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Research Article

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Characterization of Lipase Activities in Obese Pima Indians

DECREASES WITH WEIGHT REDUCTION

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ABSTRACT Adipose tissue and muscle lipoprotein lipase and postheparin hepatic and lipoprotein lipase activities have been measured in a group of 21 Pima Indian males over a wide range of body weight to determine the relationship between obesity and these lipase activities. There was a significant positive correlation between adipose tissue lipoprotein lipase and obesity; muscle and postheparin lipoprotein lipase and hepatic lipase were not related to degree of obesity. Fasting insulin levels were not related to any of the measurements of lipase activity. There were racial differences in adipose and postheparin lipoprotein lipase activities; both were significantly lower in the Pimas as compared with a group of weight-matched Caucasian males.

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INTRODUCTION

Lipoprotein lipase (LPL)[1] is a key enzyme involved in fat deposition. Human adipose tissue LPL activity has been shown to be related to obesity, since a significant correlation has been observed between adipose LPL per cell and relative body weight (1). Moreover, LPL appears to be affected by nutritional alterations (1, 2, 3–6), and several investigators have observed that, in contrast to obese rats (7), caloric restriction depresses human adipose tissue LPL activity (2–5). However, data on the response of adipose LPL to weight reduction followed by refeeding are contradictory. Schwartz and Brunzell (8) found that a group of previously obese men who had reached a stable reduced weight for at least 4 mo had adipose LPL activities much higher than those in a group of men of similar body weight who had not lost weight. They also observed that adipose tissue LPL activities after weight reduction followed by 1 wk of refeeding increased to levels several times those observed before weight reduction and suggested that adipose LPL is directly involved in the etiology of obesity (9). On the other hand, Guy-Grand (10) found a decrease in adipose LPL in patients who were on a low calorie diet; LPL increased after a normal diet was resumed but did not surpass the initial level.

We have studied a group of males over a wide range of weight to determine the relationship between obesity and several lipase activities, including adipose tissue and muscle LPL, postheparin plasma LPL, and hepatic lipase (HL). Subjects were chosen from the Pima Indians, a population that has a high prevalence of obesity (11) and, thus, provides a homogenous group in which to study the etiologic factors in human obesity. We further examined the behavior of these variables in eight Pima males after a period of weight loss including several weeks of stabilization at the reduced weight. Our results suggest that there are genetic differences in adipose LPL, and that elevated adipose LPL is not a primary determinant of obesity in this population.

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[1] *Abbreviations used in this paper*: HL, hepatic lipase; LPL, lipoprotein lipase; PDW, percent desirable weight; TG, triglycerides.

METHODS

Patients and study design. 22 male American Indians over a wide range of percentage of desirable weight (PDW) (12) were admitted to the metabolic ward of the Phoenix Clinical Research Center. Volunteers were full Indian and at least half-Pima or half-Papago (both Piman tribes), except for three: two of these were half-Indian (Piman) and the other was full Navajo. All volunteers underwent a 75-g oral glucose tolerance test, hemogram, and standard tests of renal, liver, and thyroid function, and were found to be within the normal range for this group. They were placed on a weight-maintaining diet composed of 45% carbohydrate, 35% fat, and 20% protein.

Weight-matched Caucasian male controls were selected from a larger group that had previously been evaluated on a similar diet at the metabolic ward of the Department of Medicine in Helsinki for tissue and plasma lipase activities (13). Seven Caucasian males from the Phoenix area and without known health problems were also admitted to the metabolic ward in Phoenix. The group of Caucasians from Phoenix were included in order to verify that the location of biopsy or mailing of the samples on dry ice had not caused major differences between our tissue specimens and those from Helsinki. All adipose and muscle tissue LPL, postheparin plasma LPL, and HL activities in this study were measured in the laboratories of the Third Department of Medicine, University of Helsinki. Determination of fat cell number was performed in Phoenix (Procedures).

Table I shows selected clinical characteristics of the Piman Indians and the weight-matched group of Caucasians from Helsinki. Fasting insulin levels were somewhat higher in the Piman group, and cholesterol levels were lower. Fasting and 2-h glucose values were lower in the Caucasian group.

Six subjects from the Piman cohort volunteered to undergo a period of weight reduction with repeat fat and muscle biopsies and heparin challenge after stabilization at the reduced weight. After base-line studies these six volunteers were placed on a 500-cal/d diet for 2–6 mo of the same composition (45% carbohydrate, 35% fat, and 20% protein) as the base-line diet and were given multiple vitamins. Two additional Pima males, who were not included in the cross-sectional study, underwent biopsies and heparin injection after weight reduction only. The weight reduction diet of these latter two patients consisted of 30% of the total calories required for weight maintenance and of the same composition. All subjects were refed for 2–8 wk at the end of the weight reduction period with a gradually increasing number of calories per day (beginning with 500–1,000 kcal/d with increments thereafter of 200–400 kcal/d whenever weight declined >0.5 kg), until caloric requirements were stable for 1–2 wk. Repeat studies were then performed. The total refeeding period usually required 4–6 wk.

TABLE I
Clinical Characteristics of Piman and Caucasian Groups

	Piman (n = 21)		Caucasian (n = 18)	
	Mean	Range	Mean	Range
Age	26.9	18–47	35.4	23–53
Weight, *kg*	125.9	71–192	120.7	80–181
PDW	182.7	116–287	167.7	122–238
Fasting glucose, *mg/dl*	93.0	73–109	78.5	61–94
2-H glucose, *mg/dl*	122.7	84–166	93	58–205
Fasting insulin, *μU/ml*	30.8	12–57	26.3	4–71
Plasma cholesterol, *mg/dl*	161.6	111–204	189	146–261
Plasma TG, *mg/dl*	133.4	72–222	124	65–162

Procedures. All studies were performed at 8:00 a.m. after an overnight fast (no calories after 8:00 p.m.), and no coffee or cigarettes were allowed on the mornings of procedures. Oral glucose tolerance was assessed after 75 g of glucose (Koladex, Custom Laboratories, Baltimore, MD) with plasma samples obtained for glucose and insulin determinations at −30, 0, 30, 60, 120, and 180 min. Subcutaneous adipose tissue (50–100 mg) was aspirated from the right gluteal region (after lidocaine anesthesia) with a 13-gauge aspiration needle and separated into three portions. Duplicate portions were frozen in liquid nitrogen and stored at −70°C to be mailed to Helsinki for assay of LPL activity; another portion was placed in sterile saline for osmium fixation and triglyceride determination. Muscle tissue (3–10 mg) was obtained from the right vastus lateralis with a Travenol Tru-Cut needle (Travenol Laboratory Inc., Deerfield, IL) after lidocaine anesthesia and cutaneous incision (No. 11 blade). At least 1 d after the tissue biopsies, heparin (Riker Laboratories Inc., Northridge, CA, 60 U/kg) was injected (bolus) intravenously, and blood (15 ml) was withdrawn 15 min later. Plasma was immediately separated and stored at −70°C for assay of postheparin plasma LPL and HL activities. All tissue and plasma samples for lipase activities were mailed to Helsinki on dry ice and remained frozen on arrival.

Analyses

LPL activity was measured from heparin eluates of tissue fragments using radiolabeled triolein emulsions as substrate (14). Tissue specimens were weighed, frozen, and allowed to thaw thereafter at 28°C in assay buffer. Control experiments verified that LPL activity from Pima cells resembled that from Caucasians in pH optimum, inhibition by 2 M NaCl, and stimulation by serum. Maximum elution of LPL by heparin was achieved at 10–20 mg/liter for cells from both racial groups. A heparin concentration of 50 mg/liter was used in the assay to ensure complete elution.

Postheparin plasma LPL and HL activities were measured by using an immunochemical method as described by Huttunen et al. (15). In this method, before the assay of LPL activity, HL activity was inactivated by a specific antiserum against HL. HL activity was measured at high-salt concentration that inactivates LPL activity in the samples.

Adipocyte number per gram of tissue was determined by the osmic acid-electronic counting procedure of Hirsch and Gallian (16). Glucose was measured by the ferricyanide method (17), and insulin by the Herbert modification (18) of the radioimmunoassay method of Berson and Yalow (19). Lipoproteins were isolated and cholesterol and triglyceride quantified as described previously (20). Statistical analysis was performed using the Statistical Analysis System (SAS, Cary, NC).

RESULTS

Lipase activities and obesity. Mean values for adipose tissue LPL activity per gram of tissue or per 10^6 cells (Table II) were significantly lower in the Piman group than in the Caucasians. The Phoenix Caucasian values, shown in Fig. 1, were well within the range shown for the Helsinki group, providing evidence that the racial difference observed was not a technical artifact. Postheparin LPL activity was also significantly lower in the Pimans, but skeletal muscle

TABLE II
LPL and HL Activities in Pimas and Caucasians

	Pima (n = 21)	Caucasian (n = 18)	P
	mean±SEM		
Adipose tissue LPL			
(*μmol/h/g*)	0.92±0.08	1.73±0.26	0.009
(*μmol/h/10⁶ cells*)	0.92±0.09	1.67±0.26	0.010
Muscle LPL			
(*μmol/h/g*)	0.72±0.09	0.75±0.12	NS
Postheparin LPL			
(*μmol/h/ml*)	18.1±0.94*	22.2±1.2	0.010
Postheparin HL			
(*μmol/h/ml*)	34.4±2.9*	36.02±3.8	NS

* Postheparin values not available for one subject.

LPL activity and HL activity were similar in the two groups (Table II).

The relationships between obesity and the various lipolytic activities in the Pimans are shown in Table III. Adipose LPL activity per gram of tissue was positively related to PDW but this relationship did not reach statistical significance. When adipose LPL was expressed per cell there was a significant correlation with PDW in the Piman group (Table III and Fig. 1, $r = 0.76$, $P = 0.001$) and in the Phoenix Caucasians (Fig. 1, $r = 0.98$, $P = 0.0005$). The relation between PDW and adipose LPL activity in the Helsinki Caucasians did not reach statistical significance; this has been previously observed in other studies of obese Caucasians when normal weight individuals were not included in the regression analysis (1, 2, 21, 26). The other lipase activities (postheparin LPL, muscle LPL, and HL) were not related to PDW (Table III).

Since fasting insulin levels were correlated with PDW ($r = 0.57$, $P = 0.008$, $n = 22$) in the Piman group, we examined the relationship between insulin and lipase activities (Table III). There was no relationship between fasting insulin and adipose LPL expressed per tissue weight or per fat cell, nor between fasting insulin and any of the other lipolytic activities. 2-h insulin values were not related to adipose LPL per cell ($r = 0.10$, NS) but were negatively correlated with muscle LPL values ($r = 0.59$, $P = 0.006$).

To examine whether postheparin LPL quantitatively reflected total tissue LPL, we examined the relation between postheparin LPL and tissue lipase activities (Table III). Postheparin LPL was not related to adipose LPL but showed a significantly positive cor-

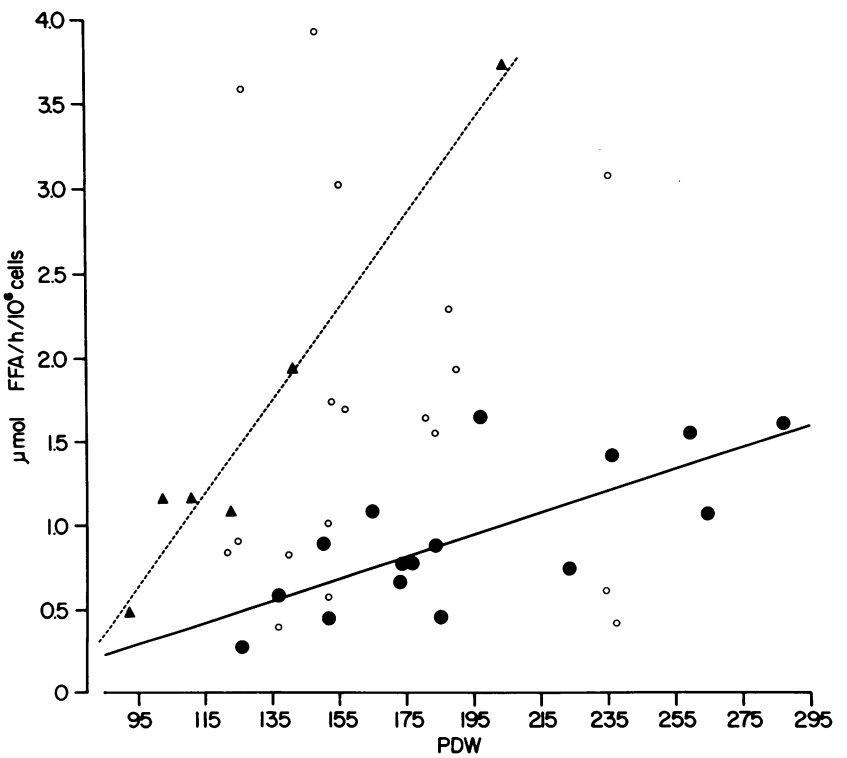

FIGURE 1 Relationship between adipose tissue LPL per cell and PDW. Phoenix Caucasians, (▲); Helsinki Caucasians, (○); Pimans, (●). Linear regression: $y = (0.00654) \times -0.329$ for Pimans and $y = (0.0277) \times -1.98$ for Phoenix Caucasians.

TABLE III
Relationships between Lipase Activities and Obesity in Pimas

	Adipose LPL		Muscle LPL	Postheparin LPL	Postheparin HL
	per cell	*per g*			
PDW	0.76*	0.35	−0.10	0.03	0.00
	0.001‡	NS	NS	NS	NS
	(15)§	(21)	(20)	(19)	(19)
Fasting insulin	0.23	0.12	−0.26	0.02	−0.05
	NS	NS	NS	NS	NS
	(15)	(20)	(19)	(19)	(19)
Postheparin LPL	−0.15	−0.19	0.48	1.0	0.39
	NS	NS	0.05	—	NS
	(14)	(19)	(18)	—	(19)

* Simple correlation coefficient (r).
‡ P.
§ Number of patients studied.

relation with muscle LPL. The relationships among lipase activities and lipoprotein levels in the Piman subjects were also examined. Very low density lipoprotein triglyceride (VLDL-TG) and high density lipoprotein cholesterol (HDL-C) were inversely correlated ($r = 0.64$, $P = 0.002$). VLDL-TG was not related to adipose LPL ($r = 0.08$, NS), but VLDL-TG was significantly related to hepatic lipase ($r = 0.68$, $P = 0.002$). There were no significant relations between lipase activities and HDL-C, although HDL-C was negatively related to HL ($r = 0.39$, $P = 0.10$).

Weight reduction. Table IV and Fig. 2 show the effects of weight reduction on the various lipolytic activities in the Pimans. The group lost an average of 27 kg per subject, and the average PDW decreased 39%. The two subjects who underwent weight reduction but had biopsies and heparin injections only after weight reduction decreased in weight from 168 to 141 kg (237 to 197% desirable weight) and from 112 to 98 kg (169 to 148% desirable weight) (Fig. 2A, open circles without arrows). Adipose LPL per gram decreased in four of the subjects, increased in one, and was unchanged in one after weight reduction. All five subjects in whom adipose cell number was available both before and after weight reduction demonstrated a decrease in adipose LPL per cell[2] (Table IV). The behavior of adipose LPL with weight reduction is further illustrated in Fig. 2 in which the regression lines calculated for the relationships between adipose LPL per gram (Fig. 2A) or LPL per cell (Fig. 2B) and PDW are superimposed. It is clear that the five subjects with values shown before and after weight loss demonstrated decreases in adipose LPL per cell with weight loss that essentially parallelled the regression line. Those additional subjects in whom adipose LPL per cell was calculated only after weight reduction clearly had postweight reduction values very close to the regression line.

Although there was a consistent reduction in adipose LPL, no consistent pattern was observed in the behavior of postheparin LPL or muscle LPL after weight reduction (Fig. 3B, C, and Table IV), however, HL was possibly affected by weight loss, since four of six subjects demonstrated decreases and two were essentially unchanged (Fig. 3D).

DISCUSSION

We have investigated adipose, muscle, and postheparin LPL activities in the Piman obese population during weight maintenance and after a period of weight reduction. The data showed a positive relationship between adipose LPL per cell and obesity in both the Piman Indians and in the group of Phoenix Caucasians. On the other hand, muscle LPL, postheparin LPL, and HL were not related to the degree of obesity in any group. There were differences between the two racial groups: adipose LPL as well as postheparin LPL were lower in the Pimans than in the Caucasians, whereas hepatic lipase and muscle LPL were quite similar in the two groups. After a period of weight reduction adipose LPL per cell and per gram declined in the Pimans; this decline appeared to follow the regression line for the relationship between adipose tissue LPL and PDW in this group. Muscle LPL and postheparin LPL were not affected by weight loss, although HL appeared to decline.

Adipose LPL was the only lipase activity related to obesity. Positive relationships have been observed previously between adipose LPL and body weight in studies that included normal weight subjects (1, 2). Although no previous study has examined all four lipase activities in obese subjects, postheparin lipolytic activity was not found to be related to obesity in obese Caucasians (13).

Relationships among the various lipase activities in obese groups seem to differ when compared with those in normal weight individuals. Postheparin LPL was modestly related to muscle LPL in the Pimans, as in obese Caucasians (13). Postheparin LPL was not related to adipose LPL; this also has been reported in other obese groups (13, 21). In contrast, postheparin LPL is strongly related to both muscle LPL and adipose LPL in lean subjects (13). It is possible that LPL activity present in postheparin plasma of obese subjects

[2] It is likely that in subject 4 (Table IV) the value for adipose LPL per cell after weight reduction represents a decrease since cell number per gram tissue would have had to decrease >60% in order for adipose LPL per cell not to have decreased.

TABLE IV

Effect of Weight Reduction on Adipose, Muscle, and HL Activities

Subject		Weight	PDW	Fasting insulin	Number of cells per tissue	Adipose LPL	Muscle LPL	Postheparin LPL	Postheparin HL
		kg	*%*	*μU/ml*	*mg*	*μmol FFA/h/g*		*μmol FFA/ml/h*	
1	Before	167	265	34	1,041	1.11	1.40	27.3	50.4
	After	124	195	9	1,528	1.40	NA*	19.7	29.5
2	Before	119	174	26	896	0.70	0.36	11.3	25.6
	After	102	149	17	1,445	0.74	0.34	17.3	27.5
3	Before	107	150	24	1,152	1.03	0.85	23.3	49.8
	After	103	145	10	1,512	0.55	0.87	17.6	41.3
4	Before	92	142	21	NA	1.17	0.47	19.3	52.0
	After	76	118	20	1,149	0.47	1.12	12.4	31.6
5	Before	192	287	44	749	1.20	0.58	15.3	39.4
	After	162	242	54	1,039	0.91	0.83	16.6	38.5
6	Before	186	259	57	872	1.36	NA	17.0	34.8
	After	137	193	20	620	0.39	0.22	17.8	22.8
Mean±SEM	Before	144±18	213±27	34±6	942±71	1.10±0.09	0.73±0.33	18.9±2.4	42.0±4.4
	After	117±13	174±19	22±16	1,215±148	0.74±0.16	0.68±0.17	16.9±1.0	31.9±2.9

* NA, not available.

may reflect tissue LPL pools in a different manner than in lean individuals, or that the distribution of LPL activity between intra- and extracellular fractions, particularly in fat tissue, may differ in obese and lean subjects. This possibility is supported by observations in rats showing that in large adipocytes more enzyme activity is located intracellularly than at the endothelium (22). Thus, it is possible that only a lim-

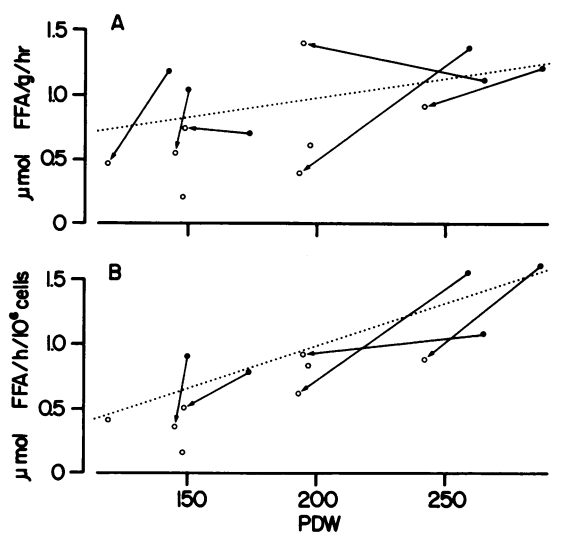

FIGURE 2 Response of adipose tissue LPL to weight reduction. The lines representing the relationships between adipose LPL per gram or LPL per 10^6 cells (Fig. 1) and PDW are superimposed on panels A and B, respectively. Subjects are shown before (●) and after (○) weight reduction. Values for two subjects in panel A and three subjects in panel B are shown only after weight reduction in unconnected open circles (Methods).

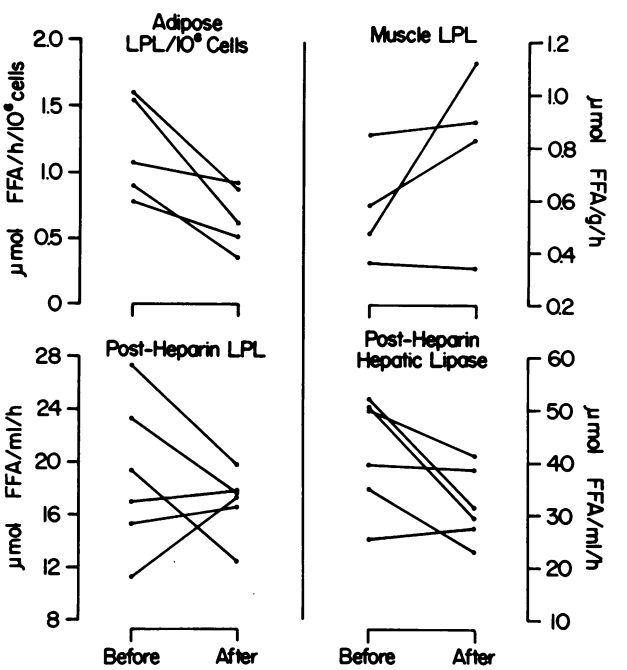

FIGURE 3 Comparisons of lipolytic activities before and after weight reduction.

ited amount of the LPL present in fat cells of obese individuals is accessible to the eluant effect of intravenous heparin in vivo.

A clear difference in the mean levels of adipose LPL and postheparin LPL activities was observed between the Piman and Caucasian obese populations. Furthermore, a third obese group, Prader-Willi patients, have levels of adipose LPL many-fold higher than those in comparable weight Caucasian controls (23). The marked difference in adipose LPL levels among these three groups (Prader-Willi $\gg$ Caucasian > Piman) is of great interest and raises the question of whether there are genetic differences among groups that determine LPL levels. One possibility is a varying sensitivity of adipose LPL to insulin and/or other hormones of importance in the regulation of LPL activity. Previous studies in the Pima Indians have suggested a higher degree of resistance to the glucoregulatory effects of insulin (24). Data presently available do not adequately elucidate whether or how insulin resistance might be related to LPL activities, although the response of adipose LPL to glucose infusion has been shown to be lower in obese subjects (5). Another possibility is that LPL activities may be regulated by availability of substrates (i.e., lipoprotein TG). VLDL levels have been shown to remain low in this population despite their obesity (25). Although the previous studies of VLDL-TG were not performed under fasting conditions similar to those in the present studies, it is possible that the low LPL may be a reflection of low VLDL concentrations. It must be emphasized that in Pimans as in all obese subjects actual removal capacity, or total adipose LPL, is high, because there is a much greater fat mass.

Fasting insulin levels were not related to adipose LPL levels in the Pimans or in the control Caucasian group. Positive correlations have been reported in other obese groups (2, 21). These findings, however, were based on the inclusion of lean individuals in the study groups; when only obese Caucasian subjects are examined, no relationship can be found (21, 26). The lack of correlation in obese subjects could be because of increased genetic heterogeneity in obese individuals, or because the elimination of the lean individuals results in a more limited distribution of insulin and LPL values. On the other hand, in obese subjects there may be defects in secretion and releasability of LPL, which obscure the observation of regulation by insulin. Stimulated (2-h postglucose) insulin levels were found to be inversely correlated with muscle LPL levels in the Pimans, consistent with the finding of Lithell et al. (27), however, no relationship was observed between adipose LPL and 2-h insulin levels. If insulin can influence both release and synthesis of LPL, then the lack of correlation of adipose LPL with insulin levels in obese groups would be consistent with the hypothesis that adipose LPL is influenced by the generalized insulin resistance that occurs in obesity.

Obese groups also show differences in relationships among lipase activities and lipoproteins. Although VLDL-TG and HDL-C were inversely related in the Pimas, there was no relationship between VLDL-TG or HDL-C and any of the LPL measurements. This was observed previously in other obese groups (13). HDL-C showed the expected (28) negative relationship with HL and, interestingly, VLDL-TG was positively related to this activity.

Weight reduction in the Pimans resulted in decreased adipose LPL. The results appear to vary with the findings of Schwartz and Brunzell (9), who found increased adipose LPL per cell after weight reduction. The differences may be a reflection of differences in study design. Adipose LPL is known to be increased after caloric loads (2, 5, 6), and composition of the diet may also influence LPL (2, 6). In the present study patients were maintained on 45% carbohydrate, 35% fat, 20% protein diet before, during, and after weight loss. They underwent a period of 2–8 wk of stabilization at their reduced weight before rebiopsy; this period of time was required for stabilization of the caloric requirements for weight maintenance during refeeding. The patients of Schwartz and Brunzell (9) were transferred from a nofat liquid formula during weight reduction to a 40% fat formula during refeeding for only 1 wk before rebiopsy. This may have produced a relatively overfed state and thus an increased adipose LPL in their patients at the time of rebiopsy. On the other hand, a second group (8) maintained elevated LPL several years after weight loss, indicating that this was not a transient phenomenon. We have recently studied a group of nonobese Caucasian females before and after weight loss.[3] Adipose tissue LPL activity decreased during caloric restriction; after caloric restriction it increased progressively up to the initial level. In the eight women, the average adipose LPL was 4.58 ± 1.16 μmol FFA $\cdot g^{-1} \cdot h^{-1}$ before, 0.81 ± 0.12 after 8 d on 400 kcal diet, 2.03 ± 0.26 after 10-d refeeding, and 4.58 ± 0.85 after 8 wk at stabilized reduced weight. Thus, it is possible that individuals may respond in several ways to weight loss: in some, obesity may be related to increased LPL (8, 9) and, therefore, LPL increases after weight loss; in others, as the Pimas, obesity may be attributable to other causes.

In conclusion the data showed that adipose and postheparin LPL were lower in obese Piman Indians than in obese Caucasians indicating that there are genetic differences in LPL activities. Furthermore, adipose LPL decreased after weight reduction. This implies that, in some groups of obese subjects, LPL activity

[3] Taskinen, M. R. Unpublished observations.

behaves like other metabolic abnormalities, such as increased fat cell size or number (29), increased plasma levels of trophic hormones (30), and increased plasma TG levels (31), which are observed in the obese state and return to normal upon weight reduction.

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