Evidence for Sex Steroid Inhibition of Lipoprotein Lipase in Men: Comparison of Abdominal and Femoral Adipose Tissue

Maria E. Ramirez, Martha P. McMurry, Gail A. Wiebke, Karon J. Felten, Kuishu Ren, A. Wayne Meikle, and Per-Henrik Iverius

Plasma estradiol has been suggested to suppress adipose tissue lipoprotein lipase (LPL) activity in women. The present study explores the regulation of LPL by sex steroids in sedentary obese men (N = 24) at their usual weight. Femoral adipose tissue LPL activity, eluted with serum and heparin or extracted with detergent, showed significant inverse correlations with plasma levels of testosterone, bioavailable testosterone, dihydrotestosterone, and estradiol. Both measures of femoral LPL activity were also correlated with the weight change occurring despite efforts to maintain a constant weight. Abdominal LPL activity showed significant but weaker inverse correlations with bioavailable testosterone only. Multivariate analysis of potential predictors for eluted femoral LPL activity showed that plasma testosterone, dihydrotestosterone, and estradiol were interdependent, whereas the rate of weight change was an independent variable. In the regression equation, only bioavailable testosterone and weight change were retained, explaining 63% of the variability ($R = .79$, $P = .0002$). These results suggest that sex steroids suppress adipose tissue LPL activity in men, and more so in the thigh than in the abdomen, thereby possibly contributing to a central fat accumulation. The data are compatible with a model from male animals suggesting that testosterone effects on adipose tissue LPL are mediated by estradiol formed locally.

OBESITY INCREASES the risk of hypertension, non–insulin-dependent diabetes mellitus, cardiovascular disease, and stroke.[1,2] It has become apparent that not only the degree of obesity but also the distribution of body fat influences these risk factors. Thus, central obesity with visceral fat accumulation, as most commonly seen in males, is more hazardous than the peripheral fat accumulation more often seen in women.[3-5]

The size of the adipose organ in a particular location is determined by the number of fat cells and their size. The latter results from the net balance of intracellular lipogenesis and lipolysis.[6] Much attention has been given to lipoprotein lipase (LPL), which supplies the adipocytes with free fatty acids for intracellular esterification by hydrolyzing triglyceride-rich lipoproteins in the circulation.[7] Because of the key role of LPL in adipocyte metabolism, it has been suggested that abnormal regulation of the enzyme may be a cause of obesity.[8]

Many features concerning the regulation of adipocyte differentiation, fat cell size, and thereby the size of the adipose organ are still obscure. This lack of understanding also applies to many aspects of adipose tissue distribution. Because the sexual dimorphism of nonreproductive tissues is generally ascribed to the action of sex steroids,[9] it is plausible that the difference in fat distribution between men and women has the same cause.

A previous study in obese women demonstrated strong negative correlations between plasma estradiol and fasting LPL activity in gluteal adipose tissue and postheparin plasma.[10] In obese men, abdominal and femoral LPL activity decreased 1 week after parenteral testosterone administration ($.1 > P > .05$). By contrast, an oral testosterone preparation administered four times daily for 6 weeks caused a significant suppression of abdominal but not femoral LPL activity.[11] In men with suspected coronary disease, a weak positive correlation between postheparin plasma LPL activity and endogenous testosterone, but not estradiol, concentration was observed.[12]

The present study was undertaken (1) to retrospectively define gender differences in the regulation of adipose tissue LPL by gonadal hormones, and (2) to determine regional differences in LPL regulation and their possible relationship to fat distribution. Estradiol appears to mediate sex steroid effects on adipose tissue LPL activity in both sexes, but the present results indicate that testosterone rather than estradiol is the most important plasma regulator in men. The data also suggest that abdominal LPL is less susceptible to suppression by sex steroids than femoral LPL.

SUBJECTS AND METHODS

Subjects

Sedentary male volunteers (N = 24) at their usual weight with a body mass index of 23.2 to 42.0 kg/m^2 (Table 1) were enrolled in the study as outpatients after informed consent had been obtained as approved by the Institutional Review Board at the University of Utah. The subjects were selected to cover a wide range of body mass indices from normal to markedly obese and thereby achieve a wider range of plasma testosterone levels when compared with a randomly selected population. The participants reported four times per week to the Clinical Research Center at the University Hospital for weighing and for collecting meals prepared in advance. The experimental diet was provided as an inducement and to maintain weight stability and a uniform meal pattern throughout the study. Basal daily energy requirements were calculated from the Food Nomogram,[14] and estimated total energy needs were determined individually by adding a 35% to 50% extra allowance for activity. The diet of 15% protein, 40% fat, and 45% carbohydrate (kilocalories per total kilocalories) was provided as three daily meals and snacks of carefully measured foods for a period of 2 weeks. The composition was chosen because this predominantly obese population

From the Department of Internal Medicine, Division of Endocrinology, Metabolism, and Diabetes, Division of Cardiology, and the Clinical Research Center, University of Utah, Salt Lake City; and the Veterans Affairs Medical Center, Salt Lake City, UT.

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Current address: M.E.R., Thera Tech Inc, 417 Wakara Way, Salt Lake City, UT 84108.

Address reprint requests to Per-Henrik Iverius, MD, PhD, Endocrinology Section (111E), Veterans Affairs Medical Center, 500 Foothill Blvd, Salt Lake City, UT 84148.

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was estimated to have a higher than average fat intake. Furthermore, a previous study in obese women was performed using a similar diet.[10] The subjects, dressed in a gown and with an empty bladder, were weighed before breakfast four times per week throughout the study. Food intake was adjusted during the first week of the study to obtain weight stability and was then maintained constant. All studies were performed during the second week. With the exception of two subjects taking fluoxetine, no other medications were allowed during the study.

Clinical Chemistry

At initiation of the study period, fasting blood samples were obtained for an automated chemical profile and assays of thyroxine and thyrotropin (TSH). All other samples were obtained in the morning during the second week. Plasma lipids were determined by a micromethod as previously described.[15] All sex steroid assays were performed by Endocrine Sciences (Calabasas Hills, CA).[16,17] Bioavailable (free) testosterone was determined after ammonium sulfate precipitation of protein-bound testosterone.

LPL Activity

LPL activity in postheparin plasma and adipose tissue was determined as described previously.[18,19] A skim-milk standard was used to correct for interassay variability, which has a coefficient of variation of 5.2%. However, the intraassay coefficient of variation for a skim-milk standard is only 1.2%.

Postheparin plasma LPL activity was calculated as the fraction of total lipase activity inhibited by 0.4 mg/mL assay mixture of a mouse monoclonal antibody (5D2) against LPL.[20] Fasting samples were obtained at 10, 30, and 60 minutes during a continuous heparin infusion that was initiated by a heparin bolus of 2,280 U/m^2 (~60 U/kg) as previously described.[21] Postprandial samples were obtained 2 days after the continuous infusion by injecting a heparin bolus 120 minutes after a liquid formula breakfast and sampling the plasma 10 minutes later.[10] The formula, which had the same macronutrient composition as the regular diet, supplied one third of the daily energy requirements. All specimens were frozen at −70°C until analyzed.

Adipose tissue biopsy specimens were obtained by needle aspiration from McBurney's point on the lower abdomen and from the anterolateral thigh. This procedure was performed 3 days after the postprandial study. Thus, ample time was allowed for recovery following the procedures involving intravenous heparin, since plasma LPL activity is usually at baseline within 6 hours after a bolus of heparin.[22] Before assay, extracellular enzyme was recovered from the tissue by elution with serum and heparin at 37°C, whereas total tissue LPL was obtained by extraction of a separate tissue sample with detergent.[18] LPL activity was normalized to wet tissue weight. Because the coefficients of variation for determination of eluted and total LPL activity were 19% and 8%, respectively, each assay was performed in quadruplicate.

Table 1. Anthropometric Measures and Laboratory Screening

Parameter	Range	Mean ± SD
Age (yr)	31-49	40.1 ± 5.5
Height (cm)	168-199	179.8 ± 7.5
Weight (kg)	72.3-138.0	104.3 ± 16.2
Body mass index (kg/m^2)	23.2-42.0	32.7 ± 5.1
Waist to hip ratio	0.78-1.15	0.98 ± 0.09
Weight change (g/d)*	−97.4-60.7	−32.3 ± 48.6
Glucose (mg/dL)†	67-119	89.0 ± 11.0
Thyroxine (μg/dL)‡	4.7-8.0	6.5 ± 0.8
TSH (μU/mL)‡	0.6-7.4	1.9 ± 1.4
Triglyceride (mg/dL)§	58-341	149 ± 71
Cholesterol (mg/dL)	144-262	195 ± 30

*The rate of daily weight change was taken as the slope of the linear regression of weight on time during 2 weeks on the prescribed diet.

†One subject had glucose intolerance (119 mg/dL).

‡One subject had mild hypothyroidism (thyroxine, 4.7 μg/dL; TSH, 7.4 μg/dL). The normal range for TSH is 0.4 to 4.5 μU/mL.

§One subject had hypertriglyceridemia (341 mg/dL) in the range above the 95th percentile for males in the age group.[13]

Data Analysis

Statistical analysis including descriptive statistics, comparison of means, testing for normality, correlations, and regressions was performed using SPSS/PC+ software (SPSS, Chicago, IL). All variables entered in parametric analyses fit a normal distribution as determined by the Kolmogorov-Smirnov test. Departure from linearity and differences between dependent R values were tested for statistical significance as described by Cohen and Cohen.[23] The SigmaPlot (version 4.04) scientific graph system (Jandel Scientific, San Rafael, CA) was used for production of graphs.

RESULTS

Characterization of the Study Population

Results of anthropometric measurements and laboratory screening are shown in Table 1. One subject each had mild hypothyroidism, glucose intolerance, and hypertriglyceridemia. However, there were no significant correlations between any measure of adipose tissue LPL activity and plasma thyroxine, TSH, glucose, or triglyceride levels, nor did deletion of these three subjects alter the correlation pattern between adipose tissue LPL and plasma sex steroid levels (data not shown). The data from two subjects who acknowledged using low-dose fluoxetine (20 mg/d) for depression after being admitted to the study were similar to those from the other subjects who were taking no medication. Measurements of LPL activity in adipose tissue and postheparin plasma and plasma sex steroid levels are summarized in Table 2.

Relationship Between LPL Activity and Rate of Weight Change

Because dietary compliance could not be monitored directly in outpatients, subjects were weighed eight times during 2 weeks using a metabolic scale and standardized conditions. The slope of the regression of weight on elapsed time showed a rate of weight change (Table 1) that was −32.8 ± 48.6 g/d (mean ± SD), with 18 subjects decreasing and six subjects increasing in weight during the study (data not shown). Figure 1 shows plots of femoral adipose tissue LPL activity eluted at 37°C and fasting 60-minute postheparin plasma activity versus rate of weight change. For both plots, parabolic regressions were significantly better than linear (Table 3). The fitted curves had minima at weight change rates of −41.5 and −21.3 g/d, respectively, which are close to the mean rate of −32.8 g/d for the group. Plots of the other parameters of fasting LPL activity in adipose tissue and postheparin plasma versus rate of weight change suggested similar relationships, but did not produce statistically significant regressions (data not shown). These results indicate that the subjects were exposed to unidentified perturbations that had effects on body mass and fasting LPL activity both in adipose tissue and postheparin plasma.

Relationship Between Adipose Tissue LPL Activity and Plasma Sex Steroid Levels

Table 4 displays a correlation matrix for measures of adipose tissue LPL activity, sex steroids, weight change, and weight change squared. Femoral adipose tissue LPL activity eluted at 37°C or extracted with detergent showed significant negative correlations with testosterone, bioavailable testosterone, dihydrotestosterone, and estradiol. By contrast, both measures of abdominal adipose tissue LPL activity were significantly correlated with bioavailable testosterone only, and with smaller correlation coefficients than those for femoral LPL activity. Plots of all measures of abdominal and femoral adipose tissue LPL activity versus the four sex steroids with the highest correlations are shown in Fig 2. These results indicate that femoral and abdominal adipose tissues are different in that femoral adipose tissue LPL activity shows significant negative correlations with plasma sex steroid levels, whereas the corresponding correlations with abdominal LPL are weaker or absent. Although differences between the r values were not significant (data not shown), they were similar for two different methods of measuring adipose tissue LPL activity. A larger study population may have shown that the femoral correlations are significantly higher.

Multivariate Analysis of Predictor Variables for Femoral LPL Activity

To determine if the potential predictor variables identified for femoral LPL (Table 4) were independent, multiple linear regression analysis was performed with LPL activity eluted at 37°C as the dependent variable (Table 5). After excluding estrone and total testosterone from the analysis, only bioavailable testosterone, weight change, and weight change squared were retained as independent predictors with a multiple correlation coefficient of .79 ($P = .0002$).

Table 2. Experimental Parameters

Parameter	Range	Mean ± SD
Adipose tissue LPL activity (nmol · min^{-1} · g^{-1})*		
Abdominal		
Eluted at 37°C	4.3-26.6	13.3 ± 5.5
Detergent-extracted (n = 23)	24.6-92.0	51.5 ± 16.6†
Femoral		
Eluted at 37°C	3.9-30.7	14.3 ± 6.9
Detergent-extracted (n = 23)	28.0-113.8	67.1 ± 24.5†
Postheparin plasma LPL activity (nmol · min^{-1} · mL^{-1})		
Fasting		
10 min	79-264	161 ± 52‡
30 min	141-311	206 ± 44
60 min	115-262	185 ± 41
Fed		
10 min	91-232	146 ± 37‡
Difference for fasting fed		
10 min	−65-131	14 ± 51
Plasma sex steroids*		
Testosterone (ng/dL)	145-534	330 ± 115
Bioavailable testosterone (ng/dL)	80-340	191 ± 63
Dihydrotestosterone (ng/dL)	16-55	28.8 ± 11.5
Estradiol (pg/mL)	14-38	24.1 ± 5.8
Estrone (pg/mL)	22-64	41.9 ± 10.2

*Samples were obtained after an overnight fast.

†A significant difference in detergent-extracted adipose tissue LPL activity between abdominal and femoral sites was obtained by paired t test ($t = -2.41$, $P = .025$, 2-tailed probability).

‡Mean values were not significantly different by paired t test ($t = 1.37$, $P = .184$, 2-tailed probability).

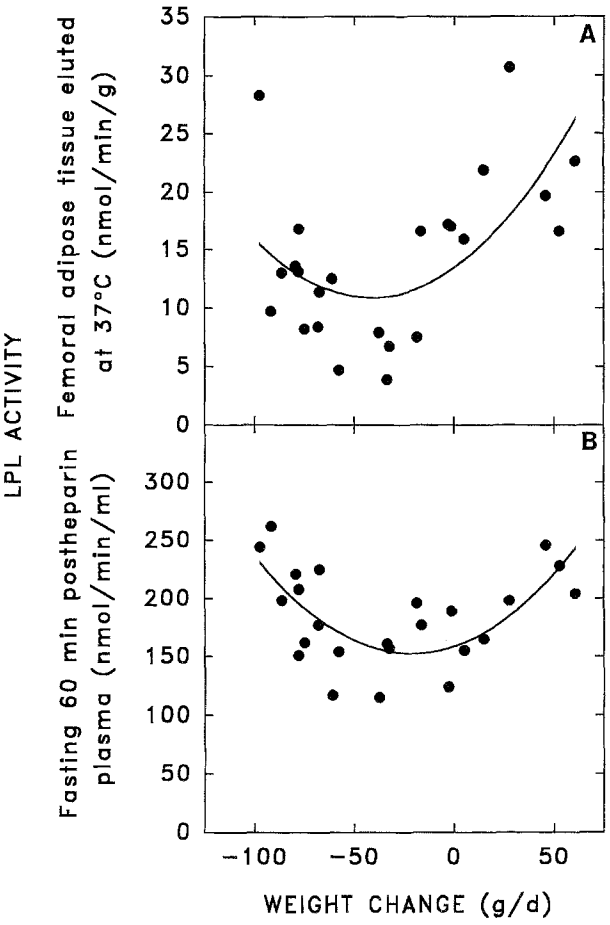

Fig 1. Nonlinear relationship between LPL activity and rate of weight change. Both femoral LPL activity eluted at 37°C (A) and fasting LPL activity in postheparin plasma sampled at 60 minutes during a continuous heparin infusion (B) showed significant parabolic relationships with weight change. Parabolic regression equations that are fitted to these plots and corresponding correlation coefficients and *P* values are shown in Table 3. The curves had minima at weight change rates of −41.5 g/d (A) and −21.3 g/d (B), respectively.

Postheparin Plasma LPL Activity

Fasting postheparin plasma LPL activity measured both early and late during a continuous heparin infusion in obese women has been shown to be strongly correlated with gluteal adipose tissue LPL activity.[18] The same postheparin plasma parameters also show strong negative correlations with plasma estradiol levels.[10] Therefore, evidence for similar relationships was sought in these obese men, assuming that gluteal and femoral adipose tissues were metabolically similar.[24] In the present study, fasting postheparin plasma LPL activity measured at various times (10, 30, and 60 minutes) during a continuous heparin infusion did not correlate either with adipose tissue LPL activity at the femoral and abdominal sites or with plasma sex

Table 3. Linear and Parabolic Regression of LPL Activity on Weight Change

Enzyme Source	Function	R	R^2	F	P
Femoral adipose tissue eluted at 37°C	Linear regression ($y = 16.25 + 0.059x$)	.416	.173	4.61	.043
	Parabolic regression ($y = 13.42 + 0.122x + 0.00147x^2$)	.601	.361	5.92	.009
	R^2 increment			6.16	<.025
Fasting 60-min postheparin plasma	Linear regression ($y = 184.73 + 0.001x$)	.001	.000	0.00	.997
	Parabolic regression ($y = 158.54 + 0.576x + 0.0135x^2$)	.683	.467	9.18	.001
	R^2 increment			18.36	<.001

NOTE. R, multiple correlation coefficients; R^2 coefficient of determination; F, F-statistic; P, probability for F-statistic. To derive the regression equations, the predictor variables, weight change (x) and weight change squared (x^2), were tested by stepwise multiple linear regression using default selection and exclusion criteria. The parabolic regressions relating LPL activity to weight change represented a genuine departure from linearity, since the incremental F test demonstrated a significant increase in R^2.[23] The fitted curves are displayed in Fig 1.

steroids (data not shown). By contrast, a positive correlation ($r = .44$, $P = .032$) was observed between postprandial LPL activity in postheparin plasma and estradiol (data not shown).

DISCUSSION

The present study demonstrated significant inverse correlations between plasma sex steroid concentrations, particularly bioavailable testosterone, and adipose tissue LPL activity. These correlations are stronger for the lower body (thigh) than for the upper body (abdomen). In this respect, men are similar to women, whose lower-body (gluteal) adipose tissue LPL activity is also inversely correlated with a plasma sex steroid (estradiol). In other regulatory aspects, men differ from women in that the fasting postheparin plasma LPL is not correlated with plasma sex steroid concentrations or with adipose tissue LPL activity. Another gender difference is found for postprandial LPL activity of postheparin plasma, which correlates with plasma testosterone concentration in women[10] but with estradiol in men. Finally, it appears that small positive or negative changes in weight are correlated with LPL activity in both adipose tissue and postheparin plasma.

It was demonstrated previously that among women LPL activity in lower-body fat is likely to be regulated by endogenous sex steroids, since gluteal adipose tissue LPL activity shows a strong negative correlation with plasma estradiol levels.[10] The present investigation extends this observation to men by showing negative correlations between femoral adipose tissue LPL activity and plasma concentrations of several sex steroids, including testosterone, dihydrotestosterone, and estradiol. Because the concentrations of all of these steroids were intercorrelated (data not shown), only bioavailable testosterone was retained as a predictor variable in a multiple regression model (Table 5). These results suggest that plasma testosterone is a significant negative regulator of adipose tissue LPL activity in men. This interpretation is supported by studies in the male rat in which adipose tissue LPL activity was suppressed by testosterone administration. The androgen effect was suggested to be mediated by estradiol formed from testosterone by aromatase and acting on estrogen receptors in the adipocytes.[25] Since aromatase activity probably is higher in human stromal cells than in adipocytes, the estradiol action on the latter is a paracrine phenomenon.[26] This notion is further supported by the fact that plasma estradiol levels in obese men were too low (≤38 pg/mL) to have the inhibitory effect observed in women.[10]

The negative correlation with plasma sex steroid levels is stronger for femoral LPL versus abdominal LPL, and would indicate that the enzyme in the lower body is more amenable to inhibition. This could result from a higher content of estrogen receptors and/or aromatase in the lower body or from other biochemical differences still unidentified, and would explain the propensity for upper-body obesity in men. Likewise, women would be prone to lower-body obesity because the inhibitory effects of estrogen on LPL are at least partly reversed by progesterone acting on adipose tissue progestin receptors, which appear to be expressed only in females.[27,28] This argument assumes that femoral adipose tissue would be more susceptible to progesterone effects than abdominal tissue.

Adipose tissue LPL activity can be normalized to weight (nanomoles per minute per gram) or to fat cell number (nanomoles per minute per 10^6 cells). Which of these parameters best reflects the ability of LPL to move fatty acids into adipocytes is unclear. In obese women,[10] the correlation between body mass index and gluteal adipose tissue LPL activity expressed per unit weight is weakly negative or absent (P.-H.

Table 4. Correlation Matrix for Adipose Tissue LPL and Potential Predictor Variables

Enzyme Source	Testosterone	Bioavailable Testosterone	Dihydrotestosterone	Estradiol	Estrone	Weight Change	Weight Change^2
Abdominal							
Eluted at 37°C	−.24	−.35‡	−.09	−.16	−.26	.00	.18
Detergent-extracted	−.29	−.47‡	−.16	−.24	−.37‡	.02	.12
Femoral							
Eluted at 37°C	−.54†	−.53†	−.44‡	−.49†	−.26	.42‡	.01
Detergent-extracted	−.58†	−.62*	−.45‡	−.39‡	−.23	.44‡	−.18

NOTE. Pearson correlation coefficients were calculated after pairwise exclusion of missing values. One-tailed significance levels are used for sex steroids, since negative correlations with LPL were anticipated based on previous studies in women and animals. For weight change and weight change squared, significance levels are 2-tailed.

*$P \leq .001$.

†$P \leq .01$.

‡$P \leq .05$.

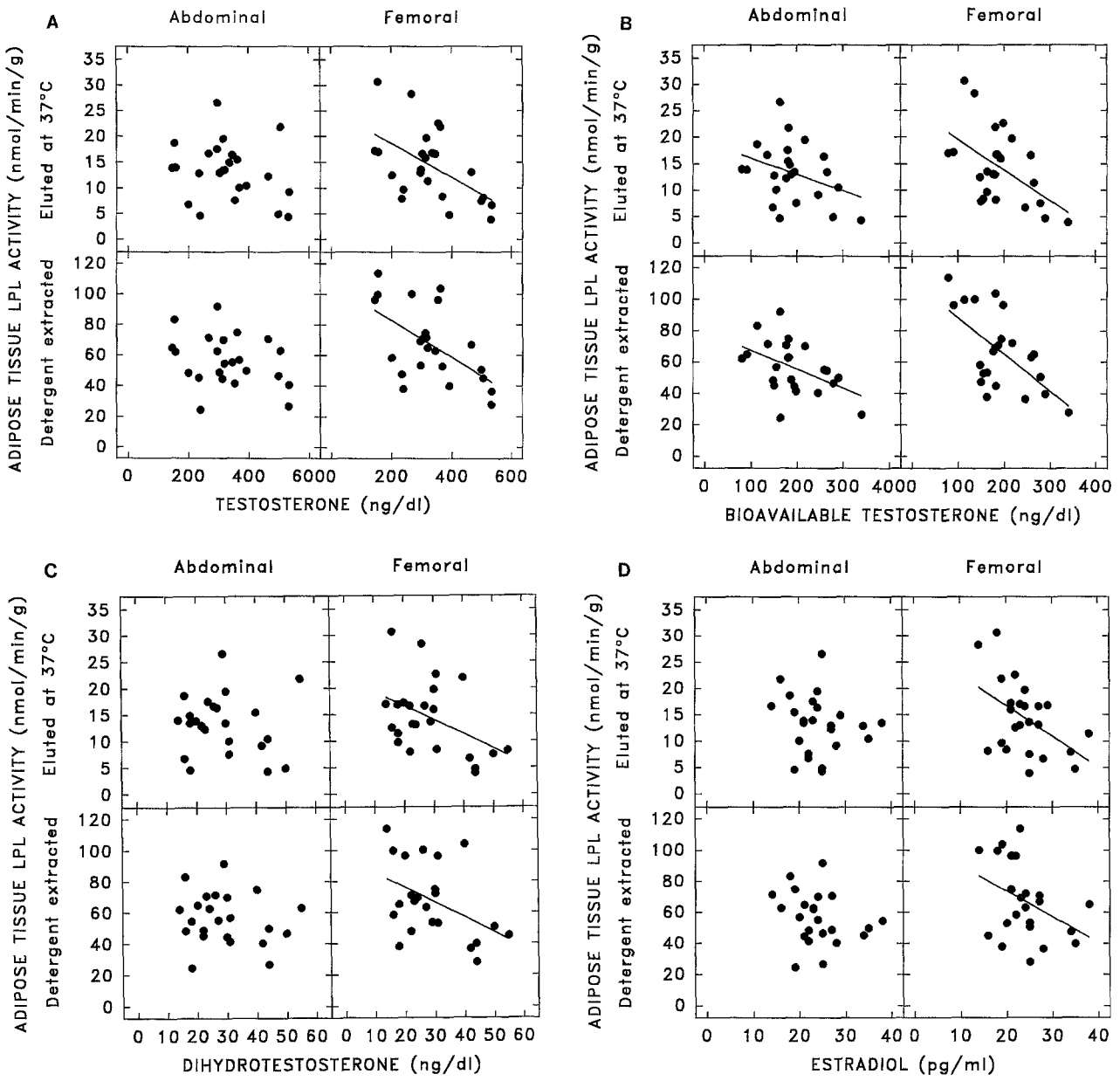

Fig 2. Relationship between adipose tissue LPL activity and plasma sex steroid concentrations. Only regression lines with significant correlation coefficients (Table 4) are shown. (A) Testosterone; (B) bioavailable testosterone; (C) dihydrotestosterone; (D) estradiol.

Iverius and J.D. Brunzell, unpublished results, September 1988.). Similarly, obese men in present study showed no significant correlations between either abdominal or femoral LPL activity and body mass index (data not shown), whereas other investigators[29] have noted lower gluteal activity with obesity. The absence of strong correlations between LPL activity and body mass index is consistent with the lack of correlation between body mass index and sex steroids in this study (data not shown) and other studies excluding massively obese men.[30] Subjects close to their usual weight therefore have similar mean levels of LPL activity at a given site regardless of their degree of obesity. LPL activity associated with adipose tissue in the steady state thus appears independent of the size of the adipose organ. However, it is apparent from the parabolic shape of the plots in Fig 1 that a narrow definition of weight

Table 5. Multiple Linear Regression Analysis of Predictor Variables for Femoral LPL Activity Eluted at 37°C

Entered Predictor Variables	Retained Predictor Variables	*r*	R	F	*P*
Estradiol					
Dihydrotestosterone					
Bioavailable testosterone	Bioavailable testosterone	−.65			.0012
Weight change	Weight change	.70			.0003
Weight change^2	Weight change^2	.54			.0102
	All retained variables		.79	11.21	.0002

NOTE. *r*, partial correlation coefficient; R, multiple correlation coefficient; F, F-statistic; P, probability for t-statistic (partial correlations) or F-statistic. Predictor variables were tested by the stepwise procedure using default selection and exclusion criteria.

stability would result in less variability and a lower mean than a wider definition. Conversely, the level of LPL activity per unit weight in an adipose tissue sample would reflect how close a subject would be to weight stability. In women, adipose tissue LPL activity normalized to tissue weight but not to cell number showed significant correlations with plasma sex steroid levels.[10] Therefore, only the former parameter was recorded in the present study, thus avoiding the additional methodological error introduced by measuring fat cell diameter.

In obese and non-obese women, respectively, other investigators have observed that LPL activity in the lower body was either higher than[31] or similar to[32] LPL activity in the upper body. By contrast, the upper body in non-obese men had higher activity than the lower body.[32] In the group of predominantly obese men studied herein, LPL activity in the lower body was similar to or slightly higher than in the upper body (Table 2). Therefore, between-site variation in LPL activity is unlikely to be related to variation in the size of different fat depots, and absolute levels of LPL activity at any site may be much less important for maintenance of the adipose tissue than variations induced by different physiological states. Furthermore, factors other than LPL may also influence the balance between adipocyte lipid accretion and lipolysis.

The parabolic relationships demonstrated between LPL activity in adipose tissue or postheparin plasma and rate of weight change represented a statistically significant departure from linearity (Table 3 and Fig 1). Furthermore, two highly significant regressions ($P = .009$ and .001) with different sets of LPL activity measurements that did not intercorrelate (data not shown) make it unlikely that the observation was spurious. The weight change could be the result of changes in salt and water balance, intestinal contents, and body fat. Conceivable causes include altered dietary composition and salt, fiber, and caloric intake, as well as noncompliance with the prescribed diet. The relationship between weight change and the nature of the presumed homeostatic adjustments leading to changes in LPL activity can only be subject to speculation at this time. Nevertheless, recording the weights and using the relationship between LPL activity and weight change could provide a useful tool for eliminating unwanted variability in human studies of LPL regulation by multivariate analysis.

The lack of correlation between fasting postheparin plasma LPL and adipose tissue LPL activity observed in the present study contrasts with the strong correlations in obese women,[10] but corroborates results from obese men.[33] Since women have a higher proportion of body fat than men at a given body mass index,[34] the lack of correlation in men could be explained by a relatively lower contribution to total postheparin plasma LPL activity by adipose tissue. Postprandial postheparin plasma LPL was correlated with estradiol in men ($r = .44$, $P = .032$). However, in women it is correlated with plasma free testosterone and was proposed to reflect a direct regulation of skeletal muscle enzyme by testosterone.[10] If the androgen indeed stimulates muscle LPL, the lack of correlation with this hormone in men would be expected if male hormone levels are sufficiently high to saturate androgen receptors. The positive correlation with estradiol observed here could conceivably be a reflection of muscle mass, since skeletal muscle appears to be a significant source of plasma estradiol in men.[35,36] However, further studies are required to explain these relationships.

In conclusion, the strong negative correlations between plasma sex steroid levels and adipose tissue LPL activity in men are compatible with a paracrine suppression of LPL by estradiol formed within the tissue from plasma testosterone, as previously demonstrated in animals. The diminished sex steroid suppression of LPL in the upper body compared with the lower body may at least partly explain the propensity for upper-body obesity in men.

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