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# Postprandial leg uptake of triglyceride is greater in women than in men

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**Horton, Tracy J., S. Renee Commerford, Michael J. Pagliassotti, and Daniel H. Bessesen.** Postprandial leg uptake of triglyceride is greater in women than in men. *Am J Physiol Endocrinol Metab* 283: E1192–E1202, 2002; 10.1152/ajpendo.00164. 2002.—The postprandial excursion of plasma triglyceride (TG) concentration is greater in men than in women. In this study, the disposition of dietary fat was examined in lean healthy men and women ( $n = 8/\text{group}$ ) in either the overnight-fasted or fed (4.5 h after breakfast) states. A [<sup>14</sup>C]oleate tracer was incorporated into a test meal, providing 30% of total daily energy requirements. After ingestion of the test meal, measures of arteriovenous differences in TG and <sup>14</sup>C across the leg were combined with needle biopsies of skeletal muscle and adipose tissue and respiratory gas collections to define the role of skeletal muscle in the clearance of dietary fat. The postprandial plasma TG and <sup>14</sup>C tracer excursions were lower ( $P = 0.04$ ) in women than in men in the overnight-fasted and fed states. Women, however, had significantly greater limb uptake of total TG compared with men on both the fasted ( $3,849 \pm 846$  vs.  $528 \pm 221$  total  $\mu\text{mol}$  over 6 h) and fed ( $4,847 \pm 979$  vs.  $1,571 \pm 334$  total  $\mu\text{mol}$  over 6 h) days. This was also true for meal-derived <sup>14</sup>C lipid uptake. <sup>14</sup>C content of skeletal muscle tissue ( $\mu\text{Ci/g}$  tissue) was significantly greater in women than in men 6 h after ingestion of the test meal. In contrast, <sup>14</sup>C content of adipose tissue was not significantly different between men and women at 6 h. The main effect of nutritional state, fed vs. fasted, was to increase the postmeal glucose ( $P = 0.01$ ) excursion (increase from baseline) and decrease the postmeal TG excursion ( $P = 0.02$ ). These results support the notion that enhanced skeletal muscle clearance of lipoprotein TG in women contributes to their reduced postprandial TG excursion. Questions remain as to the mechanisms causing these sex-based differences in skeletal muscle TG uptake and metabolism. Furthermore, nutritional state can significantly impact postprandial metabolism in both men and women.

dietary fat; gender; skeletal muscle

AN ELEVATED POSTPRANDIAL TRIGLYCERIDE (TG) excursion is a significant and independent risk factor for coronary heart disease (CHD) (15, 21, 31, 50) and carotid atherosclerosis (6, 39). In addition, a decreased ability to oxidize lipid is considered to be a risk factor for weight gain (7, 51). It is therefore important to understand the

factors that regulate the metabolic response to the ingestion of dietary fat. In this context, there are sex-based differences in the incidence of CHD (4, 22) and to a lesser extent obesity (28), which may be due in part to sex-based differences in postprandial lipoprotein metabolism. Specifically, after ingestion of a mixed meal, circulating TG levels have been shown to be significantly higher in men compared with premenopausal women (12, 18, 29) despite nearly identical glucose and insulin responses. This sex-based difference in the postprandial TG response does not appear to be explained by differences in premeal fasting TG levels (12, 18). The consequence of a lower TG response in women appears to be maintenance of a less atherogenic blood lipid profile compared with men, but this could be at the expense of greater fat storage.

The lower postprandial TG excursion in women could be due to delayed gastrointestinal absorption of dietary fat, a reduced very low-density lipoprotein (VLDL)-TG production in the postprandial state, or increased clearance of circulating TG (2, 34). Once lipid is cleared from the circulation, it is stored as TG, incorporated into functional lipids, or oxidized. A greater capacity for one or more of these processes in women could promote a more rapid TG clearance.

Consumption of dietary fat generally occurs in combination with other macronutrients (carbohydrate and protein). This makes the investigation of dietary fat metabolism, consumed in the form of a mixed meal, more relevant to normal feeding practices. Although most studies have investigated the acute metabolic response to a mixed meal after an overnight fast (9, 19, 29, 35), this is only representative of a breakfast-type meal. Over the course of a day, most food is consumed in the semifasted or fed state, and the metabolic environment in this condition will be somewhat different from the overnight-fasted state. For example, lipid absorption from previous meals may still be incomplete, resulting in higher circulating TG levels. Tissues will also have been recently exposed to insulin, leading to an “insulinized” state. The impact of these factors on

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Table 1. *Subject Characteristics*

Intake	Age, yr	Height, m	Body Weight, kg	BMI, kg/m <sup>2</sup>	Body Fat, %	FM, kg	FFM, kg	Leg Lean Mass, kg	Habitual EI, kcal/day	Habitual Fat, %
Men (n = 8)	25 ± 2	1.79 ± 0.02*	76.9 ± 2.8†	23.7 ± 0.8	20.4 ± 1.5‡	15.5 ± 1.5	61.8 ± 1.3†	18.8 ± 0.8†	2,900 ± 137†	29 ± 13
Women (n = 8)	30 ± 2	1.68 ± 0.03	60.2 ± 2.4	21.5 ± 0.7	29.6 ± 2.8	18.0 ± 2.0	42.2 ± 1.8	13.3 ± 0.6	1,849 ± 131	27 ± 1.1

Values are means ± SE. BMI, body mass index; FM, fat mass; FFM, fat-free mass; EI, energy intake. Lean leg mass is the sum of right and left leg lean mass. Significant difference between men and women: \**P* = 0.006, †*P* = 0.001, ‡*P* = 0.012.

subsequent postprandial nutrient metabolism has not been adequately addressed.

The major aim of this study was to determine whether differences in the uptake and metabolism of circulating TG, including meal-derived TG, by skeletal muscle was in part responsible for the sex-based difference in the postprandial TG excursion. To make the data more relevant to normal eating habits, a meal of mixed nutrient composition was used, and measurements were made after an overnight fast and 4.5 h after a breakfast meal (fasted and fed conditions, respectively). To achieve these aims, a radioactive lipid tracer was incorporated into a liquid meal, and postprandial metabolism was assessed using limb balance measurements, tissue sampling, and respiratory gas exchange techniques.

## METHODS

### Subjects

Normal-weight, healthy men and women (20–40 yr) were recruited for the study. Subjects were nonsmokers and relatively untrained (<90 min of aerobic exercise/wk). Women were eumenorrheic and not using any form of hormonal contraception. Women were studied during the follicular phase of their menstrual cycle. Medical exclusions included past or present history of cardiovascular disease, high blood pressure, glucose intolerance, thyroid disease, or hyperlipidemia. Subjects were screened, by use of a 4-day dietary record and food frequency questionnaire, to exclude individuals whose habitual intake of dietary fat was <20% or >40% of total energy intake. A total of 16 individuals took part in the study (8 men and 8 women). Subject characteristics are given in Table 1. The study protocol was approved by the University of Colorado Multiple Institutional Review Board for the Protection of Human Subjects. All subjects read and signed an informed consent form before admission into the study.

### Preliminary Assessments

**Body composition and leg tissue mass.** Body and limb mass and composition were determined by dual-energy X-ray ab-

sorptiometry (DPX-1Q; Lunar Radiation, Madison, WI) as previously described (33).

**Resting metabolic rate.** Resting metabolic rate (RMR) was measured using indirect calorimetry via a metabolic cart system (Sensormedics 2900; Sensormedics, Yorba Linda, CA) (46). The RMR value was used to calculate energy intake of subjects during the period of prestudy diet control.

### Prestudy Diet and Exercise Control

Subjects were fed a controlled diet for 7 days before each study. All food was prepared by the metabolic kitchen of the General Clinical Research Center at the University of Colorado Health Sciences Center. No other food was permitted. Energy intake was calculated at RMR × 1.6, the latter an activity factor used previously (17). Body weight was measured daily before breakfast was eaten to determine weight stability. A consistent (2 day) loss or gain in body weight of 0.9 kg or more resulted in an appropriate adjustment in energy intake to reestablish weight stability. The composition of the diet fed to subjects reflected that of the typical American diet [NHANES III (24)]. As a percentage of total energy intake, nutrient composition was 34% fat (13% saturated, 13.5% monounsaturated, and 7.5% polyunsaturated, P:S ratio of ~0.6), 15% protein, and 51% carbohydrate (29% complex and 21% simple sugars, with sucrose and fructose contributing 18% of the simple sugars). Table 2 shows the dietary intake information for subjects. Subjects were allowed to follow their usual activity routine for the first 6 days of the diet, and on the last day they refrained from any planned exercise. Self-report and physical activity questionnaire data suggested that there were no obvious differences in physical activity between men and women.

### Study Days

Subjects were studied in either the overnight-fasted or the fed condition. For the fasted condition, the test meal was consumed after an overnight fast (~14 h), whereas in the fed condition, subjects ate a breakfast meal (finished at ~6.30 AM) before the test meal was consumed (~11.00 AM). Eight men and eight women took part in the study. Four men and four women completed both the overnight-fasted and the fed study days. Because the test meal contained a radioactive

Table 2. *Dietary intake and body weight change before each study day*

		Av 7-day Energy Intake, kcal/day	Weight Change, kg	Breakfast Meal, kcal	Liquid Study Meal, kcal
Fasted day	Men	3,073 ± 101*	0.73 ± 0.33		860 ± 20*
	Women	2,194 ± 92	-0.23 ± 0.29		630 ± 30
Fed day	Men	2,928 ± 50*	0.08 ± 0.39	826 ± 1*	840 ± 0*
	Women	2,274 ± 74	-0.14 ± 0.30	638 ± 29	658 ± 26

Values are means ± SE. Av, average. Weight change was estimated from fasting body weight measured on the morning of the 1st day of diet control minus fasting body weight measured the morning of the study day, 7 days later. Breakfast meal was fed to subjects on the morning of the fed day, 4.5 h before consumption of the liquid study meal. Significant difference between men and women: \**P* = 0.001.

tracer,  $\geq 3$  mo separated the two study days in subjects who completed both fed and fasted days. On the second study day, baseline tracer concentrations still present in plasma,  $\text{CO}_2$ , and tissues were subtracted from samples taken after meal ingestion.

*Experimental Outline*

Figure 1 shows the experimental outline. After femoral artery (a), femoral vein (v), and antecubital vein catheterization, there were three study phases: baseline ( $\sim 3$  h), *postprandial period I* (6 h), and *postprandial period II* (18 h).

**Baseline.** After initial blood sampling, a primed, constant infusion of  $[6,6\text{-}^2\text{H}_2]\text{glucose}$  and a constant infusion of indocyanine green (ICG) dye were begun via an antecubital vein. Glucose kinetic data will be presented elsewhere. At the end of the baseline period, respiratory gas exchange was measured, and blood a-v and breath samples were taken (4 samples every 10 min). Venous samples were delayed relative to arterial sampling in an attempt to account for the non-steady-state postmeal environment. After a-v sampling, limb blood flow was also estimated by the thermodilution technique. Baseline muscle and adipose tissue biopsies were taken. A liquid test meal was then consumed over 10 min. The test meal contained 30% of the subject's total daily energy requirements, and the nutrient composition of the test meal was identical to that of the prestudy diet. Approximately  $50 \mu\text{Ci}$  of  $[1\text{-}^{14}\text{C}]\text{oleic acid}$  mixed with 1 ml of olive oil were blended into the liquid meal.

**Postprandial period I.** After ingestion of the test meal, a-v blood samples were taken over the next 6 h (Fig. 1). Leg blood flow measurements and breath sampling for  $\text{CO}_2$  were performed after blood sampling. Within the first 30 min of each hour, a 20-min measurement of respiratory gas exchange was made using indirect calorimetry. Muscle and adipose tissue biopsies were again performed 6 h after meal ingestion.

**Postprandial period II.** Femoral artery and femoral vein cannulas were removed immediately after the tissue biopsies, and pressure was applied for 30 min. A cannula was then inserted into a dorsal hand vein in retrograde fashion for subsequent blood sampling. Blood samples were drawn using the heated-hand technique (25). For fasted studies, blood and breath  $\text{CO}_2$  samples were collected at 9, 11, and 21 h postprandially. On fed study days, the 11-h sample was not taken, because this fell in the middle of the night.

*Experimental Procedures*

**Catheterization for blood sampling. FEMORAL VEIN.** Using sterile technique, the region of the right femoral triangle was infiltrated with  $< 20$  ml of 1% lidocaine without epinephrine. A custom, straight, double-lumen 6-French (F) thermodilution catheter with a 10-cm proximal port (F06TNN001; Baxter Healthcare, Edwards Critical Care Division, Irvine, CA), was used for the measurement of leg blood flow and blood sampling (48). The catheter was advanced in a cephalad direction through a 6-F introducer (504-606X; Cordis, Miami, FL) inserted in the femoral vein. The catheter was advanced into the external iliac vein, with the tip of the catheter peripheral to the end of the internal iliac vein.

**FEMORAL ARTERY.** Similarly, in the ipsilateral leg, a 12-cm, 4-F, single-lumen polyurethane catheter (C-Pum-401J; Cook, Bloomington, IN) was introduced into the femoral artery [modified Seldinger technique (13, 48)] 2-3 cm below the inguinal ligament and advanced in a cephalad direction 4-6 cm for sampling of arterial blood. The external end of the catheter was connected to a pressure bag containing normal saline, without heparin, infused at a rate of 5-10 ml/h.

**Limb blood flow by thermodilution.** Iliac venous blood flow was estimated by the thermodilution technique after a 3- to 10-ml bolus injection of sterile saline cooled to near  $0^\circ\text{C}$  through an American Edwards Laboratories-Set II (93-520). The thermodilution catheter is constructed such that the indicator (cold saline) achieves instantaneous mixing (14, 48). The accuracy and limitation of this technique have been previously documented (14, 48).

**Tissue biopsies.** Skeletal muscle biopsies were taken from the vastus lateralis muscle by means of the Bergstrom needle technique (5). Baseline and 6-h-postprandial biopsies were performed in opposite legs. Approximately 50-100 mg of muscle tissue were removed. Adipose tissue biopsies were taken from the gluteal region by needle aspiration. Approximately 100 mg of adipose tissue were removed, and the two biopsies were performed on opposite sides. Tissue samples were immediately frozen in liquid nitrogen after collection and stored at  $-70^\circ\text{C}$  until analysis.

**Collection of expired  $^{14}\text{CO}_2$ .** Subjects exhaled through a tube, connected to a one-way filter, into a scintillation vial containing 1 ml of 1 M benzathonium hydroxide and 2 ml of absolute methanol, with phenolphthalein (10 mg/100 ml) as an indicator. The subject exhaled until the pH indicator

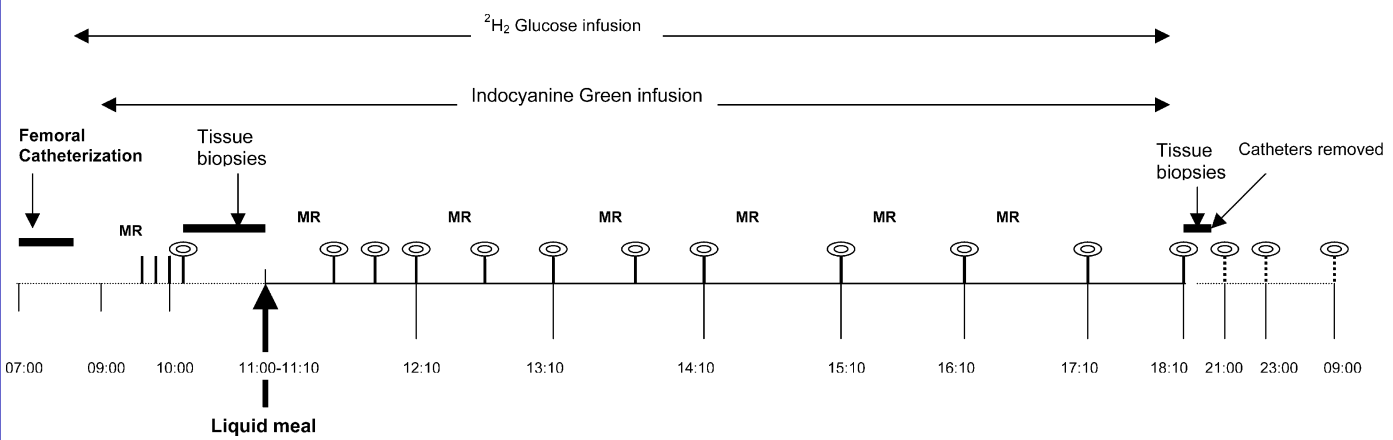


Fig. 1. Study time course. MR, metabolic rate measurement via indirect calorimetry. | = femoral artery and venous blood sampling, blood flow measurement via thermodilution. ∴ = blood sample from arterialized hand vein. ⊙ = breath collection for  $\text{CO}_2$  trapping and  $^{14}\text{CO}_2$  determination.

demonstrated that 2 mmol of CO<sub>2</sub> had been collected. Samples were capped and stored until counting.

**Respiratory gas exchange determination.** Respiratory gas exchange determinations were made using indirect calorimetry (Sensormedics 2900 metabolic cart). Subjects remained semirecumbent, and gas collections were made using the ventilated hood technique. Each measurement of gas exchange was made for 20 min. The O<sub>2</sub> and CO<sub>2</sub> concentrations in the expired air were used to calculate whole body energy expenditure (46). Total fat and carbohydrate oxidation were calculated from the respiratory exchange ratio [CO<sub>2</sub> production/O<sub>2</sub> consumption ( $\dot{V}CO_2/\dot{V}O_2$ )] after correction of gas volumes accounted for by protein oxidation (20). Protein oxidation was estimated from urinary nitrogen excretion (42). Briefly, subjects voided before consumption of the test meal, and all urine was collected over the initial 6-h postprandial period. Urinary nitrogen was measured from pooled aliquots. Each gram of urinary nitrogen was assumed to be derived from the oxidation of 6.25 g of mixed proteins.

#### Sample Analysis

**Blood analyses.** Radioimmunoassays were used to determine serum insulin (Kabi Pharmacia, Piscataway, NJ) and plasma glucagon (Linco Research, St. Louis, MO). Samples were run in duplicate with intra-assay coefficients of variation (CVs) of 10 and 9.4%, respectively. Serum glucose was measured enzymatically, in triplicate, using the hexokinase method on an automated Roche COBAS Mira Plus analyzer (intra-assay CV 0.7%). Enzymatic assays were used to determine serum TGs (in triplicate, Sigma Diagnostics, St. Louis, MO), glycerol (in duplicate, Boehringer Mannheim Diagnostics, Indianapolis, IN), and free fatty acids (FFA; in duplicate, Wako Chemicals, Richmond, VA). Intra-assay CVs were 10, 7.8, and 1.2%, respectively, on the COBAS Mira Plus analyzer. Blood lactate (Sigma Diagnostics) was run in duplicate with an intra-assay CV of 4.2%.

**Tracer measurements.** Radioactivity in breath, plasma, and tissue was determined by liquid scintillation counting (LS6500; Beckman Instruments, Fullerton, CA). For breath <sup>14</sup>CO<sub>2</sub> determination, scintillation fluid was added to the collection vials, and samples were left overnight in a dark area before being counted (to minimize chemiluminescence). For plasma <sup>14</sup>C, 200 μl of tissue solubilizer (Solvable, NEN) per 100-μl sample were added to a scintillation vial and 25 μl of hydrogen peroxide (30%). Hydrogen peroxide was used to reduce color quenching. The sample was mixed, scintillation fluid was added, and samples were left overnight before being counted. Thus plasma <sup>14</sup>C radioactivity reflected total counts in plasma. For <sup>14</sup>C in whole muscle or adipose tissue, each sample was powdered in liquid nitrogen and weighed into a scintillation vial. Three milliliters of normal saline were added, and the sample was vortexed. After addition of 1 ml of Solvable, vials were capped and incubated at 37°C for 6 h and then left overnight. The next day, 100 μl of hydrogen peroxide were added and samples were left for 2 h. After addition of scintillation cocktail (10 ml Aquasol, NEN), samples were left overnight (to minimize chemiluminescence) before being counted. Tissue <sup>14</sup>C, therefore, reflected total counts from the whole muscle or adipose tissue sample.

#### Calculations

Estimation of blood flow by the thermodilution technique is based on the change in temperature of a thermal indicator (cold saline). An American Edwards cardiac output computer (model 9520) was connected to the thermistor wire to integrate indicator dilution curves, thus providing a nearly in-

stantaneous estimation of leg blood flow. Blood flow estimates at each time point represent the average of 4–7 measurements. ICG estimates of blood flow were calculated as the ratio between the dye infusion and the plasma concentration difference of ICG across the leg (i.e., rearrangement of the Fick equation) (1). The two techniques provided similar qualitative values for blood flow. For calculations of limb balance, thermodilution-determined blood flow was used. Net substrate balance across the leg was calculated as the a-v difference multiplied by the blood flow (49). A negative value in this equation reflects net release across the leg. The total net uptake or release of a substrate during the initial 6-h postprandial period (*postprandial period I*) was calculated using the trapezoid rule and is denoted as the incremental (for substrates that increased) and decremental (for substrates that decreased) area under the curve (AUC). As the concentration of certain substrates (glucose, glycerol, FFA) returned to basal levels in under 6 h, the AUC was calculated only over the time period when values were different from baseline. Serum TG concentrations were corrected for free glycerol, because the coupled TG assay measures both free glycerol and glycerol contained in TG.

**Incorporation of meal-derived lipid tracer into breath CO<sub>2</sub>.** In each subject, the disintegrations per minute (dpm) per millimole of CO<sub>2</sub> were multiplied by the corresponding  $\dot{V}CO_2$  to provide a minimum estimate of meal tracer incorporation into breath CO<sub>2</sub>.

**Correction of tissue, breath, and blood specific activity for meal lipid specific activity.** Meal lipid specific activity was calculated for each subject and study condition. Aliquots of the liquid meal were counted in duplicate and extrapolated to the measured volume of the meal to calculate total meal lipid specific activity. The incorporation of <sup>14</sup>C into breath and tissue was then normalized to each subject's meal lipid specific activity. This was necessary because the lipid content in the test meal was greater in men than in women, but all subjects were given a similar quantity of [<sup>14</sup>C]oleic acid.

#### Data and Statistical Analysis

**Subject numbers.** Venous catheterization was not successful in all subjects, giving limb balance data as follows: fasted day, *n* = 4 men and 4 women; fed day, *n* = 4 men and 5 women. All other data (arterial concentrations, <sup>14</sup>C, and breath data) were collected with subject numbers as follows: fasted day, *n* = 5 men and 7 women; fed day, *n* = 6 men and 5 women (unless otherwise indicated).

**Statistical analysis.** Subject characteristics were compared using an unpaired *t*-test. For the comparison of discrete variables [baseline characteristics and postprandial incremental (IAUC) or decremental AUC] a 2 × 2 ANOVA was used, with gender (men vs. women) and nutritional state (fed vs. fasted) as grouping factors. Any overall effect of sex, nutritional state, or interaction between the two factors was thus established. Unless otherwise stated, data are presented as means ± SE, and statistical significance was set at *P* < 0.05.

## RESULTS

### Substrate and Hormone Changes

Pre-meal concentrations of hormones and substrates are shown in Table 3. Women had significantly lower pre-meal TG concentrations compared with men. The main effect of eating breakfast (fed state) was to significantly increase TG concentrations in both men and women (*P* < 0.05).

Table 3. Resting substrate and hormone concentrations

Variable	Men Fasted	Women Fasted	Men Fed	Women Fed
Glucose, mg/dl	87 ± 5	84 ± 3	87 ± 2	83 ± 2
Insulin, $\mu$ U/ml	6.7 ± 1.0	6.0 ± 0.6	7.3 ± 0.7	6.5 ± 1.9
TG, mg/dl	97 ± 15*	54 ± 10	147 ± 24†,‡	82 ± 23‡
FFA, $\mu$ eq/l	626 ± 109	803 ± 91	695 ± 68	651 ± 99
Glucagon, pg/ml	50 ± 6	41 ± 3	49 ± 8	37 ± 6
Glycerol, $\mu$ M	44 ± 7	50 ± 6	49 ± 5	48 ± 3

Values are means ± SE. TG, triglyceride. Significant difference between men and women: \* $P < 0.008$ , † $P < 0.05$ . Significant difference between fed and fasted day: ‡ $P < 0.05$ .

Postprandial changes in TG, glucose, and insulin concentrations are shown in Fig. 2. Women had significantly lower postprandial TG excursions compared with men. This was despite very similar glucose and insulin excursions. The overall effect of eating 4.5 h before the test meal was to significantly reduce the IAUC for the TG excursion and to significantly increase the IAUC for glucose (Fig. 2). The lower IAUC for TG was partly due to the greater initial TG concentration rather than a reduction in the peak TG or a more rapid decline in the TG concentration. In contrast, the increased postprandial glucose excursion was due, primarily, to a significant increase in peak concentration ( $P < 0.001$ ). The arterial plasma  $^{14}\text{C}$  excursion (Fig. 3) was also significantly lower in women than in men but was unaffected by study condition. FFA (Fig. 4) responses to the meal were not different between men and women or study conditions. The same was true for glycerol (data not shown).

#### Limb Balance Measurements

Limb blood flow was not significantly different between men and women at any time or between test conditions. Fasted-day blood flow at rest was  $0.50 \pm 0.08$  and  $0.39 \pm 0.10$  l/min in men and women, respectively, and peak values occurred at 20 min postprandially,  $0.64 \pm 0.13$  and  $0.61 \pm 0.16$  l/min, respectively. Corresponding values for the fed day at rest were  $0.39 \pm 0.09$  and  $0.54 \pm 0.08$  l/min in men and women, respectively, with peak values at 20 min of  $0.46 \pm 0.11$  and  $0.64 \pm 0.12$  l/min, respectively. Postprandial uptake of TG across the limb was significantly greater in women than in men whether the test meal was consumed after an overnight fast or in the fed condition (Fig. 5A). Limb uptake of the meal-derived lipid  $^{14}\text{C}$  tracer was also significantly greater in women than in men under both test conditions (Fig. 5B). This greater uptake of meal tracer was not due to a greater limb delivery of  $^{14}\text{C}$ , as the arterial  $^{14}\text{C}$  concentration was actually lower in women than in men (Fig. 3), whereas both groups had similar postprandial blood flows. It should be noted that these data are expressed as absolute net uptake of TG and tracer; thus expressing the data relative to total leg mass or leg lean mass would serve to increase the sex-based differences even further. In women only, consuming the test meal in the fed condition had a tendency to increase the net limb uptake of total TG ( $P = 0.05$ ) and meal-derived lipid  $^{14}\text{C}$  ( $P = 0.05$ ).

#### Incorporation of Meal-Derived Lipid $^{14}\text{C}$ into Tissues

At the 6-h-postprandial time point, net retention of the meal-derived lipid tracer in skeletal muscle ( $\mu\text{Ci/g}$  tissue) was significantly greater in women than in men (Fig. 6A). Extrapolating this value to the total leg lean mass gave no difference in the absolute retention of meal lipid tracer between men and women on either day due to the significantly greater lean leg mass in men vs. women (Table 1). When considered relative to the meal lipid content, tracer-determined retention of the meal-derived lipid in leg lean tissue was significantly greater in women ( $8.4 \pm 1.1\%$  fasted day,  $10.0 \pm 1.3\%$  fed day) than in men ( $5.6 \pm 1.3$  and  $6.8 \pm 1.5\%$ , respectively). There was no significant sex-based difference in the net retention of  $^{14}\text{C}$  in adipose tissue (Fig. 6B); neither was there any sex-based difference in the absolute or relative retention in adipose tissue of the meal-derived lipid tracer when extrapolated to total fat mass.

#### Lipid Oxidation and Incorporation of Meal-Derived Lipid $^{14}\text{C}$ into Respiratory $\text{CO}_2$

Nonprotein respiratory quotient (RQ) was not significantly different between men and women or between test conditions over the initial 6-h-postprandial period. Although there was a reduced appearance of  $^{14}\text{C}$  in  $\text{CO}_2$  in women, this difference disappeared when data were normalized to meal lipid content (Fig. 7, A and B, respectively). Over the initial 6-h-postprandial period, the appearance of meal-derived lipid tracer in breath  $\text{CO}_2$  was significantly greater on the fasted day than on the fed day (Fig. 7, A and B) and also tended to be greater over the total 21 h ( $P = 0.06$ ). Furthermore, the minimum estimate of the percentage of meal fat oxidized was significantly greater on the fasted than on the fed day, over both 6 h ( $4.3 \pm 0.2$  vs.  $3.5 \pm 0.2\%$ , respectively) and 21 h ( $19.4 \pm 0.6$  vs.  $17.5 \pm 0.6\%$ , respectively).

#### DISCUSSION

This study examined the differences between normal-weight men and women in postprandial lipid metabolism, with the meal consumed either after an overnight fast (14 h) or 4–5 h after breakfast. Under both conditions, women had a significantly lower postprandial TG excursion than men, and this was partly due to a greater uptake of total TG, including meal-derived lipid, across the leg. These observations were made up

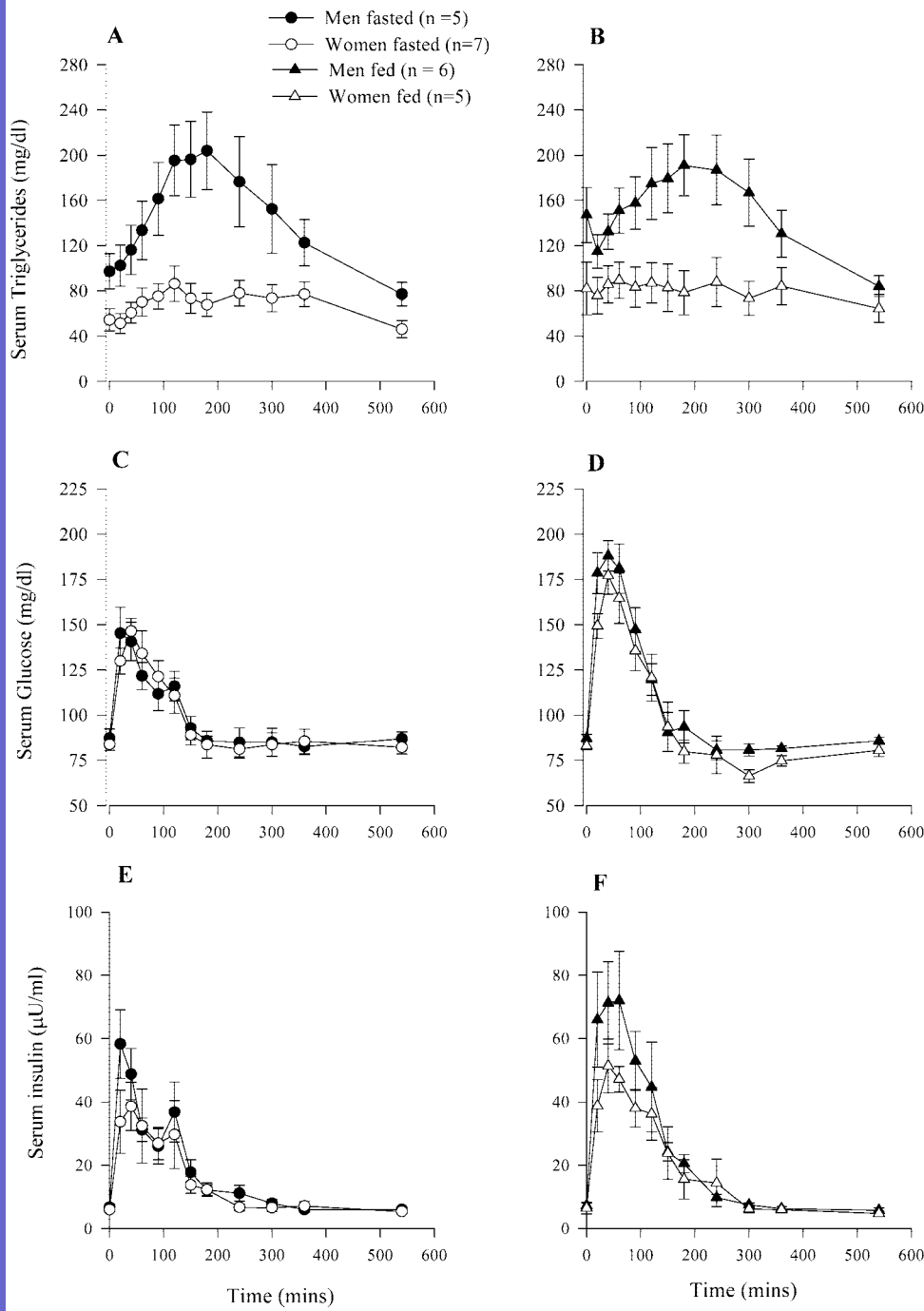


Fig. 2. For all graphs, arterial concentrations are given. *Time 0*, average of 4 premeal samples, with the liquid meal consumed ~50 min after basal sampling. *A*: serum triglyceride concentrations with the test meal consumed in the fasted state (after a 14-h overnight fast). *B*: serum triglyceride concentrations with the test meal consumed in the fed state (~4.5 h after breakfast). Significant effect of gender [incremental area under the curve (IAUC)  $P = 0.04$ ]. *C*: serum glucose concentrations with the test meal consumed in the fasted state. *D*: serum glucose concentrations with the test meal consumed in the fed state. Significant effect of condition (IAUC fed > fasted,  $P = 0.01$ ). *E*: serum insulin concentrations with the test meal consumed in the fasted state. *F*: serum insulin concentrations with the test meal consumed in the fed state.

to 6 h postprandially, and at this time point, women also had greater net retention of the meal-derived lipid in skeletal muscle.

Our results agree with previous studies that have observed a lower postprandial TG excursion in women compared with men when studied after an overnight fast (3, 12, 18, 29). The present study extends these observations to include the fed condition. Potential reasons for the lower postprandial TG levels in women vs. men include a slower rate of meal lipid absorption, a greater clearance of chylomicron (CM)-TG and/or total TG from the circulation, a greater suppression of

postprandial VLDL-TG secretion, or a combination of these. The similar initial increase in the arterial  $^{14}$ C suggests that differences in meal absorption may not account for the sex-based difference in the TG excursion. Our data relate mainly to the clearance of circulating TG. In this regard, we observed a significantly greater uptake of both total TG and meal-derived lipid across the leg in women vs. men measured up to 6 h postprandially. This finding was robust in that it was observed in both the overnight-fasted and the fed conditions. Furthermore, it appeared that the women retained more of the meal-derived lipid in the limb, as

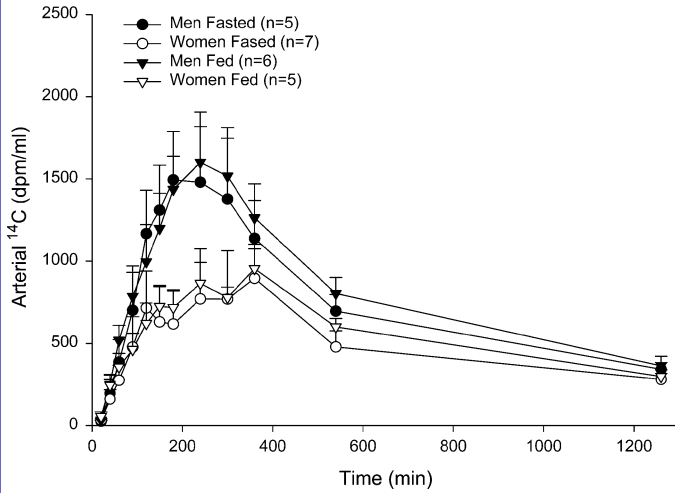


Fig. 3. Arterial blood <sup>14</sup>C as a function of time in the postprandial period. Fasted, test meal consumed after a 14-h overnight fast; Fed, test meal consumed ~4.5 h after breakfast. Data are normalized to meal lipid specific activity. Significant effect of gender (IAUC *P* = 0.04).

indicated by the significantly greater meal-derived lipid <sup>14</sup>C content of leg muscle tissue compared with men. Interestingly, recent data suggest that women have a significantly greater resting intramyocellular TG concentration compared with men (43). The current data suggest that this may be due, in part, to a greater uptake and retention of meal lipid in the muscle of women.

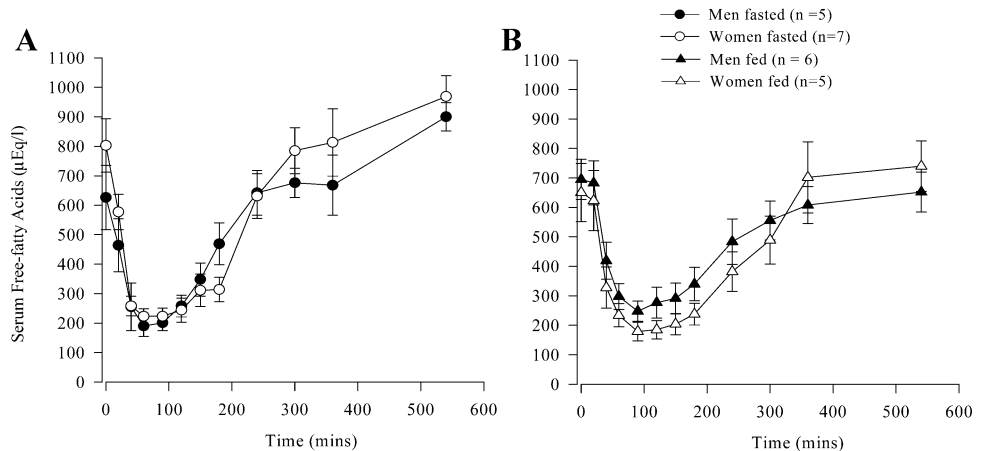
Potential reasons for the sex-based difference in the postprandial TG excursion and/or limb uptake of TG could relate to factors both internal and external to the muscle. Factors external to the muscle include the insulin and glucose responses to the meal. There was no difference, however, in the postprandial excursions for insulin and glucose between men and women on either study day. This is in agreement with other studies (18, 29, 37). Moreover, TG uptake across the limb was increased in women compared with men in both the fed and the fasted states, conditions characterized by different insulin and glucose concentrations. Furthermore, blood flow did not differ between groups

or days. Our observations of sex-based differences in TG metabolism were, therefore, independent of these circulatory factors. Under basal conditions (premeal), TG limb uptake was nonsignificantly higher in women vs. men, but with feeding this difference was pronounced, such that an increased limb TG uptake, with lower circulating TG concentration, was observed at all time points (i.e., clearance was increased under basal and postprandial conditions). Thus our results suggest that factors inherent to muscle determine the differential uptake of TG in women vs. men.

Few other studies have made a direct sex comparison of postprandial lipid metabolism including limb balance measurements. In one such study, Jensen (18) reported no sex difference in the absolute rate of TG uptake by the leg. This observation was made, however, at the end of the postprandial period (5–6 h after), a time when the plasma TG levels are not that different between men and women. In a separate limb balance study, the same group utilized a continuous-feeding protocol to obtain a steady-state rate of plasma TG appearance and disappearance (*R<sub>d</sub>*) by 5–6 h postprandially (29). At this time point, no sex-based difference was observed in the percentage of the meal TG *R<sub>d</sub>* that was taken up by the leg, whereas there appeared to be a tendency for non-CM-TG clearance to be higher in women than in men. Nevertheless, the women had a much greater limb metabolic clearance rate of CM-TG due to a lower concentration compared with men, yet a similar removal rate. These data, along with our current observations, strongly support the notion that women have a greater capacity for TG clearance at skeletal muscle postprandially compared with men.

The mechanisms responsible for the sex-based difference in skeletal muscle TG clearance are presently unknown, but recent data from our group suggest that differences in skeletal muscle lipoprotein lipase activity may not be a factor. Skeletal muscle lipoprotein lipase activity was not different in men vs. women before or after a euglycemic hyperinsulinemic clamp (32). Studies are underway to identify the intracellular mechanisms contributing to greater skeletal muscle TG clearance in women. It is important to note that,

Fig. 4. Arterial concentrations of circulating free fatty acids. *Time 0*, average of 4 premeal samples with the liquid meal consumed ~50 min after basal sampling. *A*: serum free fatty acid concentrations with the test meal consumed in the fasted state (after a 14-h overnight fast). *B*: serum free fatty acid concentrations with the test meal consumed in the fed state (~4.5 h after breakfast).



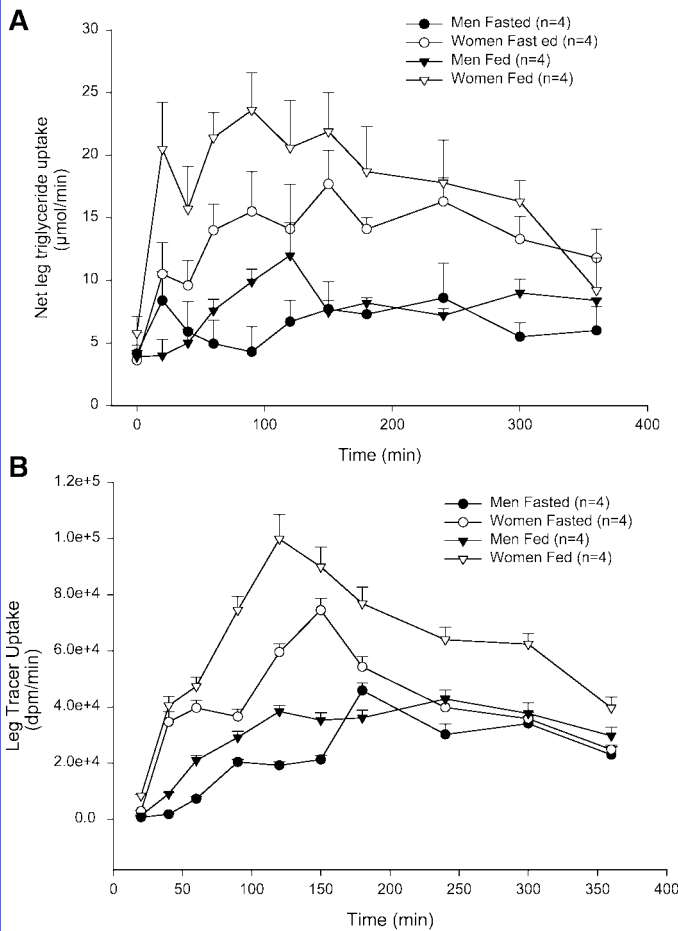


Fig. 5. A: Net leg triglyceride uptake before and after a test meal consumed in the fasted state (after a 14-h overnight fast) or fed state (~4.5 h after breakfast). Time 0, average of 4 premeal measurements with the meal consumed ~50 min later. Significant effect of gender (IAUC  $P = 0.035$  fasted day,  $P = 0.002$  fed day). Significant effect of condition in women only (fed > fasted  $P = 0.05$ ). B: net leg uptake of  $^{14}\text{C}$  after a test meal consumed in the fasted or the fed state. Significant effect of gender (IAUC  $P = 0.015$  and  $P = 0.025$ , respectively). Significant effect of condition in women only (fed > fasted  $P = 0.05$ ).

although women were characterized by increased retention of dietary lipid tracer in skeletal muscle, the sites of storage/retention in skeletal muscle (e.g., extra- vs. intramyocellular lipid; phospholipid vs. triacylglycerol) were not examined. Thus additional studies, perhaps using magnetic resonance spectroscopy, are necessary to identify the cellular location of dietary lipid storage in men and women.

In the present study, we observed significantly greater premeal (fasting) TG levels in men vs. women, similar to previous reports (11, 26, 29). It has been suggested that the higher fasting TG in men may in some way drive their higher postprandial TG response (11). Such a contention is based on data showing a significant positive correlation between fasting TG levels and the postprandial TG excursion (8, 30, 38), both of which can be related to the greater visceral adiposity in men (10, 11, 23, 38, 44). Indeed, under postprandial conditions, VLDL-TG is a significant contributor to the

total plasma TG concentration (3, 9, 16, 29, 35, 36). In the present study, we did not measure the contribution of the different lipoprotein fractions to the postprandial TG excursion, so we cannot comment on whether the sex-based difference in the postprandial TG excursion was mainly due to VLDL-TG, meal-derived lipid (CM-TG), or both. Whether there are sex-based differences in postprandial VLDL-TG secretion has never been directly addressed. It is noteworthy, however, that the greater postprandial TG excursion in men vs. women remains when groups are compared with similar fasting TG levels (3, 18) or when women are given a greater relative fat load compared with men (3). This suggests that differences in fasting TG and visceral adiposity are not the only factors responsible for the sex difference in the postprandial TG excursion. Menopause is associated with an aggravated postprandial lipemia in women matched for age and body mass index (45). Thus endogenous estrogen production may contribute to differences in postprandial TG excursions and TG metabolism. Women in the present study were in the follicular phase of their menstrual cycle. At least one study has suggested that the postprandial lipid response was not significantly different between the follicular and luteal phases of the menstrual cycle (47). Clearly, further studies are required to identify the factors regulating the lipemic response to meal ingestion in men and women.

Other possible sites of TG clearance postprandially include adipose tissue and liver. With respect to adipose tissue, we observed no difference in adipose tissue tracer content at 6 h in women vs. men. A number of studies using tissue balance measurements have shown that abdominal subcutaneous adipose tissue is a significant contributor to the removal of postprandial CM-TG (9, 35). None of these studies, however, has directly compared adipose tissue uptake and/or retention of meal lipid in men vs. women. With respect to liver clearance of TG, there are no direct data in hu-

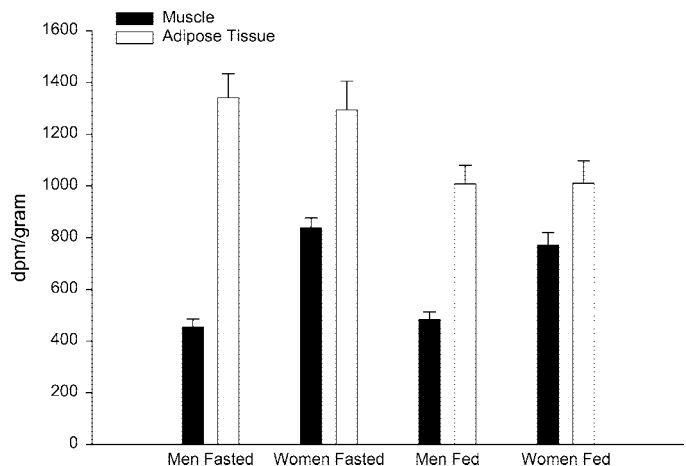


Fig. 6. Net accumulation of  $^{14}\text{C}$  in muscle and adipose tissue (dpm/g tissue) measured 6 h after consumption of the test meal. Fasted, test meal consumed after an ~14-h overnight fast; Fed, test meal consumed ~4.5 h after breakfast. Significant effect of gender for muscle tissue only ( $P = 0.006$ ).

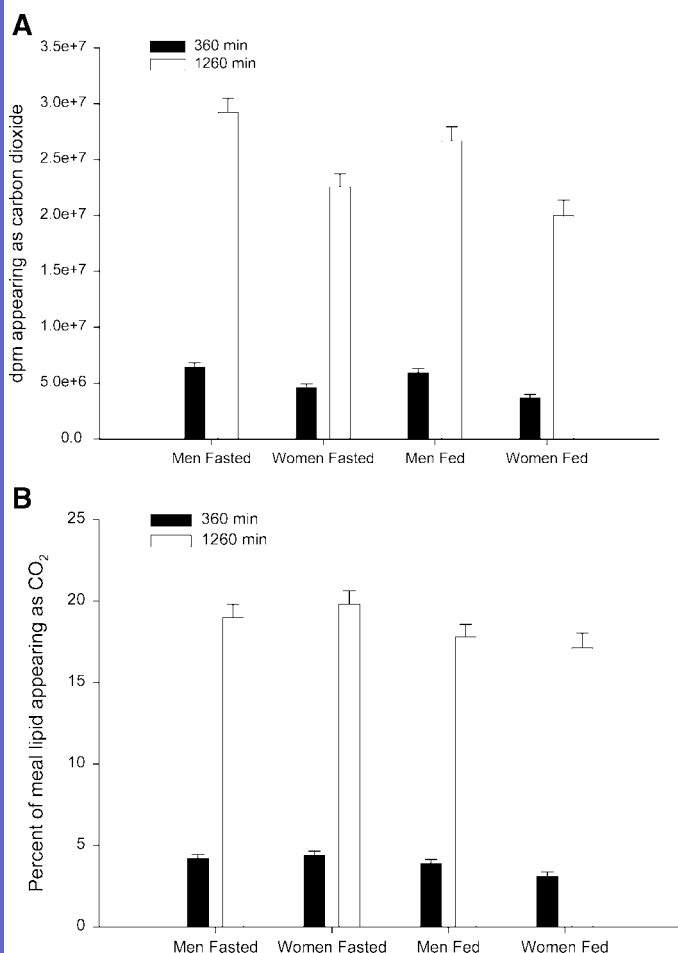


Fig. 7. **A:** cumulative dpm appearing in breath CO<sub>2</sub> over the first 6 h (360 min) and extended 21 h (1,260 min) after the test meal. Fasted, test meal consumed after an ~14-h overnight fast; Fed, test meal consumed ~4.5 h after breakfast. Data are adjusted for meal lipid specific activity. Overall effect of gender ( $P = 0.001$ , 360 min;  $P = 0.001$ , 1,260 min) and feeding condition (fasted > fed,  $P = 0.03$ , 360 min;  $P = 0.06$ , 1,260 min). **B:** estimated appearance of meal lipid in CO<sub>2</sub> expressed as a percentage over the first 6 h (360 min) and extended 21 h (1,260 min) after the test meal. Overall effect of feeding condition (fasted > fed,  $P = 0.07$ , 360 min;  $P = 0.032$ , 1,260 min).

mans. Splanchnic balance measurements have shown that meal TG removal is significantly greater in men than in women, but this was presumed to be due to a greater clearance of CM-TG by visceral adipose tissue (29), not liver. Although these data show a greater role of the splanchnic bed in postprandial TG clearance in men than in women, this certainly does not explain the greater postprandial TG excursion in men.

In the present study, we extended previous observations by comparing meal metabolism in men and women in both the overnight-fasted and fed (4.5 h after breakfast) states. Under fed conditions, the baseline preprandial TG concentration was significantly elevated compared with that after an overnight fast. Our data showed that the sex-based difference in the postprandial TG excursion was maintained even with this elevation in baseline TG concentration. Furthermore, the IAUC for the postprandial TG excursion was actu-

ally lower in both men and women in the fed than in the fasted condition. This suggests that either the rate of gastrointestinal lipid absorption was reduced or the clearance of TG was increased on the fed relative to the fasted day. Our current data would suggest that clearance of lipid at the muscle was greater in the fed than in the fasted state, particularly in the women. Interestingly, there were no differences in the peak TG concentration between the two conditions. Furthermore, it appeared that, in both men and women, glucose tolerance decreased when the test meal was consumed in the fed condition, as evidenced by the greater postprandial insulin and glucose excursions.

Another potential fate of TG, once it is cleared at tissues, is oxidation. We measured whole body lipid oxidation via indirect calorimetry. Although absolute rates of whole body lipid oxidation were greater in men than in women, this was accounted for by the sex-based differences in lean body mass. More importantly, the relative contribution of lipid to total fuel oxidation was not different, as indicated by the similar postprandial nonprotein RQ in men and women. This is in agreement with other studies (19). A relative indicator of meal lipid oxidation was taken from the incorporation of meal lipid (<sup>14</sup>C) tracer into breath CO<sub>2</sub>. The tracer incorporation into breath <sup>14</sup>CO<sub>2</sub> is not fully quantitative, but it gives a relative comparison between groups and days. Again, on an absolute basis, men had greater incorporation of the meal lipid tracer into breath CO<sub>2</sub>, but, relative to the meal fat consumed and total fat oxidized, there was no sex-based difference. Interestingly, there was a tendency for more of the meal-derived lipid tracer to be incorporated into breath <sup>14</sup>CO<sub>2</sub> with the meal consumed in the fasted vs. the fed condition. An indirect estimate can be made of meal-derived lipid oxidation at the limb from the difference between the net tracer uptake over 6 h and the net tracer retention in the muscle. When this was done, the data suggest that women were oxidizing more of the meal lipid at the muscle, at least over the initial 6 h postprandially. If skeletal muscle meal-derived lipid oxidation was truly greater in women, this was not reflected in the whole body <sup>14</sup>CO<sub>2</sub> evolution, suggesting that meal-derived lipid oxidation in men may have been greater in other tissues. It cannot be ruled out, however, that the inability to detect a sex-based difference in the incorporation of meal-derived lipid into breath CO<sub>2</sub> was due to technical limitations as discussed below.

There are a number of caveats that require discussion in terms of the study design. First, the abbreviated time course of the study meant that it was likely that not all ingested lipid had been absorbed. This would have been even more true for a solid meal, hence the choice of a liquid meal. Extending the time course of the study would have given a more comprehensive description of the fate of the meal lipid. This would not, however, have added to observations regarding the sex-based differences in the postprandial TG excursion, as TG concentrations were close to baseline values by the 6-h time point. Clearly, the incorporation of



meal-derived lipid tracer into CO<sub>2</sub> underestimates meal lipid oxidation due to both retention of tracer in the bicarbonate pool and exchange reactions in the TCA cycle. However, our conclusions regarding sex-based differences in skeletal muscle TG clearance can be made without recourse to tracer measurements (27, 40, 41).

In conclusion, this study demonstrated a significantly greater contribution of skeletal muscle to the postprandial clearance of both total and meal-derived lipid in women relative to men. This is, therefore, one factor contributing to the lower postprandial TG excursion in women compared with men. Women also retained more of the meal lipid in muscle relative to men but not in adipose tissue. There was no sex-based difference, however, in the relative contribution of lipid to whole body oxidation postprandially or any suggestion of a difference in the relative oxidation of meal lipid. These sex-based differences were robust, being observed both after an overnight fast and in the semi-fed condition (breakfast consumed 4.5 h before study). Because the insulin and glucose excursions were not different between the sexes, the observations on TG metabolism were independent of these parameters. These data strongly suggest, therefore, that there are factors inherent to the muscle of women that promote TG uptake. Further work is needed to establish whether this is a sex difference per se or related to the different sex steroid environments in men vs. women.

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