Lipid metabolism during endurance exercise[1–3]

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ABSTRACT Endogenous triacylglycerols represent an important source of fuel for endurance exercise. Triacylglycerol oxidation increases progressively during exercise; the specific rate is determined by energy requirements of working muscles, fatty acid delivery to muscle mitochondria, and the oxidation of other substrates. The catecholamine response to exercise increases lipolysis of adipose tissue triacylglycerols and, presumably, intramuscular triacylglycerols. In addition, increases in adipose tissue and muscle blood flow decrease fatty acid reesterification and facilitate the delivery of released fatty acids to skeletal muscle. Alterations in fatty acid mobilization and the relative use of adipose and intramuscular triacylglycerols during exercise depend, in large part, on degree of fitness and exercise intensity. Compared with untrained persons exercising at the same absolute intensity, persons who have undergone endurance training have greater fat oxidation during exercise without increased lipolysis. Available evidence suggests that the training-induced increase in fat oxidation is due primarily to increased oxidation of nonplasma-derived fatty acids, perhaps from intramuscular triacylglycerol stores. Fat oxidation is lower in high-intensity exercise than in moderate-intensity exercise, in part because of decreased fatty acid delivery to exercising muscles. Parenteral lipid supplementation during high-intensity exercise increases fat oxidation, but the effect of ingesting long-chain or medium-chain triacylglycerols on substrate metabolism during exercise is less clear. This review discusses the relation between fatty acid mobilization and oxidation during exercise and the effect of endurance training, exercise intensity, and lipid supplementation on these responses. *Am J Clin Nutr* 2000;72(suppl):558S–63S.

KEY WORDS Adipose tissue, intramuscular triacylglycerol, lipolysis, fatty acids, glycerol, medium-chain triacylglycerol, stable isotopes, exercise, endurance training, lipid supplementation

INTRODUCTION

Endogenous triacylglycerols represent the largest fuel reserve in the body. Most triacylglycerols are stored in adipose tissue (≈17 500 mmol in a lean adult man), but they are also present in skeletal muscle (≈300 mmol) and plasma (≈0.5 mmol). The total amount of energy stored as triacylglycerol (≈560 MJ) is >60 times the amount stored as glycogen (≈9 MJ). Thus, fatty acid oxidation during endurance exercise permits sustained physical activity and delays the onset of glycogen depletion and hypoglycemia. The use of fatty acids as a fuel requires hydrolysis of triacylglycerols (ie, lipolysis) from adipose tissue, muscle, and plasma and the delivery of the released fatty acids to skeletal muscle mitochondria for oxidation. In this article, we will discuss the relation between fatty acid mobilization and fat oxidation during exercise in humans and review the influence of lipid supplementation on substrate metabolism during exercise.

LIPID KINETICS DURING REST AND EXERCISE

After an overnight fast, most energy needs at rest are provided by oxidizing fatty acids derived from adipose tissue triacylglycerols (1). Adipose tissue lipolytic activity is regulated by the balance between hormones that stimulate (primarily catecholamines) and those that inhibit hormone-sensitive lipase (primarily insulin), which hydrolyzes triacylglycerols to fatty acids and glycerol. At rest, the amount of fatty acids released from adipose tissue typically exceeds the amount oxidized; fatty acid rate of appearance into plasma (Ra) is approximately twice the rate of fatty acid oxidation (2). Therefore, a large portion of fatty acids liberated by lipolysis of adipose tissue triacylglycerols are reesterified back into triacylglycerols, principally by the liver.

Mild- or moderate-intensity exercise [25–65% of maximal oxygen consumption ($\dot{V}O_2$max)] is associated with a 5–10-fold increase in fat oxidation above resting amounts (3) because of increased energy requirements of muscle and enhanced fatty acid availability. A large portion of the increased supply of fatty acids is provided by lipolysis of adipose tissue triacylglycerols, which increases 2–3-fold (4, 5) and is mediated by increased β-adrenergic stimulation (6, 7). In addition, the percentage of released fatty acids that are reesterified decreases by half (4), presumably because of alterations in blood flow that facilitate the delivery of fatty acids from adipose tissue to working muscles. Moderate-intensity exercise doubles adipose tissue blood flow (8, 9) and causes a >10-fold increase in skeletal muscle blood flow (10). Increasing the removal of fatty acids from adipose tissue by increasing adipose tissue blood flow may also be necessary to

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[2] Supported by National Institutes of Health grants DK 37948, RR-0036 (General Clinical Research Center), RR-00954 (Mass Spectrometry Resource), AG-13629 (Claude Pepper Older American Independence Center), AG-00078 (Institutional National Research Service Award), and DK-56341 (Clinical Nutrition Research Unit).

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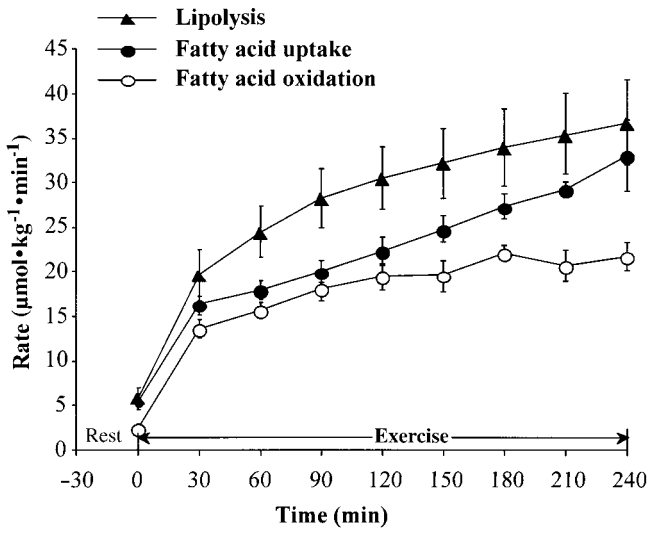

FIGURE 1. Rates of lipolysis (3 × the glycerol rate of appearance in plasma), fatty acid uptake, and fatty acid oxidation at rest and during 4 h of treadmill exercise performed at 45% of maximal oxygen uptake ($\dot{V}O_2$max) in untrained subjects. Data adapted from reference 5.

prevent potentially toxic regional fatty acid accumulation. Hodgetts et al (11) found that the ratio of fatty acid to albumin in venous blood coming from subcutaneous adipose tissue increased from 2:1 at rest to nearly 6:1 at the end of exercise. Theoretically, greater increases in local fatty acid concentration could overwhelm available fatty acid binding sites on albumin (12) and cause harmful increases in the concentration of unbound fatty acids.

The relation between lipolysis (defined as 3 × glycerol Ra, because 3 fatty acids and 1 glycerol molecule are released from 1 triacylglycerol during lipolysis), plasma fatty acid tissue uptake [fatty acid rate of disappearance from plasma (Rd)], and fatty acid oxidation at rest and during prolonged moderate-intensity exercise (45% of $\dot{V}O_2$max) is shown in **Figure 1** (5). During the first 120 min of exercise, the lipolytic rate is approximately twice the rate of fatty acid oxidation. However, plasma fatty acid uptake (fatty acid Rd) is similar to the rate of fat oxidation during this period. In fact, several investigators have reported that fatty acid Rd is lower than fatty acid oxidation during the first 1–2 h of exercise (13–15). This evidence suggests that another fat source, presumably plasma or intramuscular triacylglycerols (IMTGs), is being oxidized in addition to plasma fatty acid derived from adipose tissue.

Several studies suggest that IMTGs represent a considerable portion of the total fat used during endurance exercise (14–21). Estimates of IMTG use, calculated indirectly with isotopic tracer methods, indicate that non-plasma-derived fatty acids (presumably from IMTGs) provide > 50% of the total fat oxidized during exercise (15) and muscle contraction (22). Several studies in which muscle biopsies were taken before and after exercise found that IMTG concentration declines by 25–40% after 1–2 h of moderate-intensity cycle ergometer exercise, which could account for 60–75% of the total amount of fat oxidized (16–19, 21). In contrast, others found that IMTG concentration decreases minimally or not at all after prolonged exercise and therefore does not contribute significantly to total energy production (23–27). The reason for the discrepancies between the studies is not clear but may be related to differences in exercise protocols, variability when measuring IMTG concentration in muscle biopsies (27), and differences in the interval between the last exercise bout and the experimental trial.

Few studies have evaluated the contribution of plasma triacylglycerols to total energy production. The available data suggest that during resting conditions, plasma triacylglycerols may account for 5–10% of total fat oxidation (28, 29). There is also indirect evidence that only a small fraction of total energy production is derived from plasma triacylglycerols during exercise (30–32). For example, Kiens and Lithell (32) found that VLDL triacylglycerol uptake by skeletal muscle is negligible during exercise. We are unaware of any studies that have quantified the oxidation of VLDL triacylglycerols or plasma chylomicron triacylglycerols during exercise in humans.

Lipolysis of adipose tissue triacylglycerols, plasma fatty acid uptake, and fatty acid oxidation increase progressively throughout a bout of exercise (Figure 1). After ≈2 h of exercise, the rate of plasma fatty acid uptake becomes greater than the rate of fatty acid oxidation, suggesting that fatty acids released into plasma from adipose tissue can supply all fatty acids used by active muscles. Thus, as exercise duration increases, it is likely that the relative contribution of IMTGs to total fat oxidation declines and the contribution from plasma fatty acid increases.

ENDURANCE EXERCISE TRAINING

Endurance exercise training increases the oxidation of fat during submaximal exercise (20, 33, 34). Several factors contribute to this adaptive response: increased density of the mitochondria in the skeletal muscles, which increases the capacity for fat oxidation (35); a proliferation of capillaries within skeletal muscle, which enhances fatty acid delivery to muscle (36); an increase in carnitine transferase, which facilitates fatty acid transport across the mitochondria membrane (37); and an increase in fatty acid binding proteins, which regulate myocyte fatty acid transport (38, 39).

Data from both in vitro and in vivo studies suggest that increased lipolysis of adipose tissue triacylglycerols is not responsible for the training-induced increase in whole-body fat oxidation. Although several investigators found that maximally stimulated lipolytic activity (at epinephrine concentrations between 10^{-6} and 10^{-4} mol/L) was greater in adipocytes obtained from endurance-trained subjects than in those from untrained subjects (40–43), lipolytic activity was the same or slightly lower in adipocytes from endurance-trained subjects at physiologic epinephrine concentrations (between 10^{-10} and 10^{-8} mol/L) (41, 42). Moreover, by using microdialysis probes to measure regional glycerol release in vivo, Stallknecht et al (44) found the lipolytic response of abdominal subcutaneous adipose tissue to epinephrine infusion was the same in trained and untrained subjects.

Similarly, cross-sectional studies of trained and untrained subjects and longitudinal training studies showed that endurance training does not increase the whole-body lipolytic response during exercise performed at the same absolute exercise intensity (ie, same power output). For example, lipolytic rates (3 × glycerol Ra) measured during exercise performed at the same absolute intensity were similar in endurance-trained athletes and untrained volunteers (5) (**Figure 2**). In addition, Martin et al (15) found that after 12 wk of endurance training, plasma fatty acid Rd decreased by 30%, whereas fat oxidation increased by 45% during exercise performed at the same absolute intensity.

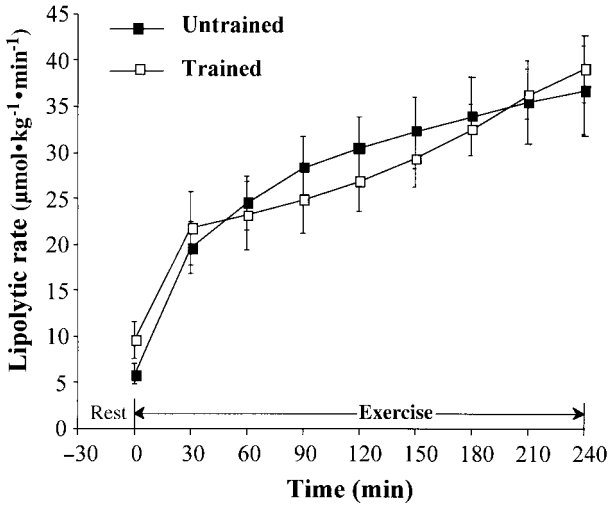

FIGURE 2. Whole-body lipolytic rates (3 × the glycerol rate of appearance in plasma) at rest and during 4 h of treadmill exercise performed at the same absolute intensity (20 mL O_2 consumed · kg^{-1} · min^{-1}) in untrained and trained subjects. Data adapted from reference 5.

The decreased contribution of plasma fatty acid to whole-body fat oxidation suggests an increased reliance on IMTGs as a source of fuel in the trained state (15, 20). However, data from studies that measured intramuscular fat content in muscle biopsies yield conflicting results. Some (19, 21) but not all (22, 23, 26) studies showed a greater depletion of IMTG during exercise performed after, rather than before, training. The technical difficulty in measuring IMTG concentration may have contributed to the differences between studies. It is also unclear how endurance training might increase IMTG lipolysis during exercise because the catecholamine response during exercise is decreased (45, 46) and skeletal muscle β-adrenergic receptor density remains the same (47). Therefore, if endurance training indeed increases reliance on IMTGs it must affect other as yet unknown factors that regulate IMTG lipolysis.

During exercise performed at the same relative intensity (ie, same % of $\dot{V}O_2$max), whole-body lipolytic rates are greater in endurance-trained than in untrained persons (48). In fact, glycerol Ra values during high-intensity exercise in endurance-trained athletes are the highest ever reported in humans (14, 48). It is not clear why training increases the lipolytic response to exercise performed at the same relative intensity. Plasma epinephrine concentrations have been reported to be both slightly lower (46) and slightly higher (49, 50) in trained than in untrained persons during exercise performed at the same relative intensity. However, endurance-trained athletes have been found to have a greater adipose tissue blood flow in response to epinephrine infusion than sedentary control subjects (44) and thus may have a greater catecholamine delivery to adipose tissue during exercise despite similar plasma catecholamine concentrations. In addition, an increase in IMTG lipolysis after endurance training may be responsible for the increased glycerol Ra in trained subjects.

EXERCISE INTENSITY

The relative contributions of plasma fatty acid and IMTGs to total fat oxidation during exercise at different intensities have been studied in highly trained but not in untrained subjects (14). The estimated relative contribution of plasma fatty acid and IMTGs to total fat oxidation during exercise at low, moderate, and high intensities (25%, 65%, and 85% of $\dot{V}O_2$max, respectively) is shown in **Figure 3** (14). During low-intensity exercise, most of the fatty acids oxidized are derived from plasma fatty acid. With increasing exercise intensity, the relative contribution of IMTGs also increases and can represent nearly half of all fat oxidized.

Despite a relatively high rate of energy expenditure during high-intensity exercise (> 70% of $\dot{V}O_2$max), total fat oxidation is suppressed to values below those observed during moderate-intensity exercise (Figure 3) (14, 51). The limitation in fat use during high-intensity exercise stems in part from a decline in circulating fatty acids caused by decreased release of fatty acids from adipose tissue (52). The decrease in fatty acid Ra is not caused by a reduction in lipolysis, because glycerol Ra, an index of lipolysis, is the same during exercise performed at both 85% and 65% of $\dot{V}O_2$max (14). Immediately after cessation of high-intensity exercise, fatty acid Ra and plasma fatty acid concentrations markedly increase without a concomitant increase in lipolysis (14). These data suggest that the decrease in fatty acid Ra during exercise may be due to increased trapping of fatty acid within adipose tissue because of decreased adipose tissue blood flow and inadequate fatty acid removal by the bloodstream (9, 11, 14, 51–53). Raising plasma fatty acid concentrations to 1–2 mmol/L by intravenously infusing a lipid emulsion and heparin during the exercise bout increases fat oxidation ≈30% (52) but does not completely restore it to the rate observed during moderate-intensity exercise (14). Thus, high-intensity exercise impairs the capacity of skeletal muscle to oxidize fatty acids (54).

The suppression of fat oxidation during high-intensity exercise may be related to increased glycogen metabolism in muscle. The high rate of muscle glycogenolysis during high-intensity exercise increases the amount of acetyl-CoA derived from glycogen, which presumably increases malonyl-CoA concentrations

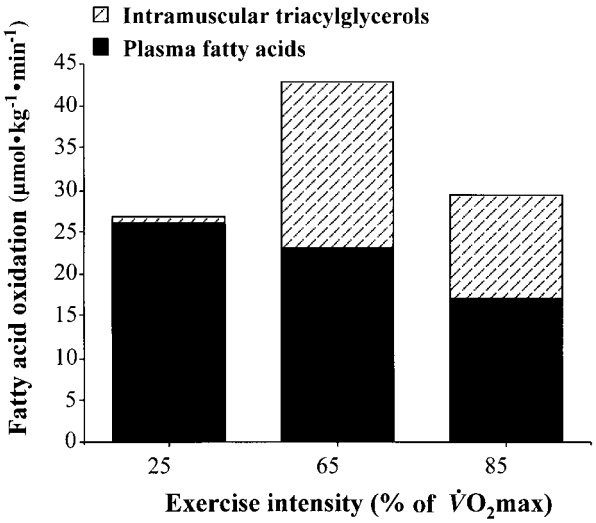

FIGURE 3. Estimated contribution of plasma fatty acid and intramuscular triacylglycerols to total fatty acid oxidation during 30 min of exercise performed at 25%, 65%, and 85% of maximal oxygen uptake ($\dot{V}O_2$max) in trained subjects. Data adapted from reference 14.

in muscle (55, 56). Malonyl-CoA, in turn, inhibits the enzyme responsible for long-chain fatty acid (ie, fatty acids with >12 carbon atoms) entry into mitochondria (carnitine *O*-palmitoyltransferase-I, or CPT-I) (57–59). Thus, high rates of glycogenolysis during high-intensity exercise may modify fat oxidation by impairing long-chain fatty acid transport into the mitochondria via CPT-I inhibition (54).

EFFECT OF LIPID SUPPLEMENTATION

Providing a lipid emulsion with heparin intravenously during exercise can increase fat oxidation by ≈30% when low endogenous fatty acid Ra and plasma fatty acid concentrations limit the rate of fat oxidation, such as during high-intensity exercise (52, 60, 61). However, lipid infusion before or during exercise is not a practical approach to enhancing fat oxidation. Eating a high-fat meal, which consists primarily of long-chain triacylglycerol (LCT), before exercise is also not practical as a direct source of fat during exercise because of delayed and limited availability of ingested fat for skeletal muscle oxidation. LCTs are emptied slowly from the stomach and must be packaged into chylomicrons, which are secreted into the lymphatic system before entering the bloodstream. Only a small portion of exogenous LCT is oxidized within 6 h of ingestion (62). Furthermore, although the addition of LCT to a high-glycemic carbohydrate meal blunts the glucose and insulin responses to carbohydrate ingestion at rest (63–66), it does not significantly alter fat oxidation or plasma glucose, fatty acid, and glycerol concentrations during the subsequent exercise bout (63).

Unlike LCTs, medium-chain triacylglycerols (MCTs) (ie, those primarily containing fatty acids with 8 and 10 carbon atoms) are emptied rapidly from the stomach and are rapidly absorbed and hydrolyzed by the small intestine (67). Furthermore, medium-chain fatty acids are not reesterified and are more easily transported into the mitochondria for subsequent oxidation than are fatty acids from LCT (67, 68). The potential usefulness of MCT as a readily available source of energy has led to its inclusion as an ingredient in some commercially available sports bars.

The amount of MCT that can be tolerated at one time is limited to 25–30 g; ingesting larger amounts causes adverse gastrointestinal symptoms, such as nausea and diarrhea (69, 70). Ingesting 25–30 g MCT before exercise does not increase total fat oxidation (69, 71) or spare muscle glycogen (70) during exercise, because this amount of ingested MCT is oxidized at a rate of only ≈6–9 g/h (71, 72) and therefore provides only a small amount of energy (≈0.2–0.3 MJ/h). More MCT can be tolerated when small aliquots are ingested throughout prolonged exercise (73, 74). Van Zyl et al (73) found that, compared with carbohydrate ingestion alone, the ingestion of MCT (≈30 g/h) added to carbohydrate during 2 h of cycling at 60% of $\dot{V}O_2$max reduced the calculated rate of muscle glycogen oxidation and slightly improved performance (≈3%) during a simulated 40-km time trial. In contrast, Jeukendrup et al (74) found that the addition of 85 g MCT to a 10%-carbohydrate solution ingested while cycling for 2 h at 60% of $\dot{V}O_2$max neither altered muscle glycogen use nor improved cycling performance during a subsequent 15-min time trial. Thus, ingestion of a large dose of MCT (≈85 g) in addition to carbohydrate during a 2-h period of exercise may reduce muscle glycogenolysis and slightly improve performance during a subsequent exercise bout lasting ≈1 h (73) but not during shorter bouts (lasting ≈15 min) (74).

FUTURE DIRECTIONS

Future studies designed to determine the factors regulating the mobilization and oxidation of fatty acids derived from different sources may improve our understanding of how to use this vast energy store during exercise. The available data suggest that the regulation of lipolysis is different for muscle and adipose tissue triacylglycerols. Moreover, adipose tissue metabolism is heterogeneous, depending on the anatomical site of the depot (visceral, subcutaneous abdominal, or subcutaneous gluteal or femoral). Little is known about the relative contribution of fatty acids derived from these different triacylglycerol sources to energy production during exercise. As discussed, indirect or imprecise methods of measuring IMTG concentration have resulted in conflicting findings regarding the use of IMTG during exercise. Improved techniques of measuring IMTG concentration will elucidate the importance of this energy source during exercise.

To date, the relative contribution of plasma triacylglycerols to energy production during exercise remains unclear. Because fat ingestion increases plasma triacylglycerol concentration, quantifying the contribution of this energy source during exercise will resolve whether lipid supplementation (ie, fat ingestion) can contribute substantially to energy production during exercise.

SUMMARY

Endogenous triacylglycerols present in adipose tissue and skeletal muscle are an important source of fuel during endurance exercise. The increased use of triacylglycerol during exercise represents a careful integration of neural, hormonal, circulatory, and muscular events that increase energy requirements and facilitate delivery of fatty acids from adipose tissue and IMTG stores to skeletal muscle mitochondria for oxidation. Exogenous triacylglycerol supplementation, via lipid and heparin infused directly into the circulation, indeed increases fat oxidation when endogenous plasma fatty acid concentration is low. However, lipid ingestion in the form of either LCT or tolerated amounts of MCT has a limited effect on substrate metabolism during exercise.

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