Oxidation of nonplasma fatty acids during exercise is increased in women with abdominal obesity

JEFFREY F. HOROWITZ AND SAMUEL KLEIN

Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri 63110

Received 11 April 2000; accepted in final form 10 July 2000

Horowitz, Jeffrey F., and Samuel Klein. Oxidation of nonplasma fatty acids during exercise is increased in women with abdominal obesity. J Appl Physiol 89: 2276–2282, 2000.—We evaluated plasma fatty acid availability and plasma and whole body fatty acid oxidation during exercise in five lean and five abdominally obese women (body mass index = 21 ± 1 vs. 38 ± 1 kg/m²), who were matched on aerobic fitness, to test the hypothesis that obesity alters the relative contribution of plasma and nonplasma fatty acids to total energy production during exercise. Subjects exercised on a recumbent cycle ergometer for 90 min at 54% of their peak oxygen consumption. Stable isotope tracer methods ([13C]palmitate) were used to measure fatty acid rate of appearance in plasma and the rate of plasma fatty acid oxidation, and indirect calorimetry was used to measure whole body substrate oxidation. During exercise, palmitate rate of appearance increased progressively and was similar in obese and lean groups between 60 and 90 min of exercise [3.9 ± 0.4 vs. 4.0 ± 0.3 μmol·kg free mass (FFM)⁻¹·min⁻¹]. The rate of plasma fatty acid oxidation was also similar in obese and lean subjects (12.8 ± 1.7 vs. 14.5 ± 1.8 μmol·kg FFM⁻¹·min⁻¹; P = not significant). However, whole body fatty acid oxidation during exercise was 25% greater in obese than in lean subjects (21.9 ± 2.2 vs. 17.5 ± 1.6 μmol·kg FFM⁻¹·min⁻¹; P < 0.05). These results demonstrate that, although plasma fatty acid availability and oxidation are similar during exercise in lean and obese women, women with abdominal obesity use more fat as a fuel by oxidizing more nonplasma fatty acids.

Exercise is a key component of the clinical management of obesity because it is associated with long-term maintenance of weight loss (20). In addition, aerobic fitness itself is associated with important health benefits that are independent of weight loss; the incidence of diabetes (45) and cardiovascular mortality (25) are much lower in obese persons who are fit than in those who are unfit. Therefore, endurance exercise may be particularly beneficial for persons with abdominal obesity because of their increased risk of diabetes and cardiovascular disease (22).

Endurance exercise stimulates the mobilization and oxidation of fatty acids from endogenous triglycerides (36). During exercise, adipose tissue releases fatty acids into plasma, which are delivered to skeletal muscle for fuel (37). In addition, lipolysis of intramuscular triglycerides (IMTG) can release fatty acids directly into the cytosol of working muscles (3). In contrast, plasma triglycerides are not normally an important fuel during exercise performed during postabsorptive conditions (30). Persons with abdominal obesity have excessive stores of the major lipid fuels used during exercise (i.e., adipose tissue and IMTG) (32). However, the relative contribution of these sources of fatty acids to energy production during exercise in obese persons is not clear.

The release of adipose tissue-derived fatty acids into plasma during moderate-intensity endurance exercise is similar in lean and abdominally obese subjects (19). The results from several studies show that whole body fat oxidation during exercise is the same or greater in abdominally obese than in lean subjects (1, 6, 19). In contrast, it has been found that basal plasma fatty acid uptake and oxidation are impaired in women with abdominal obesity when direct measurements were made across muscle tissue (7). These data suggest that, although fat oxidation during exercise may be the same or greater in abdominally obese than in lean subjects, the source of triglyceride may differ between groups.

The overall purpose of the present study was to evaluate the hypothesis that women with abdominal obesity use more fatty acids derived from IMTG and less fatty acids derived from adipose tissue triglycerides as fuel during endurance exercise compared with lean women. Specifically, we evaluated 1) whether lean and abdominally obese women differ in their use of plasma fatty acids (presumably derived from adipose tissue triglycerides) and nonplasma fatty acids (presumably derived from IMTG) as a fuel during exercise and 2) whether the ability to oxidize plasma fatty acids during exercise is impaired in women with abdominal obesity. Stable isotope tracer methods were used to measure whole body lipolytic activity, plasma fatty acid availability, and plasma fatty acid oxidation, and indirect calorimetry was used to measure whole body fat oxidation.

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METHODS

Subjects. Five class II obese women [body mass index (BMI) = 35.3–39.9 kg/m²; >40% body weight as fat] with abdominal obesity (waist-to-hip ratio >0.85; waist circumference >100 cm) and five lean women (BMI ≤ 23 kg/m²; <30% body wt as fat) participated in this study (Table 1). Lean and obese subjects were matched on peak oxygen consumption (VO₂ peak) relative to fat-free mass (FFM) because the oxidative capacity of exercising muscle can affect the metabolic response to exercise (18, 27, 33). All subjects were premenopausal and had no evidence of medical illness after a comprehensive examination, which included a history and physical examination, blood tests, and an electrocardiogram. Obese subjects had normal glucose tolerance based on a 2-h oral glucose tolerance test. No subjects were taking any medications, and all were weight stable for at least 2 mo before the study, which was performed within the first 2 wk of the follicular phase of their menstrual cycle. Written, informed consent was obtained before participation in the study, which was approved by the Human Studies Committee and the General Clinical Research Center (GCRC) Scientific Advisory Committee of Washington University School of Medicine.

Preliminary testing. Fat mass and FFM were determined by dual-energy X-ray absorptiometry (Hologic QDR 1000/W, Waltham, MA). VO₂ peak was measured by using a Vₚ max 29 metabolic cart (SensorMedics, Yorba Linda, CA) during upright cycle ergometer exercise to assess cardiorespiratory fitness. The protocol consisted of a 4-min warm-up, after which the work rate was progressively increased every minute until at least two of the following three criteria were met: 1) a leveling off of the rate of oxygen consumption (VO₂), despite increases in work-rate; 2) respiratory exchange ratio ≥ 1.15; and 3) attainment of age-predicted maximal heart rate.

Experimental protocol. Subjects were admitted to the GCRC at Washington University School of Medicine on two occasions separated by a period of 1 wk. At 1900 on the day of admission, subjects ingested a standard meal (60% carbohydrate, 25% fat, and 15% protein) containing 12 kcal/kg body wt for lean subjects and 12 kcal/kg adjusted body wt for obese subjects [adjusted body wt = ideal body wt + [(actual body wt – ideal body wt) x 0.25]]. Subjects were randomized to perform an exercise-isotope infusion study or an exercise study without tracer infusion (i.e., "background trial") the next morning. One week later, subjects were readmitted to the GCRC to perform the other study (either exercise-isotope infusion or the background trial).

Between 0915 and 0930, blood samples were obtained at −15, −10, −5, and 0 min to determine basal plasma substrate and hormone concentrations and substrate kinetics. After the last basal samples were collected, subjects exercised for 90 min on a recumbent cycle ergometer at ~50% of their VO₂ peak. Although VO₂ peak was measured in the upright position, the study protocol exercise bout was performed in the recumbent position to enhance comfort and compliance in our obese subjects. VO₂ peak was determined in the upright position because of concern that lack of familiarity with recumbent cycling, especially at high work rates, might cause some subjects to terminate the test before actually reaching their true VO₂ peak. It is possible that VO₂ peak is not identical in the upright and recumbent positions because of slight differences in muscle mass recruitment; however, the difference in VO₂ peak is very small (46). Moreover, lean and obese subjects exercised at the same relative intensity (i.e., 50% of their upright VO₂ peak) because relative exercise intensity affects the contribution of fat and carbohydrate to total energy production (36).

Blood samples were obtained every 10 min during exercise to determine substrate kinetics, and heart rate was measured every 10 min by using a telemetry heart rate monitor (Cardiochamp Sensor, Dynamics, Freemont, CA). VO₂ and carbon dioxide production (VO₂) rates were measured from 0 to 5, 25 to 35, 60 to 68, 70 to 78, and 80 to 90 min of exercise by using a Vₚ max 29 metabolic cart (SensorMedics) to ensure that the subjects were exercising at 50% of their VO₂ peak and to calculate whole body fat and carbohydrate oxidation rates. Evacuated test tubes were used to collect expired breath samples in quadruplicate from a mixing chamber at 60, 70, 80, and 90 min of exercise to determine plasma fatty acid oxidation rate. Plasma fatty acid oxidation was only measured during the last 30 min of exercise to ensure the presence of a plateau in breath ¹³CO₂ enrichment.

The background trial was performed on a separate occasion to account for the increase in background breath ¹³CO₂.

Table 1. Characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Obese</th>
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<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>20.9 ± 0.4</td>
<td>37.7 ± 0.8*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>69 ± 1</td>
<td>107 ± 2*</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>56.9 ± 2.7</td>
<td>104.2 ± 3.1*</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>42.4 ± 2.0</td>
<td>53.8 ± 3.3*</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>14.5 ± 1.2</td>
<td>50.5 ± 1.5*</td>
</tr>
<tr>
<td>Fat mass, %body wt</td>
<td>25.4 ± 1.5</td>
<td>48.6 ± 1.9*</td>
</tr>
<tr>
<td>VO₂ peak, l/min</td>
<td>2.0 ± 0.1</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>VO₂ peak, ml·kg·FFM⁻¹·min⁻¹</td>
<td>46.6 ± 1.0</td>
<td>44.3 ± 2.8</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5 subjects in each group. FFM, fat-free mass; VO₂ peak, peak oxygen consumption. *Significantly different from lean, P < 0.05.
Plasma glycerol concentration was determined by gas chromatography-mass spectrometry by using an MSD 5973 system (Hewlett-Packard, Palo Alto, CA) with capillary column (16, 31). Acetone was used to precipitate plasma proteins, and hexane was used to extract plasma lipids. The aqueous phase was dried by Speed-Vac centrifugation (Savant Instruments, Farmingdale, NY). Heptadecanoic anhydride was used to form a heptadecanoic acid derivative of glycerol, and ions were produced by electron impact ionization. Glycerol TTR was determined by selectively monitoring ions at mass-to-charge ratios 270.2 and 271.2, produced by electron impact ionization. Glycerol TTR was determined by radioimmunoassay (15). Plasma catecholamine concentrations were determined by a radioenzymatic method (40). Plasma glycerol concentration was determined by gas chromatography-mass spectrometry after [2-13C]glycerol was added to plasma as an internal standard (48). Plasma fatty acid concentrations were quantified by gas chromatography after heptadecanoic acid was added to plasma as an internal standard (48).

The tracer-to-tracee ratio (TTR) for plasma glycerol and palmitate was determined by gas chromatography-mass spectrometry by using an MSD 5973 system (Hewlett-Packard, Palo Alto, CA) with capillary column (16, 31). Acetone was used to precipitate plasma proteins, and hexane was used to extract plasma lipids. The aqueous phase was dried by Speed-Vac centrifugation (Savant Instruments, Farmingdale, NY). Heptadecanoic anhydride was used to form a heptadecanoic acid derivative of glycerol, and ions were produced by electron impact ionization. Glycerol TTR was determined by selectively monitoring ions at mass-to-charge ratios 253, 254, and 257. Free fatty acids were isolated from plasma and converted to their methyl esters with iodomethane. Ions produced by electron impact ionization, were selectively monitored. The ratio of 13CO2 to 12CO2 in expired breath was determined by isotope ratio mass spectrometry (Sira II, dual inlet-triple collector, VG Fisons, Cheshire, UK). Briefly, CO2 was isolated from the breath sample by passage through a series of traps to remove water vapor, nitrogen, and oxygen. The purified sample was then ionized by electron bombardment and repelled past a series of focusing lenses toward the detector. A magnet deflected the ions according to their masses, allowing for the measurement of the ratio of masses corresponding to 13C and 12C.

Calculations. Steady-state substrate concentrations and TTRs were achieved during basal conditions; thus basal glycerol and palmitate rates of appearance (Ra) in plasma were calculated by using Steele’s equation for steady-state conditions (44). During exercise, the non-steady-state equation of Steele (44) was used to calculate glycerol Ra, palmitate Ra, and palmitate rate of disappearance (Rd). However, during the last 30 min of exercise, the change in TTR between blood samples was very small so that Steele’s equation for steady-state and non-steady-state conditions generated similar Ra and Rd values. The effective volume of distribution was estimated to be 300 ml/kg FFM for glycerol and 60 ml/kg FFM for palmitate. However, even a 50% error in estimated effective volume of distribution would cause a 5% change in calculated Ra because of the minimal changes in TTR between samples.

The oxidation rate of plasma fatty acids was calculated as

\[ \text{Plasma palmitate oxidation} = \left( \text{ECO}_2 \cdot \text{VCO}_2 \right) / (\text{TTR}_p \cdot \text{AR}) \]

where EC02 is the 13C enrichment in breath CO2, TTRp is the average TTR in plasma between 60 and 90 min, and AR is the acetate carbon recovery factor, estimated to be 0.8 (41). Total fatty acid oxidation was calculated by dividing palmitate oxidation by the ratio of plasma palmitate to total plasma fatty acid concentration. Rates of whole body fatty acid and carbohydrate oxidation were calculated from VO2 and VCO2 values (13) and an estimate of nitrogen excretion, based on data from a previous study (80 µg·kg⁻¹·min⁻¹ in lean subjects and 80 µg·kg·min⁻¹ in obese subjects) (4). The oxidation rate of nonplasma fatty acids was calculated as the difference between the rates of whole body fatty acid oxidation and plasma fatty acid oxidation. The tracer technique that we used to determine plasma fatty acid oxidation rate requires reaching a plateau in 13CO2 enrichment in expired breath. Therefore, we limited our assessment of plasma fatty acid oxidation to the 60- to 90-min period of exercise to ensure that a plateau in breath tracer enrichment was achieved. Breath 13CO2 enrichment measurements in the first 60 min of exercise were likely to have been below plateau values, which would cause an underestimation of the rate of plasma fatty acid oxidation and an overestimation of the rate of nonplasma fatty acid oxidation.

Statistical analysis. A power analysis, based on data reported by Martin et al. (27), suggested that five subjects would be needed to detect a 30% difference in whole body and nonplasma fatty acid oxidation rates between lean and obese groups with an α value of 0.05 and a power of 0.80. A two-way ANOVA (subject phenotype × time) with repeated measures was used to test the significance of differences in glycerol Ra and palmitate Ra between lean and obese subjects throughout exercise. Significant F ratios from ANOVA were followed by the appropriate comparisons by using Tukey’s post hoc analyses. Student’s t-test for independent samples was used to test the significance of differences between lean and obese subjects for mean whole body, plasma, and nonplasma fatty acid oxidation rates during 60–90 min of exercise and mean plasma hormone concentrations at rest and during exercise. A value of P ≤ 0.05 was considered to be statistically significant. All data are expressed as means ±SE.

RESULTS

During exercise, lean and obese subjects cycled at the same relative (53 ± 3 vs. 54 ± 2% VO2 peak) and similar absolute intensity (50 ± 4 vs. 56 ± 6 W) (both P = not significant). During the final 30 min of exercise, the average rate of VO2 (24.5 ± 1.5 and 24.4 ± 2.3 ml·kg⁻¹·min⁻¹) and the average heart rate response (132 ± 6 and 131 ± 9 beats/min) were also the same in lean and obese groups, respectively.

Plasma hormone concentrations. Exercise increased plasma epinephrine and norepinephrine concentrations in both lean and obese subjects (P < 0.05), but there were no differences in plasma catecholamine concentrations between groups, either at rest or during exercise (Table 2). Basal plasma insulin concentrations were more than twice as great in obese than in lean subjects (P < 0.05) (Table 2). Although plasma insulin concentration decreased in both groups during exercise (P < 0.05), plasma insulin remained higher in obese compared with lean subjects (P < 0.05).

Glycerol and fatty acid kinetics. Basal glycerol Ra and palmitate Ra tended to be greater in obese compared with lean subjects (4.1 ± 0.5 vs. 3.3 ± 0.4 µmol glycerol·kg FFM⁻¹·min⁻¹ and 1.9 ± 0.3 vs. 1.5 ± 0.2 µmol palmitate·kg FFM⁻¹·min⁻¹), but the differences were not statistically significant, which may reflect a type II statistical error because of small sample size. During exercise, glycerol Ra and palmitate Ra in-
increased progressively in both groups \( (P < 0.05) \) (Fig. 2), and values were similar in lean and obese subjects throughout the exercise bout. Palmitate \( \text{R}_d \) also increased progressively during exercise \( (P < 0.05) \), and values were similar in both groups. Mean palmitate \( \text{R}_d \) between 60 and 90 min of exercise was 3.7 ± 0.2 and 3.4 ± 0.4 \( \mu \text{mol} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1} \) for lean and obese subjects, respectively. The percentage of palmitate released into plasma that was taken up by peripheral tissues was also similar in lean and obese subjects \( (93 ± 3 \text{ vs. 88 ± 2\%}) \).

**Plasma fatty acid concentration.** After a transient decline during the first 10 min of exercise, plasma fatty acid concentration increased throughout the exercise bout in all subjects, and there was no difference between the groups. The mean plasma fatty acid concentration during the final 30 min of exercise was 0.75 ± 0.09 and 0.69 ± 0.04 mmol/l for lean and obese subjects, respectively.

**Fatty acid oxidation.** Mean whole body fatty acid oxidation was ~25% greater in obese compared with lean subjects \( (21.9 ± 1.2 \text{ vs. 17.5 ± 1.6} \ \mu \text{mol} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1} ; P < 0.05) \) (Fig. 3A). However, the rate of plasma fatty acid oxidation during exercise was similar between the groups \( (12.8 ± 1.7 \text{ and 14.5 ± 1.8} \ \mu \text{mol} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1} \) for obese and lean subjects, respectively; \( P = \text{not significant} \)). Therefore, the increase in total fat oxidation in the obese subjects was due to an increase in the oxidation of nonplasma fatty acids \( (9.1 ± 1.4 \text{ and 3.0 ± 0.4} \ \mu \text{mol} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1} \) for obese and lean subjects, respectively; \( P < 0.05) \). The relative contribution of carbohydrate to total energy production during exercise was lower in obese than lean subjects \( (P < 0.05) \) (Fig. 3B).

**DISCUSSION**

The presence of excess abdominal adipose tissue and muscle tissue triglycerides in persons with abdominal obesity is associated with a constellation of metabolic abnormalities (insulin resistance, diabetes, dyslipidemia, and hypertension) known as the metabolic syn-

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**Table 2. Plasma hormone concentrations during rest and exercise**

<table>
<thead>
<tr>
<th></th>
<th>Lean Rest</th>
<th>Lean Exercise</th>
<th>Obese Rest</th>
<th>Obese Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, pg/ml</td>
<td>54 ± 11</td>
<td>87 ± 10†</td>
<td>37 ± 5</td>
<td>78 ± 15†</td>
</tr>
<tr>
<td>Norepinephrine, pg/ml</td>
<td>254 ± 48</td>
<td>478 ± 70†</td>
<td>262 ± 37</td>
<td>630 ± 109†</td>
</tr>
<tr>
<td>Insulin, ( \mu \text{U/ml} )</td>
<td>6.8 ± 0.6</td>
<td>3.7 ± 0.5†</td>
<td>16.3 ± 2.7*</td>
<td>8.8 ± 1.4†</td>
</tr>
</tbody>
</table>

Values are means ± SE; \( n = 5 \) subjects in each group. Exercise values are the average concentrations between 60 and 90 min of exercise. *Significantly different from lean value, \( P < 0.05 \). †Significantly different from rest value, \( P < 0.05 \).

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Fig. 2. Mean glycerol rate of appearance \( (\text{R}_a; \ A) \) and palmitate \( \text{R}_a (B) \) in the basal state and during 90 min of exercise performed at ~50% of peak oxygen consumption \( (\dot{\text{V}}\text{O}_{2\text{peak}}) \) in lean (○) and obese (□) subjects. FFM, fat-free mass. †Significant main effect for time, \( P < 0.05 \).

Fig. 3. Mean plasma (solid bars) and nonplasma (open bars) fatty acid oxidation rates (A) and the relative contribution of plasma fatty acids (solid bars), nonplasma fatty acids (open bars), and carbohydrate (gray bars) to total energy production (B) during the last 30 min (between 60 and 90 min) of exercise performed at ~50% \( \dot{\text{V}}\text{O}_{2\text{peak}} \) in lean and obese subjects. *Value significantly different from corresponding lean value, \( P < 0.05 \).
glycerol Ra between our lean and obese groups, which presumably fatty acids derived from lipolysis of IMTG. Whole body lipolytic activity (measured as either glycerol R, or palmitate Ra) and plasma fatty acid oxidation rates during exercise were similar in lean and obese groups. Therefore, the alterations in substrate use observed during exercise in our obese women reflect alterations in the metabolism of energy substrates stored in muscle rather than substrate availability and uptake from plasma.

The availability of plasma fatty acids for oxidation by skeletal muscle depends on lipolysis of adipose tissue triglycerides and subsequent fatty acid release into the circulation. Alterations in plasma fatty acid availability can affect substrate use during exercise (17, 29, 37). Our data and those reported by Kanaley et al. (19) demonstrate that whole body lipolytic rates and fatty acid availability during exercise are the same in lean and abdominally obese subjects. Furthermore, we found that plasma fatty acid tissue uptake and oxidation were similar in both lean and abdominally obese women. This evidence suggests that impairment of plasma fatty acid uptake and oxidation previously found in persons with abdominal obesity during resting conditions (7) is not present during exercise. Therefore, alterations in availability, uptake, and oxidation of plasma fatty acids during exercise cannot account for the difference in total fat oxidation that we observed between our lean and obese groups.

IMTGs are the most likely source of the additional fatty acids oxidized during exercise in our obese subjects. Although lipolysis of IMTG should release additional glycerol into the systemic circulation, we were unable to detect statistically significant differences in glycerol R, between our lean and obese groups, which may reflect a type II statistical error. It is likely that our study sample size, the relatively small amount of additional glycerol released during IMTG lipolysis in our obese subjects, and skeletal muscle metabolism of intramuscular glycerol (23) made it difficult for our tracer methods to detect differences in systemic glycerol R, between groups. It is unlikely that fatty acids derived from circulating lipoproteins were an important source of fuel, because plasma triglycerides contribute little to total energy production during exercise (30). Moreover, an estimate of maximal plasma triglyceride utilization in our obese subjects (calculated using the postabsorptive plasma triglyceride concentration of our obese subjects (94 ± 15 mg/dl), a theoretical plasma triglyceride turnover rate (0.2 pools/h) (49), and assuming that all fatty acids released from plasma triglycerides were oxidized) suggests that plasma triglycerides could not account for >5% of nonplasma fatty acids oxidized in our obese subjects.

The use of IMTG during endurance exercise is controversial. Studies that measured IMTG concentration in muscle biopsies obtained before and after exercise have found that IMTG concentration increased (2), decreased (3, 5, 18), or remained the same (21, 43, 47). These differences may be related to differences in exercise protocols between studies and the variability in the assay used to measure IMTG in muscle biopsies (47). In addition, it is likely that IMTG synthesis occurs during exercise (9), which would confound the interpretation of net concentration changes. Therefore, the indirect calculation of nonplasma fatty acid oxidation (i.e., difference between total and plasma fatty acid oxidation) may provide a more reliable measure of IMTG use during exercise. Studies that have used this calculation to assess IMTG oxidation have found that as much as two-thirds of fatty acids oxidized during moderate-intensity endurance exercise are derived from IMTG (27, 33). An increase in the use of IMTG during exercise in persons with abdominal obesity may provide metabolic and clinical benefits not previously realized. The concentration of IMTG is directly correlated with insulin-resistant glucose metabolism in rodents (28) and humans (14). Therefore, an exercise-induced decrease in IMTG content in obese persons may contribute to enhanced insulin sensitivity associated with exercise (39) and decreased risk of diabetes associated with aerobic fitness (45).

Although persons with abdominal obesity have an increased amount of IMTG (32), IMTG concentration is not correlated with percent body fat or BMI (32). Therefore, high concentrations of IMTG may be a specific characteristic of abdominal obesity rather than obesity per se. The mechanism responsible for increased IMTG in persons with abdominal obesity is not known but may be related to alterations in regulating lipolysis of adipose tissue triglycerides. Basal postabsorptive lipolytic rates (16, 26) and postprandial fatty acid availability (38) are greater in abdominally obese than lean persons and are likely to enhance skeletal muscle fatty acid uptake and IMTG synthesis (10) in obese persons. Therefore, a chronic increase in fatty acid availability to muscle and a high rate of muscle fatty acid uptake relative to fat oxidation may increase intramuscular fatty acid esterification and IMTG content.

The factors that regulate lipolysis and oxidation of IMTG in human skeletal muscle are not clear. Hormone-sensitive lipase (HSL), the enzyme responsible for triglyceride hydrolysis in adipose tissue, has been found in isolated skeletal muscle (24). Therefore, catecholamines, which increase HSL activity, may also be important in stimulating IMTG lipolysis. In fact, it has been shown that β-adrenergic-receptor stimulation by epinephrine stimulates muscle HSL activity (24), and IMTG use during exercise is inhibited by β2-receptor blockade (5). However, other factors may also be important regulators of IMTG lipolysis. Muscle contraction increases HSL activity by an unknown mechanism
that is independent of β-adrenergic-receptor action (24). In addition, IMTG utilization during exercise may be regulated by substrate availability. It has been found that the use of IMTG during exercise is directly proportional to IMTG concentration (12). Moreover, there are also interactions between the use of plasma fatty acids, intramuscular glycogen, and IMTG as fuels during exercise.

Several studies have demonstrated the reciprocal regulation between fat and carbohydrate metabolism during exercise (11, 17, 29, 37). For example, increasing muscle glycolytic flux during exercise either by glucose infusion or by increasing exercise intensity decreases fatty acid oxidation (8, 42). The resultant accumulation of intracellular fatty acids may inhibit IMTG lipolysis and oxidation (10). Conversely, increasing the availability of fatty acids to muscle by intravenous lipid infusion increases fat oxidation and reduce muscle glycogen oxidation during exercise (17, 29, 37). The mechanism responsible for this relationship may be that increased muscle fatty acid availability and oxidation reduces intracellular concentrations of inorganic phosphate and adenosine monophosphate (11), which serve as substrate and activator of glycogen phosphorylase, respectively (35). Therefore, an increase in cytosolic fatty acids derived from IMTG lipolysis should inhibit muscle glycogen metabolism, which could explain the lower carbohydrate oxidation rate observed in our obese compared with our lean subjects. In summary, we found that total fat oxidation during moderate-intensity endurance exercise was greater in abdominally obese than in lean women because of an increased oxidation of nonplasma fatty acids, presumably derived from IMTG. Rates of fatty acid appearance in plasma, plasma fatty acid tissue uptake, and plasma fatty acid oxidation during exercise were similar in lean and obese women. These results suggest that endurance exercise may be particularly beneficial in persons with abdominal obesity by decreasing IMTG content.

We thank Renata Braudy and the nursing staff of the GCRC for help in performing the experimental protocols, Dr. Guohong Zhao and Weiqing Feng for technical assistance, and the study subjects for participating in this study.

This study was supported by the National Institutes of Health Grants DK-37948 and RR-00036 (General Clinical Research Center), RR-00954 (Mass Spectrometry Resource), AG-13629 (Claude Pepper Older American Independence Center), AG-0078 (Institutional National Research Service Award), and DR-56341 (Clinical Nutrition Research Unit).

REFERENCES


