

## Exercise and postprandial lipid metabolism

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Energy expenditure and fat oxidation are both profoundly increased in exercise. In absolute terms, fat oxidation is greatest during exercise of moderate intensity (60–65 % maximum  $\text{O}_2$  uptake,  $\dot{V}_{\text{O}_2\text{max}}$ ) when subjects following a mixed diet may oxidize between 0.3 and 0.7 g fat/min, representing up to 60 % of energy expended (Saltin & Åstrand, 1993). Because the capacity of muscle fibres to synthesize fatty acids *de novo* is limited (Saggerson *et al.* 1992), the bulk of fatty acids has to be supplied from extracellular sources. It is likely, therefore, that postprandial lipid acquisition by muscle will be modified during and/or after exercise.

### Lipid substrates for skeletal muscle during exercise

Fatty acids are available for oxidation by contracting muscle from several sources: adipose-tissue depots, via albumin-bound plasma non-esterified fatty acids (NEFA); triacylglycerol (TAG) within muscle fibres; TAG in adipose tissue located between muscle fibres; and plasma TAG-rich lipoproteins. The weight of the evidence shows that, during exercise, plasma NEFA are the most important of these, accounting, for example, for almost all fat oxidation measured in low-intensity exercise (Romijn *et al.* 1993). There is conflicting evidence, however, concerning the roles of intramuscular TAG and plasma TAG and almost no information on which to assess a potential contribution from adipocytes situated between muscle fibres.

Direct evidence for the hydrolysis of intramuscular TAG during exercise in man has mostly come from comparison of the TAG content of needle-biopsy samples of muscle, before and after exercise. An inherent difficulty is the extent to which the sample biopsied is representative of the exercised muscle mass; different biopsies will not have exactly the same fibre type composition and type I fibres are known to have a higher TAG content than type II fibres (Essén, 1978). There are reports of a decrease in muscle TAG concentration after exercise, varying in duration from 0.5 h (Fröberg *et al.* 1971; Costill *et al.* 1973; Essén, 1978; Hurley *et al.* 1986) to many hours (Fröberg & Mossfeldt, 1971), but several studies have not found a quantitatively important decrease (Jansson & Kaijser, 1982; Kiens *et al.* 1993) in either trained or untrained subjects (Turcotte *et al.*

1995). It is difficult, however, to envisage a role for intramuscular TAG other than as a substrate for energy metabolism.

A commonly-held view is that the contribution to exercise metabolism from oxidation of NEFA derived by hydrolysis of TAG-rich lipoproteins is small (van der Vusse & Reneman, 1996), perhaps contributing between 5 and 15 % of the energy derived from fat oxidation. In reality there is a paucity of information, and rather a strong case, theoretically, for its re-examination. TAG-rich lipoproteins represent a potentially-rich source of fatty acids for the working muscle, particularly after consumption of a fat-containing meal when chylomicron concentrations are high. Also, because of the insulin response to co-ingested carbohydrate, plasma concentrations of NEFA fall postprandially and this could increase the contribution of fatty acids from lipoprotein-TAG. Finally, high rates of fatty acid oxidation in contracting muscle may enhance the rate of removal of NEFA from the site of TAG hydrolysis, decreasing substrate inhibition of lipoprotein lipase (EC 3.1.1.34; LPL) and favouring hydrolysis of the TAG core of lipoprotein.

Prolonged exercise is associated with a small decrease in the plasma concentration of TAG, which could reflect use of VLDL-TAG as a fuel for exercise (Nagel *et al.* 1989). It could be attributed equally, however, to decreased hepatic secretion of VLDL, secondary to reduced blood flow. A number of studies have measured plasma TAG uptake by muscle during exercise in fasted subjects. Several have found no significant extraction (Havel *et al.* 1967; Kaijser & Rössner, 1975; Olsson *et al.* 1975). However, Kiens *et al.* (1993) estimated total degradation of VLDL-TAG (from integrated areas under TAG concentration *v.* time curves multiplied by plasma flow) and concluded that this could cover a major part of fat oxidation during exercise, despite the fact that there was no consistently detectable arterio-venous difference for TAG.

Surprisingly, there are few reports describing the extent to which muscle takes up chylomicron TAG in man. In dogs, chylomicron TAG uptake by muscle has been reported to increase significantly during exercise, with a complementary decrease in uptake by adipose tissue (Terjung *et al.* 1983); if totally oxidized, the TAG-derived fatty acids could account for approximately 11 % of the

**Abbreviations:** LPL, lipoprotein lipase; NEFA, non-esterified fatty acids; TAG, triacylglycerols;  $\dot{V}_{\text{O}_2\text{max}}$ , maximum  $\text{O}_2$  uptake.

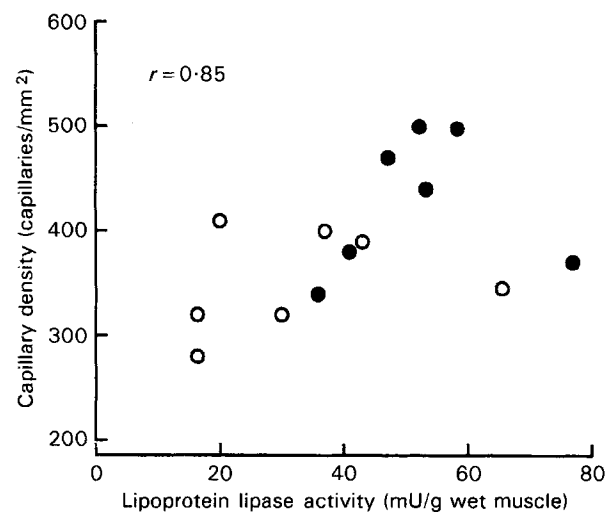
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total O<sub>2</sub> consumption during the exercise. In one study of human volunteers no net extraction of TAG across working muscle in the fed state was detected, although there was indirect evidence for this through production of HDL (Ruys *et al.* 1989). Later study of substrate exchange during 1 h of forearm exercise found that, in contrast to the post-absorptive state, muscle extracted TAG when exercise was performed 3 h after consumption of a meal containing both fat and carbohydrate (Griffiths *et al.* 1994). In the latter study, however, isometric contractions were performed intermittently and the measured muscle uptake of TAG would incorporate 'recovery' as well as contraction phases. Thus, the evidence concerning the contribution of TAG-derived fatty acids to muscle metabolism during exercise is equivocal and more studies of the postprandial state are needed.

TAG-rich lipoproteins may not play a major role in supplying fatty acids to skeletal muscle during exercise but they are clearly important in replenishing muscle TAG after exercise. Chylomicrons and VLDL are cleared by a common saturable pathway (Björkengren *et al.* 1996), the rate-limiting step of which is hydrolysis of core TAG by LPL. Most tissues express LPL but its activity is highest in the myocardium, adipose tissue and skeletal muscle (besides lactating mammary gland). Because of their mass, adipose tissue and muscle are probably the major sites of TAG removal but their relative importance remains a matter of debate.

Early studies using nephelometry to assess plasma turbidity found that muscle cleared 50% of a fat emulsion infused intravenously, compared with 13% by adipose tissue (Rössner, 1974). This conclusion is not supported, however, by recent findings. Chylomicron uptake has been measured across the splanchnic bed (reflecting uptake into visceral fat) and across the leg (Nguyen *et al.* 1996). These workers found that uptake into the splanchnic bed accounted for 70 and 20% of meal TAG disappearance in men and women respectively. By comparison, the uptake by the legs was small (12 and 8%). Nguyen *et al.* (1996) interpreted leg uptake as 'presumably in (leg) adipose tissue', ignoring the possibility of a contribution from skeletal muscle. Arterio-venous differences for chylomicron TAG and VLDL-TAG have also been measured across subcutaneous abdominal adipose tissue and forearm muscle after consumption of a mixed meal (Potts *et al.* 1991b). Fractional extraction of chylomicron TAG over a 6 h period was threefold lower in muscle than in adipose tissue. Neither of these studies, however, gave information about the exercise status of the subjects, long or short term, and both could be relevant because recent exercise is probably the most important determinant of muscle TAG concentration and, hence, the need for replenishment.

Long-term regular exercise has considerable potential to enhance muscle TAG uptake via (1) increases in muscle mass and (2) structural changes in its microcirculation. Endurance-trained individuals (Ingjer, 1979) have more capillaries around each muscle fibre and more capillaries per unit cross-sectional area of muscle. The implication of this for LPL activity has been elegantly demonstrated; in men who trained one leg but not the other at 65%  $\dot{V}_{O_{2max}}$  for 8 weeks, capillarization was 20% greater in muscle from the trained leg than from the untrained contralateral leg, with 35–46% higher LPL activity (Kiens & Lithell,



**Fig. 1.** Relationship between lipoprotein lipase (*EC* 3.1.1.34) activity and capillary density measured in the same needle-biopsy sample of *vastus lateralis* after 8 weeks of training of the knee extensors of one leg but not the other. (●), Endurance-trained muscle; (○), untrained muscle. 1 mU enzyme activity was defined as 1 nmol fatty acid released per min. (After Kiens & Lithell, 1989.)

1989). Moreover, muscle LPL activity was related to capillary density (Fig. 1). The acquisition of fatty acids from TAG-rich lipoproteins is thus facilitated in trained muscle. This ties in persuasively with the enhanced utilization of muscle TAG reported for trained individuals (Hurley *et al.* 1986) and perhaps also with evidence (in the rat) of a close coupling between the size of muscle TAG stores and uptake of plasma TAG-derived fatty acids (Tan *et al.* 1977).

#### Influence of training on postprandial lipaemia

Endurance-trained individuals exhibit plasma concentrations of HDL-cholesterol 20–30% higher than those of their sedentary counterparts, as well as low plasma concentrations of TAG in the fasted state (for review, see Durstine & Haskell, 1994). Attention has focused on HDL-cholesterol levels but these may be a metabolic marker for their enhanced metabolic capacity for TAG degradation. The reason is that high concentrations of TAG-rich lipoproteins provide increased opportunity for exchange of TAG with cholesteryl esters from HDL and as a consequence the cholesterol measured in HDL decreases (Patsch *et al.* 1992).

#### Cross-sectional studies

An individual's metabolic capacity for TAG is challenged during the postprandial period (or some model for this) when concentrations of TAG-rich lipoproteins are at their highest. A number of studies have compared trained people with untrained or sedentary controls, using different methodologies, i.e. oral fat tolerance tests (Cohen *et al.* 1989; Merrill *et al.* 1989; Hartung *et al.* 1993; Isherwood, 1996), intravenous infusion of lipid emulsion (Björntorp *et al.* 1972; Ericsson *et al.* 1982; Sady *et al.* 1988; Cohen *et al.* 1989; Podl *et al.* 1994) and, in one case (Cohen *et al.* 1989), duodenal perfusion with lipid emulsion. In the

earliest of these, middle-aged men who trained and competed in orienteering and cross-country skiing showed a high TAG removal rate, compared with controls, although rates in the trained men were not exceptional in relation to controls with similarly low fasting plasma TAG concentrations (Björntorp *et al.* 1972). Confirmatory evidence of faster TAG removal in young athletes than in controls matched for height and weight was published 10 years later (Ericsson *et al.* 1982). Subsequent studies have also found enhanced TAG clearance rates in male (Sady *et al.* 1988) and female (Podl *et al.* 1994) endurance athletes.

Studies using an oral fat challenge (40–140 g) have produced broadly similar findings, i.e. the magnitude of postprandial lipaemia (measured as the area under the plasma TAG concentration *v.* time curve over 8 h) has been found to be lower in endurance-trained men than in controls (Cohen *et al.* 1989; Merrill *et al.* 1989; Hartung *et al.* 1993; Isherwood, 1996). Patients with coronary artery disease who had participated in a rehabilitation programme ( $\geq 3$  months) also had a 28% lower lipaemic response than men with similar disease status who had elected not to follow the programme (Yanes *et al.* 1989), suggesting that exercise may improve postprandial lipaemia even in individuals who are symptomatic for atherosclerotic disease. However, aspects of the rehabilitation programme other than the exercise could have influenced these findings. For example, there was clearly a difference in dietary practice, patients following the rehabilitation programme consumed less fat (28 *v.* 41% daily energy intake) and more carbohydrate (55 *v.* 39% daily energy intake) than the comparison group.

Several potentially confounding issues need to be considered. First, because chylomicrons and VLDL are cleared by a common pathway, levels of postprandial lipaemia are related to the size of the endogenous TAG pool (O'Meara *et al.* 1992). In several of the cross-sectional studies described, TAG concentrations in the fasted state were lower in the exercise groups (Björntorp *et al.* 1972; Ericsson *et al.* 1982; Sady *et al.* 1988; Hartung *et al.* 1993). Two studies have attempted to control for this difference by matching athletes and controls for fasting TAG concentration; even in these circumstances, chylomicron half-life was lower (3 *v.* 4 min; Cohen *et al.* 1989) and the area under the plasma TAG concentration *v.* time curve above the fasting level was lower (by 45%) in athletes (Merrill *et al.* 1989), showing that differences between groups could not be attributed entirely to the fasting TAG pool size.

Second, athletes have different dietary practices from sedentary controls; typically, energy intake is greater, with a larger proportion of total energy derived from carbohydrate (Walker, 1986). This may influence indices of TAG clearance because high-carbohydrate diets up-regulate, and high-fat diets down-regulate, the activity of LPL in adipose tissue (Eckel, 1989), with opposite effects in skeletal muscle (Jacobs *et al.* 1982). The implications for comparisons between athletes and others cannot be stated, however, because of the complexity of these influences and their potential interactions with co-existing differences in body composition.

Finally, differences in muscle fibre population could contribute to the high metabolic capacity of athletes for

TAG because, based on animal studies, LPL activity is highest in type I fibres (Borensztajn *et al.* 1975). Endurance athletes typically possess a larger proportion of these highly oxidative fibres (Costill *et al.* 1976), which could enhance their whole-body response to a TAG challenge. Indeed, after a mixed diet, muscle LPL activity has been reported to be directly related ( $r$  0.95) to the proportion of type I fibres in needle-biopsy samples of human skeletal muscle (Jacobs *et al.* 1982).

Overall, the evidence from cross-sectional studies is that postprandial lipaemia following an oral fat challenge is 27–59% lower, and removal rates of intravenous TAG 26–92% higher, in endurance-trained individuals (middle-aged men as well as young men and women) than in untrained or sedentary controls. Trained people exhibit these characteristics despite their low levels of body fat, the tissue with highest LPL activity per unit mass, suggesting that the quantity and/or the quality of their skeletal muscle is important. In the 'real-life' situation of normal meals, related characteristics of the trained state probably contribute. These would include, for example, improvements in insulin sensitivity, with implications for the integration of postprandial responses; even, speculatively, enhancement of the insulin-stimulated increase in muscle blood flow (Ebeling *et al.* 1993).

One final point should be made. Individual sessions of exercise can profoundly influence fasting and postprandial TAG metabolism (see pp. 66–67). Measures of fat tolerance in cross-sectional studies have often been made in reasonably close proximity to a training session, the interval between training and testing being reported as, for example, 'about 12 h' (Björntorp *et al.* 1972), '1 d' (Merrill *et al.* 1989; Isherwood, 1996), and 'at least 24 h' (Sady *et al.* 1988). Other investigators have allowed subjects to follow their customary training regimen on the day before the test (Cohen *et al.* 1989; Podl *et al.* 1994); yet others provide no information. Athletes will invariably train unless specifically requested not to do so, because this is their habit. Consequently, although these findings describe accurately the good fat tolerance in trained people in everyday life, they do not permit a conclusion to be drawn on whether long-term adaptations to training exert an influence on postprandial lipaemia beyond the effects of a single session of exercise.

#### *Intervention studies*

Early studies described the influence of 8–10 weeks of training on postprandial TAG concentrations (Altekruse & Wilmore, 1973) and the optical density of serum samples (Zauner & Benson, 1977). The decrease in lipaemia was of the same order in both studies (24%), although this was not statistically significant in the latter study of men selected for their abnormally high response to an oral fat tolerance test. Patsch *et al.* (1983) described the postprandial responses to dietary fat for two men during a 4-year training period. Full data were presented for one subject only, in whom postprandial lipaemia decreased with training by 95%, with an increase in HDL<sub>2</sub>-cholesterol.

In a detailed study of six healthy men before and after 7 weeks of jogging training, Weintraub *et al.* (1989)

controlled diet carefully to ensure that subjects did not lose body weight. Based on the vitamin A-fat loading test, chylomicron retinyl palmitate levels were reduced by 37% with training. There was no relationship between chylomicron lipaemia and HDL-cholesterol, the authors suggesting that a longer period of training may be needed before this complementary change is evident. (This is consistent with the case study referred to earlier where the first sign of an increase in HDL-cholesterol was after 7 months.) A longer study, with 32 and 48 weeks of training, found an increase (13%) in HDL-cholesterol alongside a 49% improvement in the capability to clear an intravenous fat load (Thompson *et al.* 1988). The latter finding, alongside training-induced increases in heparin-releasable LPL activity (Thompson *et al.* 1988; Weintraub *et al.* 1989), suggests that improved TAG clearance, as opposed to decreased appearance, is responsible for these improvements in the plasma TAG response to dietary fat.

Two studies (both randomly controlled) report conflicting findings of no significant improvement in fat tolerance with training. In one, men with primary hyperlipidaemia ( $n$  17, type IV, high fasting TAG;  $n$  6, type IIb, high total and LDL-cholesterol) were studied using an intravenous fat challenge (Wirth *et al.* 1985). Clearance rates for TAG improved by an average of 8% in the men who trained but did not differ significantly after training from rates measured in controls. Improvements could have been restrained by the patients' pathologies, but as seven of nine patients who trained showed increased clearance, the low power to detect a change may be a factor. In a more recent study, healthy middle-aged women (thirteen exercisers, thirteen controls) trained over 12 weeks by brisk walking (Aldred *et al.* 1995). Despite clear improvements in endurance fitness there was no change in the plasma TAG response to an oral fat load. One possibility is that the intensity of training, i.e. approximately 60%  $\dot{V}_{O_{2max}}$ , was insufficient to stimulate morphological changes in skeletal muscle. It is noteworthy, however, that the two studies with 'negative' findings were specifically designed to exclude effects of recent exercise; subjects were studied between 48 and 72 h after (Wirth *et al.* 1985) and 48 h after (Aldred *et al.* 1995) the last training session, which raises again the issue of the timing of post-training assessments.

A preliminary study in our laboratory found a marked increase in postprandial lipaemia in endurance athletes who refrained from exercise for 6 d, most of this increase occurring in the first 60 h (Lawrence *et al.* 1997). On this evidence, effects of a recent training session would have contributed to the improvement in fat tolerance reported in the intervention study by Thompson *et al.* (1988) because post-training measurements were made only 10 h after the last training session. Effects of training on the findings of other studies where measurements were made 36 h and 4 d respectively, after athletes' last exercise are less likely (Weintraub *et al.* 1989; Drexel *et al.* 1992). In the latter study, however, a combined intervention of diet restriction and exercise was employed so the findings are not directly comparable.

There are some indications in these findings of potential mechanisms; the lower lipaemic response after training appears to reflect mainly differences in chylomicron levels

(Weintraub *et al.* 1989; Drexel *et al.* 1992), which might be expected if training increases LPL activity and chylomicrons are the preferred substrate for LPL (Potts *et al.* 1991a). This suggestion is supported by the 'dramatic' effect on chylomicron and chylomicron remnant metabolism when trained men interrupt their training for 2 to 3 weeks (Mankowitz *et al.* 1992); de-training increased the areas under the plasma concentration *v.* time curves by 41 and 37% respectively.

### Effects of single exercise sessions

It has been known since the early 1960s that a session of exercise diminishes postprandial lipaemia. For example, Cohen & Goldberg (1960) examined the effect of a 10 km walk on plasma turbidity during the hours following a high-fat meal; the lower turbidity during the exercise trial was attributed to improved clearance of dietary fat. Plasma turbidity was also lower in patients who were ambulatory after a fatty meal than in those who were confined to bed (McDonald & Fullerton, 1960). In the first study to measure (serum) TAG directly, forty army recruits were divided into two groups, one of whom marched 16 km after consuming a fatty meal (Nikkilä & Kontinen, 1962). The control group rested during this period. Serum TAG concentrations were significantly lower in those who marched than in those who rested. These findings appear to conflict with the view (discussed previously) that muscle does not increase its uptake of TAG during exercise. Exercise decreases splanchnic blood flow (Rowell, 1993), however, and rates of appearance of exogenous TAG could be lower during exercise, contributing to the decrease in serum TAG concentration (or turbidity).

The effect of exercise on postprandial lipaemia has subsequently been examined in laboratory conditions. For example, postprandial TAG concentrations at 4, 6 and 8 h after consuming a high-fat breakfast were higher when men ( $n$  6) had exercised at 75%  $\dot{V}_{O_{2max}}$  for 30 min, starting 1 h after the meal, than in a rested control trial (Klein *et al.* 1992). A similar approach (a high-fat meal followed by exercise or rest in a repeated-measures design) has been employed to study the effects of cycling (Schlierf *et al.* 1987) and treadmill walking (Hardman & Aldred, 1995). In both studies, subjects exercised at 40%  $\dot{V}_{O_{2max}}$  for 90 min, starting 1.5 h after the test meal. Postprandial lipaemia was lower in the exercise trial by 34 and 24% respectively (Schlierf *et al.* 1987; Hardman & Aldred, 1995). However, inspection of the TAG responses shows that most of, or all, this difference was evident during the period of recovery after exercise. This ties in with the finding that exogenous TAG was taken up in resting forearm muscle, with no increase during exercise (Kajiser & Rössner, 1975). Exercise influences postprandial intestinal activity (Soffer *et al.* 1991), however, and the findings of studies where exercise is performed during the postprandial period may be influenced by altered gut function. For this reason and because exercise-induced changes in LPL activity appear to be delayed, studies examining fat tolerance some hours after a session of exercise provide a clearer picture of exercise-induced changes in postprandial lipid metabolism.

Fasting TAG concentrations are reduced the day after prolonged exercise, alongside increases in LPL activity measured in post-heparin plasma (Kantor *et al.* 1984). It might be expected, therefore, that the plasma TAG response to dietary fat consumed the day after exercise would also be decreased. For example, in one study, young adults walked for 2 h at about 40% of  $\dot{V}_{O_{2max}}$  in the afternoon and their fat tolerance was tested the following morning (Aldred *et al.* 1994). Postprandial lipaemia (6 h area under the plasma TAG concentration *v.* time curve after a high-fat meal) was nearly one-third lower than that for a no-exercise control trial. In contrast, Cohen *et al.* (1989) found little effect on lipaemia in sedentary men who performed 1 h of exercise 12 h before an oral fat tolerance test. This could reflect the lower exercise energy expenditure in the latter study. The energy expended during exercise seems to be a determinant of its effects on lipaemia (Fig. 2); sessions of moderate- or low-intensity exercise of equivalent energy expenditure (1.5 h at 60%  $\dot{V}_{O_{2max}}$  *v.* 3 h at 30%  $\dot{V}_{O_{2max}}$ ) resulted in identical decreases in lipaemia (Tsetsonis & Hardman, 1996).

The evidence points to enhanced plasma clearance of TAG-rich lipoproteins as the major determinant of exercise-induced decreases in postprandial lipaemia. For example, in male distance runners, clearance of intravenous fat was 76% greater the morning after a marathon run than when measured 24 h before the race (Sady *et al.* 1986). Fasting TAG levels were reduced by 26% and plasma post-heparin LPL activity increased by 46%. Other studies report increases of 22 and 66% in removal rates of intravenous fat administered the morning after 3 h exercise sessions (Dufaux *et al.* 1981; Annuzzi *et al.* 1987). Moreover, in the studies of the plasma TAG response described previously (Aldred *et al.* 1994; Tsetsonis & Hardman, 1996; Tsetsonis *et al.* 1997), the long interval

between the end of exercise and assessment of postprandial lipaemia makes an effect on chylomicron appearance rate an unlikely explanation for the lower plasma TAG levels. In all these studies, fasting and postprandial plasma NEFA concentrations were higher the morning after exercise than after 1 d of minimal activity; as substrate delivery to the liver is the major determinant of VLDL secretion (Sniderman & Cianflone, 1993), this would not be consistent with decreased hepatic secretion of these lipoproteins after exercise.

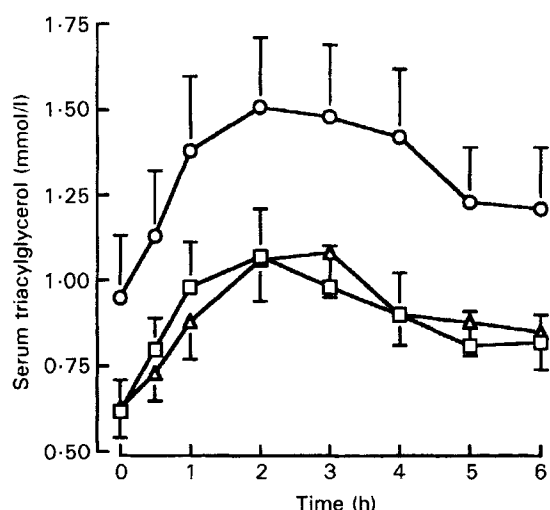
Supporting, although indirect, evidence comes from an examination of the effect of previous exercise on postprandial substrate metabolism in middle-aged women. When a high-fat mixed meal was ingested the morning after exercise, the women oxidized more fat than they did during a control trial, regardless of their training status (Tsetsonis *et al.* 1997). This is also consistent with increased TAG uptake into muscle. It is not known, however, whether or not the recently-ingested fat was the source of the additional fat oxidized.

### Role of lipoprotein lipase

Although the mechanisms by which exercise mitigates postprandial lipaemia are not well understood, effects on LPL activity, the 'metabolic gatekeeper' for lipid energy storage, appear to play a key role.

Post-heparin plasma LPL activity has been reported to be higher in endurance-trained individuals than in inactive controls (Kantor *et al.* 1987; Podl *et al.* 1994; Isherwood, 1996). This reflects increased activity in skeletal muscle (Nikkilä *et al.* 1978), but there are also reports of higher activity in adipose tissue (Nikkilä *et al.* 1978) and of a positive relationship between adipose-tissue LPL activity and indices of training volume (Nikkilä *et al.* 1978; Marniemi *et al.* 1980). These findings on adipose tissue do not fit well, however, with other evidence. For example, a 2-week de-training period in athletes resulted in decreased LPL activity in muscle with parallel increases in adipose tissue (Simsolo *et al.* 1993); and a short period (5–13 d) of exercise in sedentary people resulted in a 35% increase in LPL activity in muscle, with no change in activity in subcutaneous adipose tissue (Seip *et al.* 1995). The latter findings seem biologically plausible, with complementary changes in LPL activity partitioning more lipoprotein-TAG into muscle for oxidation in the trained state. Whatever the site(s) of the increased LPL activity, its functional significance is clear from the positive relationships between plasma LPL activity and clearance rate in an intravenous fat tolerance test in male (Sady *et al.* 1988) and female (Podl *et al.* 1994) runners (Spearman's rank order correlation coefficients 0.74 and 0.61 respectively).

Focusing on skeletal muscle, intervention studies have largely confirmed the findings of cross-sectional studies. After training periods of 7, 14 or 15 weeks, the corresponding increases in plasma LPL activity were 16 (Weintraub *et al.* 1989), 19 (Thompson *et al.* 1988) and 33% (Peltonen *et al.* 1981). More recently, an 80% increase in plasma LPL was observed when obese women followed an exercise programme for 6 months (Lamarche



**Fig. 2.** Postprandial plasma triacylglycerol response to a high-fat meal consumed the morning after: a day of minimal activity (control; —○—); walking for 3 h at 30% maximum  $O_2$  uptake (low intensity; —□—); and after walking for 1.5 h at 60% maximum  $O_2$  uptake (moderate intensity; —△—). Values are means with their standard errors represented by vertical bars for nine young adults (five men, four women). (Reprinted, with permission, from Tsetsonis & Hardman, 1996.)

*et al.* 1993); no parallel changes in body weight or composition occurred and these variables were unrelated to total plasma LPL activity, suggesting that the increase might be attributable to changes in enzyme activity in some other tissue, presumably muscle.

As mentioned previously, the increase in muscle LPL activity with training could be related to improvements in the microcirculation. A period of 8 weeks of cycle-ergometer training resulted in a 19% increase in capillary density accompanied by an approximately 50% increase in muscle LPL activity (Svedenhag *et al.* 1983). No relationship was found between these two variables, but this may be because they were determined in different biopsy samples. Where measurements have been made in the same sample (Kiens & Lithell, 1989) a rather close relationship was evident, as mentioned earlier and shown in Fig. 1. In the latter study, uptake at rest of VLDL-TAG by trained muscle was markedly greater than that by untrained muscle.

Thus, trained muscle is well-adapted to the utilization of lipoprotein-TAG; its extensive capillary network provides more binding sites for LPL, closer proximity of myocytes to capillaries will improve diffusion conditions, and increased capacity for  $\beta$ -oxidation may mean more entrapment of the fatty acid products of hydrolysis. These characteristics are likely to be restricted to endurance-trained muscle; capillarization is not enhanced to the same degree in sprint-trained athletes (Tesch *et al.* 1984) who also exhibit lower LPL activity (Nikkilä *et al.* 1978) and probably a higher lipaemic response to dietary fat than endurance-trained athletes (Lee *et al.* 1993).

Evidence of a relationship between capillarization and LPL activity suggests that the link is long-term structural adaptations in muscle. However, an increase in muscle LPL activity seems to occur during the first 2 weeks of training (Seip *et al.* 1995), with a rapid loss on de-training (Simsolo *et al.* 1993). These findings suggest that the increase in enzyme activity may partly be a response to the very early stages of training, perhaps even to a single exercise session.

Studies in human subjects have shown striking increases of 46 (Sady *et al.* 1986) and 74% (Kantor *et al.* 1984) in plasma LPL activity measured 18 h after prolonged exercise lasting several hours, and smaller increases after more modest exercise (Kantor *et al.* 1987). There may also be a stimulus to adipose-tissue LPL activity; this was increased by 20% in well-trained men who ran 20 km, but the increase in muscle LPL activity was greater (112%; Taskinen *et al.* 1980). An increase in adipose-tissue LPL measured immediately after 1 h of exhaustive cycling has also been reported, but in this case with no change in activity in muscle (Lithell *et al.* 1979a). Subjects of this study were in the fed state, however, and results from animal studies suggest that food intake blunts the exercise-induced increase of muscle LPL activity (Nikkilä, 1987).

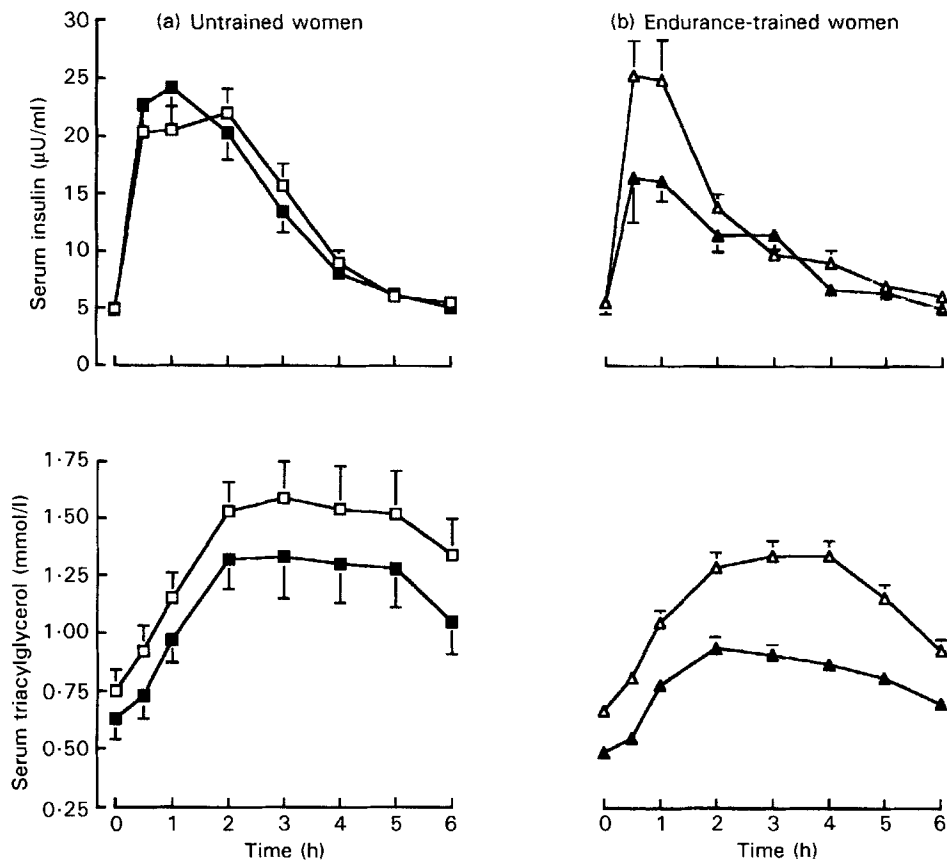
LPL activity in skeletal muscle has been reported to be profoundly increased (by 200–240%) when measured after intense exercise (Lithell *et al.* 1979b, 1981, 1984). In later studies using one-leg knee-extension exercise, findings were less clear (Kiens & Lithell, 1989; Kiens *et al.* 1989). When measured immediately after either 1 or 2 h of knee-extension exercise, muscle LPL activity was unchanged

from that at rest; an increase of 60% was found 4 h, but not 8 h, after exercise. One explanation for these apparently conflicting findings may be that knee-extension exercise, unlike whole-body exercise, evokes little catecholamine response. Catecholamines increase cAMP levels, which leads in turn to activation of LPL (Newsholme & Leech, 1994). There is some evidence supporting this explanation; in soldiers taking part in a 10 d mountain expedition, exercise-induced increases in muscle LPL activity and urinary excretion of adrenaline were strongly related, the latter accounting for more than 70% of the variance in LPL activity (Lithell *et al.* 1981). The absence during single-leg knee-extension exercise of the hormonal changes which accompany exercise with large muscle groups may diminish use of endogenous TAG by muscle, with a corresponding increase in reliance on blood-borne lipid substrates (Kiens *et al.* 1993) and a reduced need for replenishment of muscle TAG.

There is also new evidence that some of the confusion regarding exercise-induced changes in skeletal-muscle LPL activity derives from differences in the timing of biopsies in which enzyme activity is measured. A single session of moderate exercise (85–90 min at 65%  $\dot{V}_{O_{2max}}$ ) resulted in an increase in LPL mRNA, with increases in LPL protein mass following this message (Seip *et al.* 1997); LPL mass was unchanged directly after exercise, but was 53% higher after 4 h and 93% higher after 8 h, with indications that this rise continued after the observation period. These effects were transient, however, and by 20 h had dissipated. Thus, the maximal increase in muscle LPL activity is probably somewhere between 8 and 20 h after exercise. No comparable information is available on exercise-induced changes in adipose tissue.

Finally, mention should be made of the interactions between exercise and training and insulin sensitivity and their implications for postprandial TAG disposition. First, regulation of LPL activity is tissue specific; insulin stimulates enzyme activity in adipose tissue with opposing, although weaker, effects in skeletal muscle (Farese *et al.* 1991). Second, these effects differ in non-exercised muscle and in muscle which has recently been exercised (Kiens *et al.* 1989); insulin decreases LPL activity in non-exercised muscle but this influence is over-ridden in exercised muscle by some other local, exercise-related effect. Third, in non-exercised muscle LPL activity covaries with insulin sensitivity (Kiens *et al.* 1989). These issues are made more complex by the influence of training on insulin sensitivity in muscle. The enhanced sensitivity has been described as a 'genuine effect of training, but short-lived' (Dela *et al.* 1992).

These findings are important. They lead us to question how meaningful intravenous tolerance tests are, because of the absence of an insulin response; they demonstrate the need for clear thinking and careful study design in respect of recent exercise sessions; they underscore the need for whole-body studies in human volunteers consuming 'normal' meals containing a mixture of macronutrients; they show that the habitual physical activity levels of such volunteers will influence the outcome. An example of the latter point comes from a study which compared the effect of walking for 1.5 h at 60%  $\dot{V}_{O_{2max}}$  on the lipaemic and



**Fig. 3.** Postprandial serum triacylglycerol concentrations after consumption of a high-fat meal (1.70 g fat, 1.65 g carbohydrate, 0.25 g protein/kg fat-free mass) the morning after 1 d of minimal activity (control trial; □, △) and the morning after walking for 1.5 h at 60% maximal  $O_2$  uptake (exercise trial; ■, ▲) in middle-aged women. (a) Untrained women ( $n$  13) who ingested, on average, 75.8 g fat, 73.7 g carbohydrate, 11.2 g protein; (b) endurance-trained women ( $n$  9) who ingested, on average, 77.0 g fat, 75 g carbohydrate, 11.4 g protein. Values are means with their standard errors represented by vertical bars. (Reprinted, with permission, from Tsetsonis *et al.* 1997.)

insulinaemic responses to a high-fat mixed meal in endurance-trained and untrained women (Tsetsonis *et al.* 1997). Both groups showed a reduction in lipaemia after exercise (greater in the trained women, i.e. 28 v. 17%) but only the trained women showed lower insulinaemia (Fig. 3).

### Conclusion

Exercise exerts a potent influence on postprandial lipid fluxes, altering lipid disposition and increasing lipid oxidation. Endurance-trained individuals exhibit low levels of postprandial lipaemia which appear to reflect enhanced uptake of TAG-rich lipoproteins. This could derive from the high level of LPL activity in their large, capillary-dense muscle mass, but the possibility exists also of increased activity of this enzyme in adipose tissue. The low lipaemic response of athletes increases rapidly, however, after a few days without exercise. Short-term effects of individual exercise sessions are, therefore, also important determinants of postprandial lipaemia. These are probably

mediated through delayed effects on the activity of LPL in muscle during the hours following exercise.

Repeated episodes of exaggerated postprandial lipaemia constitute an atherogenic stimulus. This is because prolonged residence in the circulation of TAG-rich lipoproteins leads to a depletion of HDL-cholesterol and a preponderance of small, dense LDL, a combination known as the atherogenic lipoprotein phenotype (Austin *et al.* 1990). Regular, frequent exercise will exert a restraining influence on the postprandial rise in plasma TAG concentrations, with the possibility of a reduction in this aspect of the risk of atherosclerosis. The indications are that moderate amounts and intensities of exercise may be effective, provided a reasonable amount of energy is expended on most days.

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