	0.51¶
FPG	0.32‖	0.36§	0.34§	0.36§
%IBW	0.36§	—	0.28‖	—
Change from 0 to 1 mo of therapy (N = 29)				
Δ GHb†	0.59¶	0.56#	0.73¶	0.72¶
%Δ GHb‡	0.43‖	0.43‖	0.50**	0.49**
Change from 0 to 3 mo of therapy (N = 41)				
ΔGHb†	0.60¶	0.57¶	0.68¶	0.66¶
%Δ GHb‡	0.66¶	0.66¶	0.54¶	0.52¶
Change from 1 to 3 mo of therapy (N = 29)				
ΔGHb†	0.31	0.33	0.59¶	0.59¶
%Δ GHb‡	0.41‖	0.40‖	0.53#	0.54#

Abbreviations: NIDD = non-insulin-dependent diabetics; GHb = glycosylated hemoglobin; FPG = fasting plasma glucose; %IBW = percentage of ideal body weight.
*Adjusted by partial correlation analysis.
†Δ GHb versus Δ triglyceride or Δ cholesterol.
‡%Δ GHb versus %Δ triglyceride or %Δ cholesterol.
§$P < 0.02$.
‖$P < 0.05$.
¶$P < 0.001$.
#$P < 0.005$.
**$P < 0.01$.

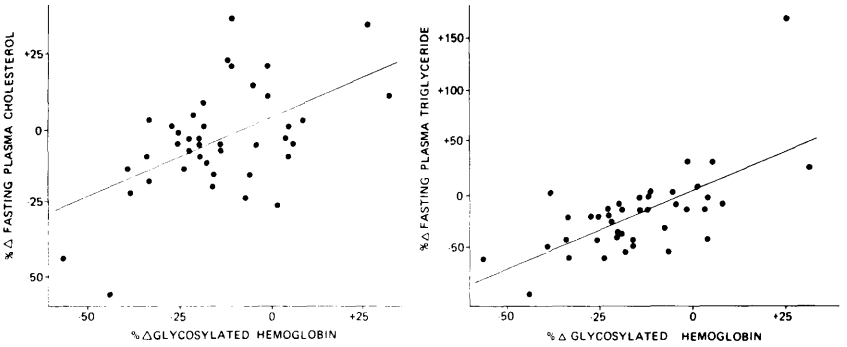

FIGURE 1. Relationships between percent change in glycosylated hemoglobin (GHb) and percent change in plasma cholesterol (left panel) and triglyceride concentrations (right panel) after 3 mo of treatment with insulin (N = 12), sulfonylureas (N = 22), or placebo (N = 7). There was a significant linear relationship between the percent change in GHb and both percent change in plasma cholesterol (r = 0.54, P < 0.001) and percent change in plasma triglyceride (r = 0.66, P < 0.001).

decrease in plasma lipids. A change in glycemic control even after treatment had begun was associated with a further change in plasma triglyceride and cholesterol.

Plasma postheparin lipoprotein lipase and hepatic lipase activity. Figure 2 shows that in the control subjects the release of lipoprotein lipase activity (LPLA) peaked in the first phase and reached a plateau during the second phase of the heparin infusion as has been previously noted.[12,18] There was no relationship between relative body weight or age and either the first or second phase of LPL activity in the control subjects, confirming other studies.[4]

Both the first phase of LPLA and the second phase of activity were decreased in the untreated subjects with NIDD (both $P < 0.05$, Table 3). Following 1 mo of treatment for hyperglycemia in these NIDD subjects, the first phase of LPLA increased ($P < 0.02$; Table 3, Figure 3) and was similar to the control subjects. No further increase was noted after 3 mo of therapy. However, after 1 mo of therapy, there was no change in the late phase of LPL activity (Table 3, Figure 3), and it remained lower than in the normal subjects ($P < 0.05$). After 3 mo of therapy the late-phase LPL activity was increased ($P < 0.05$) and was similar to levels seen in the control subjects.

The concentration of GHb was not related to either the first or second phase of LPL activity in the untreated NIDD subjects. However, the decrease in GHb at 1 mo of therapy correlated with the increase in first phase LPL activity ($r = 0.88$, $P < 0.01$), but did not correlate significantly with the increase in second phase ($r = 0.61$, P = NS). The decrease in GHb at 3 mo correlated with the change in second phase LPL activity ($r = 0.94$, $P < 0.005$), but not the change in first phase ($r = 0.41$, P = NS). These correlations were performed after exclusion of one "outlier" subject who had a marked decrease in GHb both at 1 and 3 mo of therapy.

In the untreated diabetics, neither the early- nor the late-phase plasma postheparin hepatic lipase activities were less than those of the normal subjects and neither of these phases changed with therapy (Table 3).

DISCUSSION

These studies demonstrate a decrease in plasma triglyceride and cholesterol concentrations in untreated NIDD subjects without a familial lipid disorder after treatment with insulin or oral sulfonylureas and supports previous findings.[1,15] The present studies also demonstrate a relation between glycemia (GHb) and triglyceride and cholesterol concentrations in untreated NIDD patients. This has previously been reported in patients with IDD[23–29] and in a mixture of patients with IDD and NIDD.[30,31] Uniquely, this study demonstrates that the decrease in plasma triglyceride and cholesterol correlates with the magnitude of the change in glycosylated hemoglobin. Thus, the greater the initial hyperglycemia and the larger the change with therapy, the greater the fall in plasma triglyceride and cholesterol concentrations with antihyperglycemic therapy.

Plasma postheparin LPL but not hepatic lipase activities were decreased in the untreated subjects throughout the duration of the heparin infusion. Although Nikkilä et al.[4] demonstrated a decrease in first phase plasma LPL activity in untreated NIDD with hypertriglyceridemia and a similar degree of fasting hyperglycemia, some of his subjects may have had an independent familial form of hypertriglyceridemia.[16] This present study clearly shows that LPL activity is decreased in untreated NIDD subjects without familial hypertriglyceridemia.

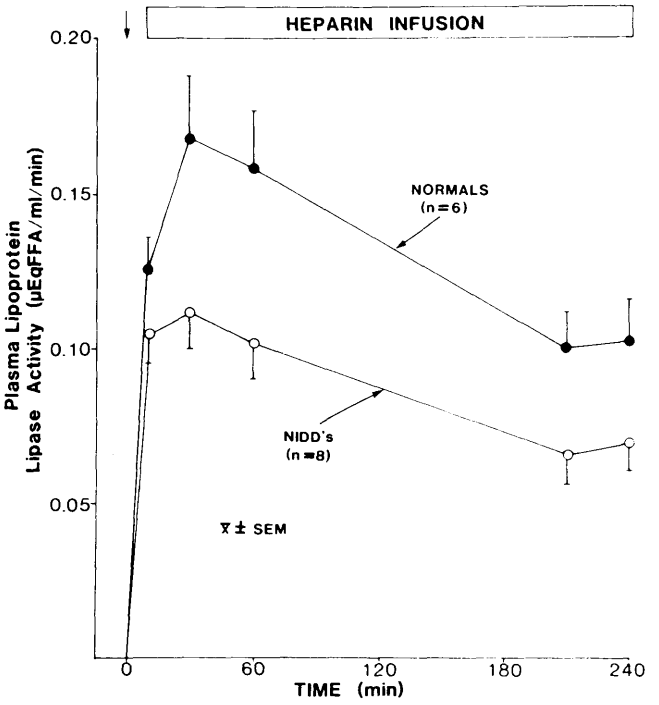

FIGURE 2. Plasma post-heparin lipoprotein lipase activity in normals (N = 6) and untreated non-insulin-dependent diabetic subjects (N = 8). A heparin pulse of 2280 U/m² was administered at time zero (↓). A 1986-U/m²/h i.v. infusion of heparin was begun 10 min after the pulse and continued for a total of 4 h.

TABLE 3
Lipoprotein and hepatic lipase activities in normals and NIDD before and during therapy

	Age	%IBW	GHb (%)	FP triglyceride (mg/dl)	Lipoprotein lipase activity		Hepatic lipase activity	
					Early phase* (μeq/ml/min)	Late phase† (μeq/ml/min)	Early phase* (μeq/ml/min)	Late phase† (μeq/ml/min)
Normal subjects (N = 6)	31 ± 4	106 ± 6	8.5 ± 0.2	76 ± 5	0.152 ± 0.016	0.102 ± 0.012	0.196 ± 0.026	0.163 ± 0.020
Diabetic subjects (N = 8)								
Untreated	51 ± 6‡	115 ± 9	13.8 ± 1.2‡	260 ± 83‖	0.107 ± 0.009‖	0.068 ± 0.010‖	0.221 ± 0.033	0.185 ± 0.024
1 mo of therapy	—	119 ± 8	11.3 ± 0.5‡§	151 ± 31‖§	0.142 ± 0.018¶	0.069 ± 0.009‖	0.225 ± 0.036	0.194 ± 0.030
3 mo of therapy	—	122 ± 8§	10.6 ± 0.6‡§	128 ± 34§	0.149 ± 0.019¶	0.090 ± 0.011§	0.201 ± 0.037	0.204 ± 0.040

All values are $\bar{X} \pm$ SEM. Abbreviations: %IBW = percentage of ideal body weight; GHb = glycosylated hemoglobin; FP triglyceride = fasting plasma triglyceride.
*Early phase = $\bar{x}$ of 10-, 30-, and 60-min value after the heparin pulse.
†Late phase = $\bar{x}$ of 210- and 240-min value after the heparin pulse.
‡$P < 0.02$ versus normal subjects, nonpaired *t* test.
§$P < 0.05$ versus untreated values, paired *t* test.
‖$P < 0.05$ versus normal subjects, nonpaired *t* test.
¶$P < 0.02$ versus untreated values, paired *t* test.

Following treatment with insulin or sulfonylurea, the magnitude of the change in GHb correlated with the improvement in first phase LPL activity. The second phase of LPL activity increased only after 3 mo of therapy, at which time the improvement in this LPL activity correlated with the decrease in GHb. Other studies have shown that plasma LPL activity is low also in untreated IDD subjects[4,6] and increases to normal with chronic therapy.[4,25]

One of the unique findings in the present study relates to the two phases of LPL activity. We have postulated that the first phase originates from muscle, while the second phase stems from adipose tissue.[16,18] This hypothesis was supported by the discovery of two subjects with primary chylomicronemia due to abnormalities in lipoprotein lipase.[18] One subject who had normal first-phase LPL activity and absent second phase had no adipose tissue LPL activity. The other who had absent first phase and the presence of a second phase had normal adipose tissue LPL activity. We suggest that further support for these tissue origins at these phases of activity comes from the duration of therapy (3 mo) required to correct the second phase of LPL activity and adipose tissue LPL activity in untreated NIDD subjects.[32] Since muscle LPL activity is improved in untreated insulin-dependent diabetics after 2 wk of treatment,[6] muscle may contribute to first phase LPL. The present study demonstrates that the duration of therapy required to normalize first phase LPL activity was less than 1 mo while it took longer to correct the second phase to normal levels of activity.

The changes in LPL activity seen in untreated diabetes may be physiologically important. Nikkilä et al. were able to demonstrate significant correlations between plasma first phase LPL activity and the fractional removal of Intralipid and the fractional catabolic rate of glycerol labeled very low density lipoprotein triglyceride.[4] Utilizing the heparin infusion technique for measurement of triglyceride turnover,[13] this laboratory was able to demonstrate significant relationships among the maximal removal capacity for plasma triglyceride, late-phase PHLA, and plasma glucose concentrations in untreated NIDD subjects. All these parameters corrected to normal after therapy. In nondiabetic subjects, adipose tissue LPL activity has been shown to determine the rate of VLDL fractional catabolism.[33] However, the kinetics of very-low-density lipoprotein catabolism were not measured in the present study.

We hypothesize that a decrease in triglyceride removal is present in that subset of untreated subjects who have decreased LPL activity. These could be the subjects who have not recently been on treatment and who have the highest hyperglycemia and/or the greatest degree of insulin deficiency. To support this hypothesis, simultaneous measurements of LPL and triglyceride turnover will be needed to be performed while at the same time considering the severity of the untreated diabetes mellitus.

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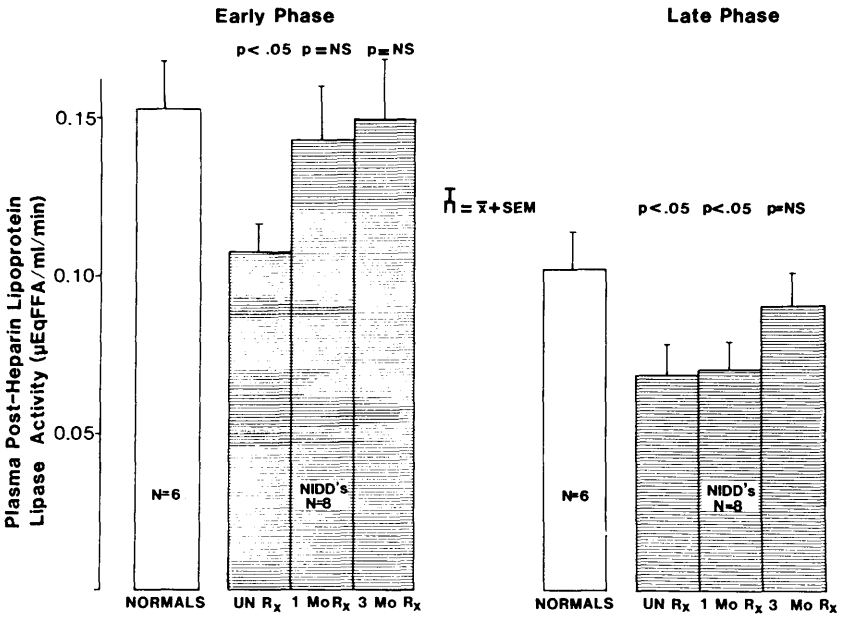

FIGURE 3. The early-phase (mean of 10-, 30-, and 60-min values, left panel) and late-phase (mean of 210- and 240-min values, right panel) of plasma postheparin lipoprotein lipase activity in normals and non-insulin-dependent diabetic (NIDD) subjects before and after 1–3 mo of anti-hyperglycemic therapy. Both the early and late phases were less in the untreated NIDD subjects than in normal subjects. The early-phase response returned to near-normal values after 1 mo of therapy and remained improved after 3 mo of therapy. Late-phase responses did not change after 1 mo of treatment, but improved to near-normal values after 3 mo of therapy.

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