Sex differences in abdominal, gluteal, and thigh LPL activity

Susanne B. Votrubas and Michael D. Jensen
Endocrine Research Unit, Mayo Clinic, Rochester, Minnesota

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Votrubas SB, Jensen MD. Sex differences in abdominal, gluteal, and thigh LPL activity. Am J Physiol Endocrinol Metab 292: E1823–E1828, 2007. First published February 20, 2007; doi:10.1152/ajpendo.00601.2006.—Lipoprotein lipase (LPL) activity is necessary for adipocytes to take up triglycerides from the circulation, and regional differences in LPL activity could help determine regional fat storage. LPL activity has been reported to increase as a function of fat cell size, but this issue has not been extensively evaluated in different depots comparing sexes. Our objective was to determine whether sex alters the relationship between LPL activity and fat cell size. Subcutaneous adipose tissue biopsies were taken from the abdomen and thigh after an overnight fast and 1 h after a meal in 65 females (BMI 25.4 ± 0.8, means ± SE) and 41 males (BMI 23.7 ± 0.3); gluteal adipose samples were obtained in 47 of the females and 27 of the males. Fat cell size was greater in females than males in thigh (P < 0.005) and gluteal (P < 0.05) regions but not in the abdomen. There was a relationship between fasting LPL activity/fat cell and fat cell size in females (abdomen r² = 0.52, P < 0.0001; gluteal r² = 0.23, P < 0.005; thigh r² = 0.19, P < 0.005). In males, this relationship was seen only in the abdomen (r² = 0.51, P < 0.0001) and thigh (r² = 0.17, P < 0.05). Males and females had a significantly different relationship in the thigh only in the fasted state. Similar results were found in the fed state, although the strength of the relationship decreased in the abdominal regions for females only. This suggests fundamental differences in the regulation of triglyceride uptake between males and females and adipose regions.

lipoprotein lipase; body fat distribution; postprandial; adipose tissue biopsies

THE ADVERSE EFFECTS OF OBESITY are linked to regional fat distribution. Fat in the upper body region is associated with greater health risks than fat in the lower body regions. An upper body fat distribution is typically seen in males, and even lean males carry a greater proportion of their body fat in this region than lean females. Lipoprotein lipase (LPL) is needed for adipocytes to take up triglycerides from the circulation, and we have recently shown that interindividual differences in postprandial adipose tissue LPL activity are strongly associated with regional differences in meal fat uptake (20). Therefore, understanding the regional regulation of LPL activity could help us understand the determinants of body fat distribution.

Adipose tissue LPL activity has been expressed in a variety of ways, depending on the study question. When LPL activity is expressed per fat cell (1, 6, 14) it has been reported that enzyme activity increases with fat cell size, even when studied in vitro (2). Björntorp and Smith (3) suggested that expression per fat cell is appropriate if the functional status of the tissue is to be addressed. At times, however, it may be helpful to express enzyme activity per unit tissue weight (1, 13, 20), particularly if one is interested in the ability of the adipose tissue to perform a metabolic task relative to the mass of tissue (3).

Although expressing enzyme activity per cell may be helpful, especially in situations where fat cell sizes are expected to be similar between different study groups, it may be misleading if fat cell size differs between sites or between populations. For example, average fat cell size may differ greatly between sexes, regional adipose tissue depots, and lean and obese individuals. In these cases, expressing enzyme activity solely per fat cell may overlook the functionality of the adipose tissue as a whole. Therefore, the aim of this study was to determine whether sex alters the relationship between LPL activity and fat cell size. Furthermore, we wished to determine the strength of this relationship in three subcutaneous adipose tissue depots: abdominal, gluteal, and femoral.

METHODS

Subjects. This analysis utilized data from studies of regional meal fat uptake, some of which have been published (20). Each study was approved by the Mayo Clinic Internal Review Board, and informed consent was obtained from each subject. Patients on medications known to affect substrate metabolism, with the exception of oral contraceptives, were excluded from the studies. All volunteers were between the ages of 18 and 50 and were weight stable for ≥2 mo prior to the study. All women were premenopausal. A complete blood count, electrolytes, and liver and kidney function chemistries were documented to be within normal limits prior to study participation.

Protocol. All three studies used similar protocols to assess regional fat cell size and regional LPL activity. The overall protocol has previously been described (20). One study included lean men (n = 21) and women (n = 20) and was designed to address the regional deposition of meal fat from a single high-fat (~70%) meal compared with a normal-fat (~30%) meal, with 3Htriolein incorporated into the experimental meals (20). A second study had the same research question and tracer but involved only overweight and obese women (n = 21; unpublished data). The third study again included lean men (n = 12) and women (n = 15) and examined regional meal fat disposal from a single normal-fat meal using a 14Ctriolein tracer (unpublished data). Participants were chosen for inclusion in this analysis if at least one LPL activity value was available for them together with a fat cell size measurement at the same site. Prior to participation in each study, body composition was assessed using dual energy X-ray absorptiometry (DEXA) and a single-slice abdominal computed tomography scan (see below). The volunteers were fed at the Mayo Clinic General Clinical Research Center (GCRC) metabolic kitchen for ≥3 days before the study to ensure constant macronutrient intake, as previously described (15, 19, 20).

Participants were admitted to the GCRC the evening before the start of the 24-h study day. After an overnight fast, participants received a liquid meal (Ensure Plus; Ross Laboratories) that contained calories equal to 40% of each participant’s individual resting energy expenditure, as determined by indirect calorimetry. Thirty-five of the participants...
participants also received an additional 80 g of unlabeled triolein in the breakfast meal. These meals contained either [3H]triolein (80 µCi) or [14C]triolein (20 µCi). One hour after a midday meal we performed subcutaneous adipose tissue biopsies (fed) for measurement of fat cell size and LPL activity when enough adipose tissue was available. Adequate adipose tissue (100–200 mg for LPL and fat cell size) was available in the fed state to assess LPL activity in the abdomen (men n = 20, women n = 40), gluteal (men n = 19, women n = 38), and thigh (men n = 18, women n = 39) regions. Participants also received an evening meal at 1800 and remained in the GCRC for another night. The next morning another set of subcutaneous adipose tissue biopsies (fasted) were taken and LPL activity and fat cell size was measured in the abdomen (men n = 28, women n = 48), gluteal (men n = 15, women n = 39), and thigh (men n = 28, women n = 54) regions. Following the biopsies the volunteers were discharged from the GCRC.

Assays. DEXA (DPX-IQ; Lunar Radiation, Madison, WI) was used to determine total body fat, fat-free mass, and leg fat. A single-slice computed tomography scan at the level of the L2–3 interspace was taken and used in combination with DEXA abdominal fat analysis to determine visceral fat mass (8, 11). Adipose tissue lipids were extracted using the standard procedures of Folch et al. (5), and fat cell size was measured using photomicrographs as previously described (18). Heparin-releasable LPL activity was measured as described by Nilsson-Ehle and Schotz (9) when the number of fat cells per gram of adipose tissue (regional fat cells/g) was estimated by using the average lipid content of adipose tissue (µg lipid/cell) and females (thigh = 0.59 ± 0.03 µg lipid/cell; males = 0.46 ± 0.04 µg lipid/cell) combined or considered separately (at least P < 0.05). Additionally, thigh fat cells were larger than gluteal fat cells (males = 0.48 ± 0.03 µg lipid/cell; females = 0.59 ± 0.03 µg lipid/cell) when both sexes were combined (P < 0.0001) or considered separately (at least P < 0.005). Gluteal fat cell size was significantly greater than abdominal fat cell size in females only (P < 0.05).

The fasted and fed regional LPL activity in µg free fatty acid (FFA) release·h⁻¹·g⁻¹ is shown in Fig. 2. In the fasted state, thigh (P < 0.0001) and gluteal (P < 0.05) LPL activity was greater in females (thigh = 0.51 ± 0.06 µg FFA release·h⁻¹·g⁻¹; gluteal = 0.31 ± 0.03 µg FFA release·h⁻¹·g⁻¹) than in males (thigh = 0.20 ± 0.02; gluteal = 0.19 ± 0.04) but not different in abdominal fat (females = 0.28 ± 0.02; males = 0.23 ± 0.03). Fed LPL activity remained significantly greater in females than in males in the thigh (females = 0.64 ± 0.06; males = 0.31 ± 0.03; P < 0.0001) and gluteal (females = 0.54 ± 0.05; males = 0.38 ± 0.05; P < 0.05) regions but was also greater in abdominal fat (females = 0.53 ± 0.05; males = 0.36 ± 0.05; P < 0.05). LPL activity was significantly greater in the fed than fasted state in all three adipose regions (P < 0.0001) when both sexes were analyzed together. When the data from females were analyzed separately, the increase in LPL activity from the fasting to the fed state remained significant in the abdomen (P = 0.0001), thigh (P = 0.0005), and gluteal (P < 0.0001) regions. In males, however, both thigh (P < 0.005) and gluteal (P < 0.005) LPL activity increased with feeding, but abdominal LPL activity did not.

The relationship between fat cell size and LPL activity per fat cell is shown in Fig. 3. Figure 3, A, B, and C, depicts fasting LPL activity relative to fat cell size in males and females. In the abdominal region, fasting LPL activity/cell is positively correlated with fat cell size (females: r² = 0.52, P < 0.0001; males: r² = 0.51, P < 0.0001), and no interaction between sex and cell size was found. Similar positive relationships were found with gluteal (r² = 0.23, P < 0.005) and thigh (r² = 0.19, P < 0.005) fat cells in females but only in the thigh region in males (r² = 0.17, P < 0.05). Of note, the association between thigh fat cell size and fasted LPL activity/cell (Fig. 3C) was significantly different for males and females (sex × cell size interaction, P < 0.05), indicating a different slope for the relationship.

The fed LPL activity/cell in women was significantly correlated with fat cell size (Fig. 3, D, E, and F) in the abdominal (r² = 0.16, P < 0.05), gluteal (r² = 0.13, P < 0.05), and thigh regions (r² = 0.17, P < 0.01). A significant relationship was detected between fed LPL activity and abdominal fat cell size (r² = 0.23, P < 0.05) and thigh fat cell size (r² = 0.28, P < 0.05) in men; we could not detect such a relationship between

Table 1. Participant characteristics

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<th>Females</th>
<th>Males</th>
<th>P Value</th>
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<td>Abdominal fat, kg</td>
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<td>0.1964</td>
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Values are means ± SE. BMI, body mass index.
gluteal cell size and fed LPL activity. The interaction term between fat cell size, fed LPL activity, and sex was not significantly different for any of the regions.

DISCUSSION

This analysis was performed to determine whether the relationship between LPL activity and fat cell size is the same in men and women. We found that, although LPL activity per cell increases as a function of abdominal and thigh fat cell size in both sexes, this relationship was not found for males when the gluteal region was tested. Additionally, we found that the relationship between thigh fat cell size and LPL activity in the fasted state was different between males and females despite being significantly positive in both groups. We also found that gluteal and thigh LPL activity expressed as μg FFA released·h⁻¹·g⁻¹ adipose tissue was different between males and females both in the fed and fasted state. These data suggest a fundamental difference in the physiology of triglyceride uptake in the lower body adipose tissue between males and females as mediated through LPL.

It has been proposed (3) that LPL activity is best expressed per fat cell rather than per tissue weight to best describe the functional status of the adipocyte. Yet published results differ in the units of reporting for LPL activity across and within papers. For example, several investigators have published LPL activity findings both per gram lipid/tissue weight and per fat cell or fat cell number, with concordant (7, 17) or discordant (1, 2, 14) results, depending on the method of data expression. This alone should raise concern over whether a single approach is satisfactory and suggests that data should be expressed both ways to provide the most possible information for the reader.

Our analysis of fasting LPL activity and fat cell size disclosed a clear sex difference in the relationships. Although men and women had similar characteristics with regard to abdominal and, to some extent, thigh LPL/fat cell size relationships, postabsorptive LPL activity did not increase in relation to gluteal fat cell size in males. To assess whether these apparent differences were the result of a wider range of fat cell size in women compared with men we reanalyzed the data, excluding those females with gluteal fat cell sizes larger than males (>0.75 μg lipid/cell); the relationship between fasted gluteal fat cell size and gluteal LPL activity/cell in females was attenuated ($r^2 = 0.06, P = 0.1847$). Thus, lack of comparable fat cell size range in the two groups may explain this observation.

In this population, both fed and fasted LPL activity, expressed as μg FFA released·h⁻¹·g⁻¹, was greater in females than males in all adipose depots, with the exception being the abdominal region in the fasted state. Some investigators (1, 10, 13, 16, 17) have found similar differences in LPL activity per lipid or tissue weight between depots, but very little data exist providing a comprehensive comparison of regional differences in LPL activity between males and females. Arner et al. (1) reported significantly greater fasting adipose tissue LPL activity in women than in men in both abdominal and gluteal regions, whereas we did not find ($P = 0.11$) greater fasting abdominal LPL activity in females. Fried and Kral (6) also reported greater LPL activity/cell in females vs. males in some subcutaneous and visceral fat depots collected from morbidity

Fig. 1. Fat cell size in μg lipid/cell in females and males in the abdominal, gluteal, and thigh adipose tissue regions. Data are expressed as means ± SE.

Fig. 2. Fasted (left) and fed (right) lipoprotein lipase (LPL) activity in μg free fatty acid (FFA) release·h⁻¹·g⁻¹ of regional adipose tissue in females and males. LPL activity data in the fasted state were available in 28 men and 48 women in the abdomen, 15 men and 39 women in the gluteal region, and 28 men and 54 women in the thigh area. In the fed state, LPL activity was assayed in 20 men and 40 women in the abdomen, 19 men and 38 women in the gluteal region, and 18 men and 39 women in the thigh area *$P < 0.05$; #$P < 0.0001$. 

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obese patients undergoing surgical procedures. Consistent with our findings, Taskinen and Nikkila (17) reported that fasting LPL activity was greater in gluteal than abdominal sites in obese females. Little data have been published on fed LPL activity aside from situations of weight loss (7, 17) or dietary macronutrient manipulation (21). An increase in gluteal LPL activity following a high-fat or high-carbohydrate meal has been reported (12), although others have found no effect of macronutrient content on gluteal fed (6 h postprandial) LPL activity (4, 21). We found greater fed LPL activity in lean...
females than lean males in the thigh but not in the abdominal region (20). The discrepancies in these various findings may relate to the timing of the postprandial adipose tissue biopsies as well as to the means of data expression (per fat cell or per tissue), given our findings.

The relationship between LPL activity and fat cell size differed somewhat between the fed and fasted states. Whereas a significant, positive relationship between the two parameters was found in all three adipose depots in women, the slope of the relationship between LPL activity/cell and fat cell size was significantly greater in the fed state $(P < 0.01)$. In contrast, in the thigh region, the relationship was similar in the fasted and fed states in both sexes. In the fasted state only, the relationship between LPL activity/cell and fat cell size was different between men and women. To the extent that fasting LPL activity can regulate VLDL-triglyceride uptake [as opposed to chylomycin-triglyceride uptake being associated with fed state LPL activity (20)], these findings may indicate differential adipose uptake of endogenous circulating triglyceride between women and men. Our data suggest that the relationship between fat cell size and LPL activity/cell in gluteal fat differs from that in both the abdomen and thigh regions regardless of sex and nutritional status. These data are in concordance with past reports (15) that make gluteal adipose tissue difficult to classify, i.e., as upper or lower body fat, in particular in relation to meal fat uptake. Although we expected to see an increase in postprandial LPL activity (4, 17, 20, 21), we were surprised that the slope of the relationship with fat cell size changed to a significant degree only in abdominal subcutaneous fat. This suggests that thigh and abdominal adipocytes may process LPL quite differently in response to meal ingestion.

The finding that fasted and fed LPL activity per gram of fat is less in men than in women, combined with the lesser amounts of subcutaneous fat in men, implies that whole body adipose tissue LPL activity is considerably less in men compared with women. This might explain the observation that men have much greater postprandial chylomicron concentrations than women (15, 20). Alternatively, men may have a greater LPL activity in the visceral adipose tissue and may have increased storage in that region. Direct comparisons between visceral adipose tissue LPL in males and females are rare; however, Panarotto et al. (10) did report similar fasted LPL activity (U/mg) in omental fat as well as subcutaneous abdominal fat. Despite this, however, visceral fat cannot be discounted as a contributor to the differences between males and females because postprandial visceral LPL activity is not known, and these studies are complicated to perform at best.

It should be noted that some of the volunteers in this protocol received a high-fat (~70% fat) breakfast the day of the fed state adipose biopsy, whereas most consumed a normal-fat meal (~30% fat) (20). We performed multiple regression analysis to determine whether the high-fat meal was a significant contributor to fasted LPL activity and found that the meal fat content was not a predictor of this relationship in any of the three adipose tissue regions.

In summary, we found a difference in the relationship between fat cell size and LPL activity based on adipose region and nutritional state (fed vs. fasted). In females, fat cell size is positively related to LPL activity, although the relationship is blunted somewhat in the abdominal area in the fed state. In men, the same relationship is seen between fat cell size and LPL activity in the abdominal and thigh regions both in the fed and fasted states. In both sexes, the gluteal region does not appear to follow the same pattern as the abdominal and thigh. We also report that the relationship between fat cell size and LPL activity is different between men and women in the thigh region, which may indicate a different processing of triglycerides into leg fat. These data caution against the expression of adipose tissue LPL activity in relation to a single adipose parameter (mass or fat cell size), particularly when addressing sex and regional differences. We suggest that it will be important to present this data using both formats to avoid drawing erroneous conclusions due to the choice of data expression.

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