

Nutrient Physiology, Metabolism, and Nutrient-Nutrient Interactions

The Elevation of Ingested Lipids within Plasma Chylomicrons Is Prolonged in Men Compared with Women¹

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ABSTRACT The lipemic response to a high-fat meal is greater in men than in women. However, sex-related differences in the metabolic fate of ingested fat are not well understood. The purpose of this study was to measure the recovery of ingested fat in plasma fractions of chylomicrons (CHYLO), VLDL, and plasma fatty acids, as well as in expired breath (i.e., oxidation) in men and women. Nonobese subjects ($n = 10$; 5 men, 5 women) consumed 0.7 g fat/kg body weight containing 7 mg/kg of [1,1,1-¹³C]-trioleate the morning after an overnight fast. Plasma total triglyceride (TG) concentration and ¹³C recovery in the CHYLO, VLDL, and plasma fatty acid fractions, as well as expired breath samples, were measured over the 11-h period after the meal. Plasma total TG excursion was greater ($P < 0.05$) in men than in women during the 11-h period after the meal. Similarly, the recovery of the ingested tracer-labeled fat in the CHYLO fraction was greater in men than in women (main effect for sex; $P < 0.05$). Recovery of ingested tracer-labeled fat in VLDL, the plasma fatty acid fraction, and expired breath did not differ in men and women. Therefore, the elevated postprandial lipemia found in men compared with women was due to a prolonged availability of the lipid in chylomicrons, but was not related to differences in oxidation rates or incorporation of the ingested lipid into VLDL by the liver. *J. Nutr.* 136: 1498–1503, 2006.

KEY WORDS: • fat metabolism • VLDL • cardiovascular disease • fatty acids • sexual dimorphism

Although cardiovascular disease (CVD)³ is the leading cause of death among women, on average, the development of CVD is delayed ~10 y in women compared with men (1). The factors responsible for this sex-related difference in the development of CVD are not completely understood. It has been widely reported that the plasma triglyceride (TG) response to meals is markedly reduced in premenopausal women compared with men of similar age (2–6). Because the postprandial rise in plasma TG is an independent risk factor for the development of atherosclerosis and CVD (7), sex-related differences in the regulation of postprandial lipid metabolism may contribute to the differences between men and women in the development of CVD.

Although prolonged elevation of plasma TG concentration after a meal is linked with advancement in the development of CVD (7,8), the health risk associated with elevated plasma lipids is largely dependent on the dynamic metabolic processes of the different major lipoprotein fractions [i.e., chylomicrons (CHYLO), VLDL, LDL, and HDL] (9). Therefore, simply

measuring the concentration of circulating TG after a meal provides limited information about the atherogenic potential of the ingested lipids. In contrast, measuring the incorporation of the ingested fat into different lipid fractions, as well as its oxidation rate (i.e., the “metabolic fate” of the ingested fat) provides a more comprehensive depiction of the atherogenic properties of a meal (9). Ingested lipids are first absorbed through the intestinal wall and packaged into large TG-rich CHYLO particles, which follow a well-defined catabolic pathway (9). In general, fatty acids from TG within the CHYLO particles may be taken up into tissues for storage or oxidation, or they may be released into the circulation (10). The ingested lipids can also be incorporated into other lipoproteins (i.e., VLDL) within the liver (11,12). Even though it is clear that the plasma TG response after a meal is greater in men than in women (2–6), differences between men and women in the “metabolic fate” of ingested fat are not well described. The purpose of this study was to compare the metabolic fate of a fat meal in premenopausal women and age-matched men by measuring the recovery of ingested tracer-labeled fat in plasma fractions of CHYLO, VLDL, plasma fatty acids, as well as expired breath (i.e., oxidation).

SUBJECTS AND METHODS

Subjects

Five men and five women participated in this study. Subjects were lean (BMI: 22.8 ± 0.8 and 21.2 ± 0.8 kg/m² for men and women, respectively) and considered to be in good health after completing a medical history and physical examination, 12-lead electrocardiogram,

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³ Abbreviations used: apo, apolipoprotein; CHYLO, chylomicron; CVD, cardiovascular disease; %EN, percentage enrichment; FFM, fat-free mass; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; LPL, lipoprotein lipase; Sf, Svedberg flotation index; TG, triglyceride; VCO₂, rate of carbon dioxide production; VO₂, rate of oxygen consumption.

and measurement of fasting plasma glucose, insulin, and TG concentrations. No subject had any evidence of metabolic or cardiovascular disorders nor were any of them taking prescription medications. Subjects were informed of the procedures and the possible risks and signed an informed consent document that was approved by the University of Michigan Institutional Review Board.

Preliminary testing

We measured body composition in all subjects at least 1 wk before their participation in the study experiments. Body composition was measured by hydrostatic weighing via the 2-compartment method (13), and residual lung volume was measured by the oxygen dilution method (14).

Experimental protocol

For the 2 d preceding the experimental trial, subjects were instructed to maintain their normal diet and to refrain from exercising. All of the women were studied during the follicular phase of their menstrual cycle. Subjects were admitted to the General Clinical Research Center at the University of Michigan Hospital at 1800 the evening before the experimental trial and were given a standardized meal (50.2 kJ/kg body weight; 0.4 g fat/kg, 1.8 g carbohydrate/kg, and 0.3 g protein/kg) at 1830. After the evening meal, subjects were allowed only water, and spent the remainder of the evening restricted to their beds. At 2130, subjects were given an evening snack (29.3 kJ/kg body weight; 0.2 g fat/kg, 1.1 g carbohydrate/kg, and 0.2 g protein/kg), which was completed by 2200.

The next morning, a Teflon catheter was inserted into an antecubital vein of one arm for blood sampling and a basal blood sample was obtained at 0600. Basal whole-body fat oxidation was then assessed for 20–30 min by measuring resting oxygen consumption (VO_2) and carbon dioxide production (VCO_2) using a ventilated canopy system (Delta Trac; SensorMedics). After this measurement, expired breath samples were collected in sealed evacuated test tubes (Exetainer, Labco) as subjects breathed through a mouthpiece and 2-way valve for 5 min. These breath samples were used to determine the background enrichment of expired $^{13}\text{CO}_2$. At 0700 (after a 9-h fast) subjects consumed a high-fat meal (29.3 kJ/kg body weight) of heavy whipping cream (0.7 g fat/kg, 0.05 g carbohydrate/kg, 0.04 g protein/kg; Land O'Lakes) with 36 mg of saccharin added for flavor. Exactly 7 mg/kg of [1,1,1- ^{13}C]-trioleate (Cambridge Isotopes) was mixed/sonicated in with this fat meal to allow us to trace the metabolic fate of the ingested fat. The amount of heavy whipping cream and tracer ingested by the subjects was provided relative to body mass to normalize the dose between men and women. This also normalized the dose of fat ingested relative to the plasma volume in men (3.04 ± 0.10 g fat/L plasma) and women (3.03 ± 0.09 g fat/L plasma). Plasma volume was estimated from hematocrit and lean body weight measurements (15). After ingestion of the fat meal, subjects were restricted to sitting comfortably, upright in bed for the next 11 h. Blood samples were taken 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, and 11 h after the meal. Fat oxidation was measured over a 20-min period using the ventilated canopy system 1 h after the meal and every 90 min thereafter. In addition, expired breath samples were collected over a 5-min period in evacuated test tubes at 2.5, 4, 5.5, 7, and 11 h after the meal to assess changes in expired $^{13}\text{CO}_2$ after the ingestion of the tracer-labeled fat.

Blood sample preparation

Blood samples were collected into chilled test tubes containing EDTA (0.03 mmol/L) and aprotinin (500 trypsin inhibitory units/L) for analysis of TG, glucose, fatty acid, and insulin concentrations, as well as basal plasma total cholesterol, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C). All samples were kept on ice and then centrifuged ($1600 \times g$ for 15 min at 4°C) within 30 min of collection. After centrifugation, the plasma from each sample was divided and transferred into two 12×75 mm plastic culture tubes. One tube was immediately frozen and stored at -80°C for later analysis of plasma concentrations of TG, glucose, fatty acid, and insulin; the other

was stored at 4°C for isolation of CHYLO and VLDL lipoprotein fractions.

Separation of CHYLO and VLDL fractions. Chylomicron and VLDL particles were separated from plasma by density gradient ultracentrifugation, as described by Redgrave and Carlson (16), with minor modification. Briefly, aliquots (1 mL) of refrigerated plasma samples were suspended in 3.7 mL saline ($\delta = 1.006$ kg/L) and centrifuged (Beckman Optima LE-80K ultracentrifuge, SW 41 T₁ rotor) at $180,000 \times g$ for 32 min at 5°C . To obtain the CHYLO fraction, the top ~ 1.5 mL was cut from the tube and removed (Optiseal Centrifuge Tubes, Beckman), isolating lipids with a Svedberg flotation index (S_f) > 400 , which are primarily chylomicrons (17). The remaining material (not in the top 1.5 mL) was resuspended in saline and centrifuged at $180,000 \times g$ for 18 h at 12°C . The top 1.5 mL was cut from this tube to isolate lipids with S_f 20–400, which are primarily VLDL particles (17). All CHYLO and VLDL fractions were isolated within 72 h of sample collection, and the resultant fractions were frozen at -70°C until further analysis.

Isolation of TG from lipoprotein fractions and fatty acids from plasma. Aliquots (750 μL) of plasma samples and the isolated CHYLO and VLDL lipoprotein fractions were deproteinized with 3 mL acetone, centrifuged ($1600 \times g$ for 15 min at 4°C), and the supernatant dried under vacuum (SpeedVac, ThermoSavant) before isolating either fatty acids or TG using TLC. Briefly, dried samples were resuspended in chloroform:methanol (3:1), spotted on a LK6D silica gel plate (60 Å silica gel, 250 μm layer thickness; Whatman), and developed with heptane:diethyl ether:formic acid (80:20:2) solvent in an enclosed developing chamber. The fatty acid band was identified in TLC lanes spotted from plasma samples and TG were identified in the TLC lanes from the CHYLO and VLDL fractions. These bands were cut from the TLC plate into 13×100 test tubes; the lipids were extracted from the silica gel with chloroform:methanol (3:1) and dried under vacuum. Finally, the dried samples were hydrolyzed and methylated by resuspending the samples in 10% acetyl chloride:methanol for 30 min at 70°C before they were dried under vacuum and stored for later analysis.

Analytical procedures

Plasma substrates and insulin concentrations. Commercially available colorimetric assays were used to measure plasma concentrations of TG (ThermoTrace), glucose (ThermoTrace), as well as total cholesterol, LDL-C, and HDL-C concentrations (Diagnostic Chemicals). Plasma insulin concentration was measured by RIA (Linco Research). Plasma fatty acid concentration was measured by an internal standard method using GC with flame ionization detection (Agilent 6890 Series, GC System, Agilent Technologies) (18). Heptadecanoic acid was used as the internal standard (elution time ~ 7.5 min), and the samples were run on an Omegawax 250 column (Supelco) under the following conditions: starting oven temp at 60°C , $30^\circ\text{C}/\text{min}$ ramp to 240°C , and held there for 8 min. Methyl oleate eluted at ~ 8.2 min.

Recovery of ingested tracer in plasma samples. Tracer recovery was measured using GC-MS (Agilent 5973Networks, Mass Selective Detector, Agilent Technologies). Samples were run on a DB-17 column (J&W Scientific) under the following conditions: starting oven temp at 70°C , $40^\circ\text{C}/\text{min}$ ramp to 230°C , 1.2-min hold, $70^\circ\text{C}/\text{min}$ to 270°C , 6.73-min hold. Methyl oleate eluted at ~ 6.5 min. The amount of tracer in the sample was determined from extracting ions at a mass-to-charge ratio (m/z) of 296 and 297 m/z .

Recovery of ingested tracer in expired breath samples. The amount of $^{13}\text{CO}_2$ in the breath samples collected in evacuated test tubes was measured with a Finnigan BreathMat Plus continuous flow gas isotope ratio mass spectrometer (Finnigan MAT). Briefly, after injection of the breath sample into the instrument, water was removed from the sample by passing it across a desiccant column. A timing program identified the CO_2 portion of the breath sample and introduced it into the isotope ratio mass spectrometer. The ratio of $^{13}\text{CO}_2$ to $^{12}\text{CO}_2$ (mass 45 to mass 44) was measured in the sample and compared with a reference gas (5% CO_2 , balance 75% N_2 , 20% O_2).

Calculations

Recovery of ingested tracer in blood lipid fractions. Recovery of ingested tracer in the CHYLO, VLDL, and fatty acid fractions was

expressed as the percentage enrichment (%EN). The %EN in the different lipid fractions refers to the percentage increase in tracer enrichment in the samples taken after ingestion of the tracer-labeled meal compared with the endogenous background tracer enrichment before the meal, calculated as:

$$\%EN = \%EN_{(t)} - \%EN_{(t_0)},$$

where $\%EN_{(t)}$ is the percentage enrichment of oleate in the sample at time t [$^{13}\text{C-oleate}_{(t)}/(^{13}\text{C-oleate}_{(t)} + ^{12}\text{C-oleate}_{(t)}) \times 100\%$], and $\%EN_{(t_0)}$ is the percentage enrichment of oleate in the basal state [$^{13}\text{C-oleate}_{(t_0)}/(^{13}\text{C-oleate}_{(t_0)} + ^{12}\text{C-oleate}_{(t_0)}) \times 100\%$]. %EN reflects the incorporation of ingested fat into the CHYLO, VLDL, and plasma fatty acid fractions.

Whole-body fat oxidation. Resting whole-body rate of fat oxidation was calculated from V_{O_2} and V_{CO_2} values using the equation of Frayn (19) and an estimated rate of nitrogen excretion of $80 \mu\text{g}/(\text{kg} \cdot \text{min})$ (20).

Whole-body fat oxidation

$$\begin{aligned} & \{ \mu\text{mol}/[\text{kg fat-free mass (FFM)} \cdot \text{min}] \} \\ & = \{ [(1.67 V_{\text{O}_2} - 1.67 V_{\text{CO}_2}) \\ & \quad - [1.92 \times (8 \times 10^{-5} \times \text{kg body weight})]] \\ & \quad \div 860 \text{ g/mol} \} \times 10^6 \\ & \div \text{FFM}. \end{aligned}$$

Oxidation of ingested fat. The rate of exogenous fat oxidation was calculated from V_{CO_2} and the percentage enrichment in expired CO_2 (E), where E is calculated as $= ^{13}\text{CO}_2/(^{13}\text{CO}_2 + ^{12}\text{CO}_2) \times 100\%$. The equation used to calculate the oxidation of ingested fat [$\mu\text{mol}/(\text{kg FFM} \cdot \text{min})$] was:

Oxidation of ingested fat

$$\begin{aligned} & = V_{\text{CO}_2} \times [(E_{(t)} - E_{(t_0)}) \div (E_{(exo)} - E_{(t_0)})] \\ & \quad \times 1/k \times 1/0.6 \times 1000/884 \\ & \div \text{FFM}, \end{aligned}$$

where $E_{(t)}$ is the percentage enrichment of the expired CO_2 at time t , $E_{(t_0)}$ is the percentage enrichment of the expired CO_2 at time zero, $E_{(exo)}$ is the percentage enrichment of the ingested meal, k is the volume of CO_2 provided by the oxidation of fat (1.444 L/g), 0.6 is a correction factor for incomplete recovery of [^{13}C]bicarbonate (21), and 884 is the molecular weight of triolein. $E_{(exo)}$ was calculated for each subject based on the amount of tracer and tracee in the ingested fat meal assuming that 1.1% of the carbon atoms in heavy whipping cream were ^{13}C :

$$\begin{aligned} \text{tracer} & = (F_s \times 0.011) + (T_s \times 3)/57 \\ \text{tracee} & = (F_s \times 0.989) + (T_s \times 54)/57 \\ E_{(exo)} & = \text{tracer}/(\text{tracee} + \text{tracer}), \end{aligned}$$

where F_s is the amount of fat ingested in the heavy whipping cream and T_s is the amount of ^{13}C -triolein ingested.

Statistical analysis

A 2-way ANOVA (sex \times time) for repeated measures with Tukey's post hoc analysis was used to test for significant differences in plasma concentrations of TG, fatty acid, insulin, and glucose, whole-body fatty acid oxidation, oxidation of the ingested lipid, as well as %EN in the CHYLO, VLDL, and fatty acid fractions. A student's t test was used to test for significant differences in all subject characteristics. Statistical analyses were performed using SigmaStat for Windows (version 3.0.1a; Systat Software). Statistical significance was defined as $P < 0.05$. All results are presented as means \pm SEM.

RESULTS

Subject characteristics. Subject characteristics are reported in Table 1. Although all subjects were lean, as expected, women had a greater fat mass than men, whereas FFM was greater in men than in women. After an overnight fast, plasma total cholesterol and plasma HDL-C concentrations also did not differ between men and women. However, fasting plasma LDL-C concentrations tended to be greater in men than in women ($P = 0.1$).

Plasma TG, glucose, and insulin concentrations. After an overnight fast, plasma total TG concentration did not differ between men and women (0.90 ± 0.08 and 0.95 ± 0.15 mmol/L, respectively). However, the plasma TG response to the lipid load differed between the sexes ($P < 0.05$) (Fig. 1). In women, the plasma TG concentration reached a peak 2 h after ingestion of the fat meal and decreased progressively over the next few hours before returning to baseline levels ~ 6 h after the lipid ingestion. In contrast, in men, the peak plasma TG concentration was delayed until 3–4 h after ingestion, and did not return to baseline levels until 9 h after ingestion (Fig. 1). The average plasma glucose and insulin concentrations did not differ between men and women after they ingested the lipid load (glucose: 4.8 ± 0.1 and 4.8 ± 0.2 mmol/L; insulin: 65.2 ± 7.1 and 77.1 ± 8.1 pmol/L, respectively).

Incorporation of ^{13}C -oleate in plasma lipid fractions. The recovery of ^{13}C -oleate in TG within the plasma CHYLO pool was significantly greater in men than in women (main effect for sex; $P < 0.05$) (Fig. 2A). Much of the difference in the percentage enrichment between men and women occurred during the period 5–11 h after ingestion. The recovery of ^{13}C -oleate in TG did not differ within the VLDL (Fig. 2B). Women tended to have a greater recovery of ^{13}C -oleate in the plasma fatty acid fraction (Fig. 2C; $P > 0.2$; main effect for sex). The plasma fatty acid concentration did not differ between men and women (data not shown).

Fatty acid oxidation. Average fatty acid oxidation did not differ between men and women [1.53 ± 0.11 and 1.73 ± 0.12 $\mu\text{mol}/(\text{kg FFM} \cdot \text{min})$, respectively] throughout the 11-h period after lipid ingestion. In addition, despite the difference in the plasma TG response to the meal, oxidation of the ingested lipid, calculated from $^{13}\text{CO}_2$ recovery in expired breath, did not differ between men and women throughout the 11-h period after the meal (Fig. 3).

TABLE 1

Subject characteristics¹

	Men	Women
Age, y	26 \pm 1	22 \pm 2
Body mass, kg	70.1 \pm 4.6	61.1 \pm 2.8
BMI, kg/m ²	22.8 \pm 0.8	21.2 \pm 0.8*
% Body fat	12.6 \pm 1.7	26.2 \pm 1.8*
Fat free mass, kg	61.2 \pm 3.7	45.1 \pm 2.5*
Fat mass, kg	8.9 \pm 1.5	15.9 \pm 1.3*
Plasma lipids, mmol/L ²		
Triglycerides	0.90 \pm 0.08	0.95 \pm 0.15
Total cholesterol	4.6 \pm 0.3	4.5 \pm 0.4
LDL-C	2.7 \pm 0.4	2.3 \pm 0.4
HDL-C	1.5 \pm 0.2	1.6 \pm 0.1

¹ Values are means \pm SEM, $n = 5$ for each sex. *Different from men, $P < 0.05$.

² Assays were conducted using blood obtained from fasting subjects.

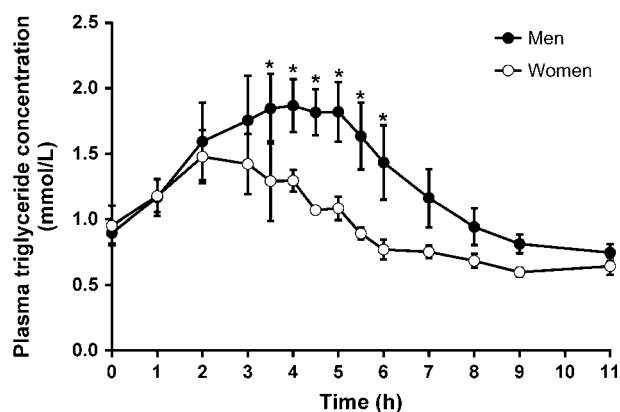


FIGURE 1 Plasma triglyceride concentration before and during the 11-h period after a fat meal in men and women. Values are means \pm SEM, $n = 5$ for each sex. *Different from women, $P < 0.05$.

DISCUSSION

Differences in lipid metabolism between men and women have been reported for decades (2,4,22). In particular, women were found to exhibit a lower postprandial rise in plasma TG after eating a fatty meal compared with men (4–6). The main finding from this study was that the greater plasma lipid response to the fat meal in men compared with women was due only to a prolonged recovery of ingested TG in CHYLO lipoproteins in men, whereas the recovery of the ingested lipids in VLDL, the plasma fatty acid pool, and expired breath did not differ between men and women. Because alterations in lipid metabolism are linked to CVD risk, these differences in the lipemic response to a meal may be associated with the earlier development of CVD in men compared with women.

Recovery of the ingested lipid tracer was evident in the CHYLO, VLDL, and fatty acid fractions 2 h after consumption of the meal in both men and women. In agreement with our findings, Binnert et al. (23) reported a progressive rise in the recovery of ingested lipid in these same lipid fractions from 1 to 4 h after a fat meal in healthy women. Contrary to our findings, however, these investigators reported a rapid decline in the recovery of ingested lipid in the CHYLO fraction after 4 h (23). This discrepancy is likely explained by the fact that our subjects ingested about twice as much fat and ^{13}C -triolein compared with that provided by Binnert et al. (23). In agreement with data in healthy women (23), the recovery of the ingested fat in the VLDL and fatty acid fractions in both men and women remained elevated for several hours. The prolonged elevation of the ingested TG in these fractions likely reflected the relatively slow rate of incorporation of ingested fatty acids into VLDL in the liver, and a relatively stable turnover of labeled fatty acids from both CHYLO and VLDL into the plasma fatty acid pool.

Much of the prolonged recovery of the ingested lipids in the CHYLO fraction in men was likely due to a more rapid clearance of ingested CHYLO TG after a meal in women than in men (24). Hydrolysis of plasma TG is regulated primarily by the enzyme lipoprotein lipase (LPL), which resides on the endothelial wall of capillaries in skeletal muscle, adipose tissue, and the heart. Regulation of LPL differs in men and women (25), as well as in various tissues (26,27) and regions of the body (27,28). The primary site of postprandial plasma TG hydrolysis and the ultimate fate of the fatty acids derived from ingested fat in men and women are controversial (4,29). Romanski et al. (29) reported that more ingested fatty acid tracer was recovered in abdominal subcutaneous adipose tissue

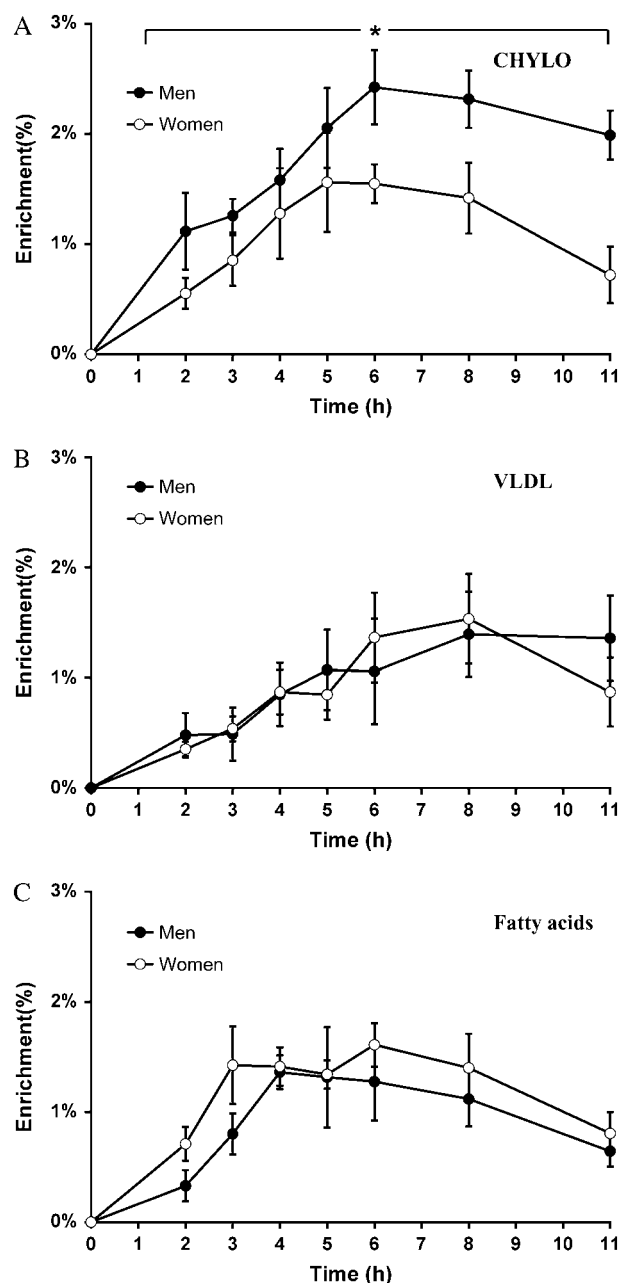


FIGURE 2 Recovery of ingested lipid as ^{13}C -oleate percentage enrichment in chylomicron triglycerides (A), VLDL triglycerides (B), and plasma fatty acids (C) before and during the 11-h period after a fat meal in men and women. Values are means \pm SEM, $n = 5$ for each sex. (A) *Main effect for sex, $P < 0.05$.

in women than in men. Alternatively, Horton et al. (4) found that women took up and stored more ingested fat in skeletal muscle than men. Fatty acids liberated by skeletal muscle LPL are taken up and stored and/or oxidized primarily locally within muscle (10,30,31). In contrast, fatty acids liberated by LPL in adipose tissue are largely released into the systemic circulation (10,30). Evans et al. (10) demonstrated that in the few hours after a meal, only $\sim 50\%$ of the fatty acids derived from adipose tissue LPL hydrolysis were taken up locally by adipose tissue, and almost all of the TG-borne fatty acids were released into the systemic circulation (i.e., very little taken up locally) in the postabsorptive state. Therefore, if adipose tissue was the primary site for a more rapid rate of hydrolysis of the ingested

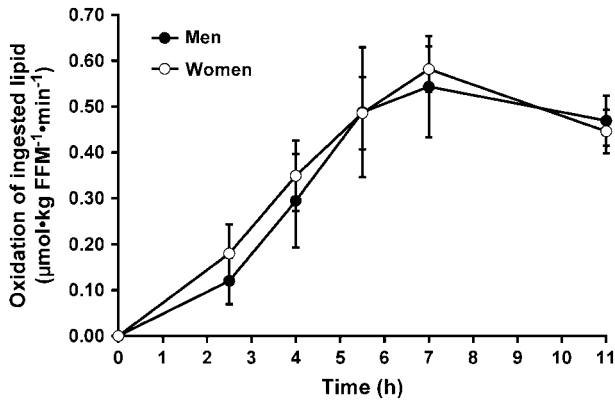


FIGURE 3 Oxidation of ingested lipid as measured by $^{13}\text{CO}_2$ recovery in breath samples before and during the 11-h period after a fat meal in men and women. Values are means \pm SEM, $n = 5$ for each sex.

lipids in the women in our study compared with the men, we would expect to see a greater recovery of the tracer-labeled fat in the plasma fatty acid pool in women. Although we cannot directly determine the primary site of CHYLO TG hydrolysis in our subjects, our observation that the recovery of the ingested fat in the fatty acid pool was the same in the men and women agrees with Horton et al. (4) by suggesting that skeletal muscle may be the primary site of an increased rate of hydrolysis and uptake of CHYLO-TG in women compared with men. This notion is consistent with several reports demonstrating that intramuscular TG stores are greater in women than men (32,33).

The nearly identical recovery of the ingested fatty acid tracer in the VLDL fraction in men and women in this study suggests that liver incorporation of exogenous TG into lipoproteins was similar between the sexes. Ingested fat can become incorporated into VLDL in the liver either through hepatic uptake of fatty acids that were released into the systemic circulation from the exogenous TG hydrolyzed by lipoprotein lipase in adipose, skeletal muscle, and cardiac muscle, or through the local lipolytic action of hepatic lipase on TG in chylomicron particles. Postheparin hepatic lipase was found to be as much as 2-fold greater in men compared with women (34,35), which was attributed to differences in testosterone (36,37) and estrogen (38). More recent data indicate that intra-abdominal fat content plays a major role in the sex-related difference in hepatic lipase activity (39). We did not measure intra-abdominal adiposity in our study; because our subjects were lean, the difference in intra-abdominal adiposity between the men and women was likely rather small. Therefore, the intra-abdominal fat content may have had little effect on hepatic lipase in our subjects, which might help explain the similar rates of incorporation of the ingested lipids into VLDL in men and women.

The oxidation of ingested lipids also did not differ in men and women. Because the liver is responsible for about one-third of the fat oxidized in resting humans (40), this provides additional evidence that hepatic metabolism of the ingested fat was similar in the men and women in our study. After the liver, skeletal muscle is the next greatest source of fat oxidation in resting humans (41). Horton et al. (4) reported that although uptake of ingested fat into skeletal muscle was greater in women than in men, similar to our findings, they reported no difference in the oxidation of ingested fat between the sexes. A greater rate of uptake than oxidation in skeletal muscle will result in an accumulation of lipid within the muscle cell, which again is consistent with previous work indicating that women have a greater storage of intramuscular TG than men (32,33).

Alterations in chylomicron metabolism, which we found to explain much of the sex-related difference in post-prandial lipemia, may also help dictate sex-related differences in cardiovascular health. Chylomicrons and chylomicron remnants have potent atherogenic properties (42–44). Chylomicron remnants are the product of partial metabolism and modification of chylomicron particles. They penetrate the endothelial cells of the arterial wall where they can be taken into macrophages (45), facilitating foam cell development and ultimately leading to the formation of atherosclerotic lesions. Prolonged availability of chylomicron particles in the circulation increases the opportunity for remnant formation and for cholesterol-ester exchange from other circulating lipoproteins (46), thereby increasing the atherogenic potential of the chylomicron particles. Therefore, the delayed clearance of chylomicron TG in the men in our study may help explain the earlier development of CVD risk factors in men compared with women.

Interpretation of our findings requires confidence in the methods we used to isolate the different lipid fractions. Using methods similar to those described in the present study, Karpe et al. (47–49) reported that the abundance of apolipoprotein (apo) B-100 (strictly a component of liver-derived VLDL particles) in the $S_f > 400$ fraction was negligible after a fat meal, whereas the abundance of apo B-48 (strictly a component of intestinally derived chylomicron particles) increased markedly in this fraction after a fat meal. These findings indicate that changes in $S_f > 400$ lipids after a fat meal represent primarily changes in chylomicron particles. Similar analysis of the $S_f 20$ –400 fraction demonstrated that the apo B-100 content of this fraction after a fat meal was ~ 50 -fold greater than that of apo B-48, indicating that the $S_f 20$ –400 lipids are primarily VLDL particles (47–49). The small amount of apo B-48 within the $S_f 20$ –400 lipids most likely represents chylomicron remnants (50). The validity of density gradient ultracentrifugation to isolate chylomicron and VLDL particles in $S_f > 400$ lipids and $S_f 20$ –400 lipids, respectively, was also supported by a comparison of the ultracentrifugation technique with NMR in quantification of CHYLO and VLDL particles after a fat meal (51).

In summary, we found that the difference in postprandial lipemia between men and women was due to a more prolonged elevation of the ingested TG in chylomicrons in men compared with women. Interestingly, recovery of ingested TG in VLDL, the plasma fatty acid fraction, and expired breath (i.e., oxidation of ingested fats) did not differ between men and women. A more prolonged elevation of ingested TG in the chylomicron fraction provides a greater opportunity for chylomicron remnant formation and for cholesterol-ester exchange from other circulating lipoproteins. This would increase the atherogenic potential of each meal and may help explain the earlier development of cardiovascular disease risk factors in men than women.

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