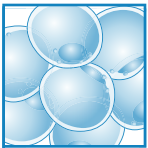


PHYSICAL ACTIVITY AND EXERCISE IN THE REGULATION OF HUMAN ADIPOSE TISSUE PHYSIOLOGY

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Thompson D, Karpe F, Lafontan M, Frayn K. Physical Activity and Exercise in the Regulation of Human Adipose Tissue Physiology. *Physiol Rev* 92: 157–191, 2012; doi:10.1152/physrev.00012.2011.—Physical activity and exercise are key components of energy expenditure and therefore of energy balance. Changes in energy balance alter fat mass. It is therefore reasonable to ask: What are the links between

physical activity and adipose tissue function? There are many complexities. Physical activity is a multifaceted behavior of which exercise is just one component. Physical activity influences adipose tissue both acutely and in the longer term. A single bout of exercise stimulates adipose tissue blood flow and fat mobilization, resulting in delivery of fatty acids to skeletal muscles at a rate well-matched to metabolic requirements, except perhaps in vigorous intensity exercise. The stimuli include adrenergic and other circulating factors. There is a period following an exercise bout when fatty acids are directed away from adipose tissue to other tissues such as skeletal muscle, reducing dietary fat storage in adipose. With chronic exercise (training), there are changes in adipose tissue physiology, particularly an enhanced fat mobilization during acute exercise. It is difficult, however, to distinguish chronic “structural” changes from those associated with the last exercise bout. In addition, it is difficult to distinguish between the effects of training per se and negative energy balance. Epidemiological observations support the idea that physically active people have relatively low fat mass, and intervention studies tend to show that exercise training reduces fat mass. A much-discussed effect of exercise versus calorie restriction in preferentially reducing visceral fat is not borne out by meta-analyses. We conclude that, in addition to the regulation of fat mass, physical activity may contribute to metabolic health through beneficial dynamic changes within adipose tissue in response to each activity bout.

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I. INTRODUCTION AND OVERVIEW

We are in the midst of a well-publicized global epidemic of obesity with an attendant inflated risk of chronic disease (278). The social causes of this phenomenon are complex but, given that physical activity and exercise are key components of energy expenditure and therefore energy balance, it is reasonable to suspect that a decline in these behaviors is at least partially involved and could be part of a solution. So, from this perspective alone, there is good reason to be interested in the physiology of physical activity in the regulation of adipose tissue

mass. However, the underlying biology of adipose tissue is much more interesting (and complex) than energetics and masses alone. A minority of people with greatly expanded fat depots can be overtly healthy (2, 112, 118, 119), and the surgical removal of fat alone does not yield a clear benefit in risk factors for disease (131). Moreover, lean women can have as much body fat as obese men (114), so clearly relative adipose tissue mass is not the only consideration. In this review, we provide a synthesis of the current understanding of the acute and chronic impact of physical activity and exercise in the regulation of adipose tissue mass and function. We restrict our review to human studies to avoid potential diversions due to interspecies differences.

II. OVERVIEW OF ADIPOSE TISSUE STRUCTURE AND FUNCTION

Adipose tissue is specialized for storage of energy in the form of triacylglycerols. It is also an endocrine organ, releasing a number of peptides and other factors that can act in an endocrine or paracrine fashion. Adipose tissue typi-

cally makes up ~20% of body weight in men and 28% in women (233) but in obese people can expand manyfold to >80% of body weight. Adipose tissue contains many cell types including endothelial cells and fibroblast-like adipocyte precursors and, particularly in obese people, there may also be macrophages and other leukocytes. Adipocytes typically constitute 80–90% of adipose tissue volume, but only 60–70% of cell number (144).

Adipose tissue triacylglycerol content reflects energy balance. Because the body's capacity to store glycogen is finite and relatively small, long-term imbalances between energy intake and energy expenditure are reflected in a change in the amount of triacylglycerol stored in adipocytes. Adipocyte triacylglycerol content in turn reflects the balance between the processes of fat deposition and fat mobilization. It follows that these processes must be regulated in relation to whole body energy balance. Fat mobilization is readily stimulated by β -adrenergic activation (99, 218). However, the diurnal fluctuation in fat mobilization, which is high after an overnight fast but suppressed after meals, seems to depend more on changing insulin concentrations. Local infusion of propranolol (β -adrenergic blocker) in the postabsorptive state does not change lipolysis (8), although phentolamine (α -adrenergic blocker) causes a large increase, suggesting α -adrenergic inhibition of lipolysis. However, the effect of α -adrenergic blockade may be secondary to changes in blood flow (75). Fat deposition after meals also appears largely to depend on insulin stimulation, which increases the activity of lipoprotein lipase, responsible for hydrolysis of circulating triacylglycerol (270) and increases fatty acid uptake and re-esterification in the adipocytes (69). Regulation of fat storage and mobilization in the context of exercise and physical activity will be reviewed below.

Mature adipocytes develop from precursor cells known as preadipocytes by accumulating triacylglycerol. There has been debate as to the extent of cell turnover in human adipose tissue. In recent years, measurements made by isotope incorporation have shed light on this. One study showed fractional turnover of the mature adipocytes of ~0.2–0.3%/day, corresponding to a half-life of ~300–400 days (247). Another study based on incorporation of radioactive fallout suggested a turnover of ~10%/year, with half the adipocytes replaced every 8 yr (236). These estimates may differ because of differing populations and methodologies, but nevertheless, turnover of fat cells clearly occurs, albeit slowly. Despite turnover, the total number of adipocytes appears to be relatively constant throughout adult life (236).

Adipose tissue is arranged in discrete depots, and these depots have different relationships to health. In general, accumulation of adipose tissue in the upper part of the body (abdominal obesity) is associated with detrimental effects on metabolic health and mortality (193), whereas lower-body fat accumulation (gluteofemoral obesity) is associated with protective effects especially after adjustment for upper-body fat and other

risk factors for cardiovascular disease (164). Upper-body fat accumulation usually reflects accumulation of both intra-abdominal fat and subcutaneous abdominal fat. In turn, intra-abdominal fat can be divided into that which is intraperitoneal and drains mostly into the hepatic portal vein, and retroperitoneal depots such as perirenal. Although these are both sometimes referred to as “visceral fat,” in this review we will reserve that term for the intraperitoneal depots as suggested by Mårin et al. (165). The quantification of visceral fat volume depends on the imaging method, strategy, and site of measurement (140, 253). There is on-going debate about whether the adverse effects of abdominal obesity reflect particularly the accumulation of visceral fat, or whether subcutaneous abdominal fat (which is usually a considerably larger depot than visceral fat) is also involved. Longitudinal studies of the development of insulin resistance in Japanese Americans suggest that the visceral fat depot has a particularly adverse role (89), but visceral and subcutaneous depots are highly correlated in cross-sectional studies (64), making it very difficult to disentangle these relationships to health. Whilst subcutaneous and visceral fat are highly correlated within a given population (64, 255), at an individual level, a small proportion of people can show specific phenotypes such as “thin-on-the-outside fat-on-the-inside” or TOFI (255).

Adipose tissue is highly vascularized. Blood flow through adipose tissue in the fasting state is greater than that through resting skeletal muscle (68). Furthermore, adipose tissue blood flow is highly regulated according to nutritional state, increasing rapidly after ingestion of a carbohydrate-rich meal (248) or even pure glucose (120). We will review below the effects of acute exercise and of physical training on adipose tissue blood flow. Adipose tissue blood flow in the fasting state is regulated to a major extent by endothelial nitric oxide (6) and to a smaller extent by angiotensin (84), with a small vasoconstrictory α -adrenergic component (6, 75). The postprandial increase in adipose tissue blood flow, in contrast, appears to depend largely on activation of β -adrenergic receptors (6, 230). The sympathetic innervation of adipose tissue is well-developed but not uniformly distributed (10, 11, 62, 66). There has been some uncertainty as to whether the sympathetic nerve terminals reach the adipocytes themselves, or are purely vascular (68), although newer methodology suggests that the adipocytes are indeed targeted (11). In contrast, there is ongoing debate about the presence of parasympathetic innervation (11, 81, 137).

III. PHYSICAL ACTIVITY AND EXERCISE: KEY TERMS AND DEFINITIONS

Physical activity is defined as any movement (or force) exerted by skeletal muscle that leads to an increase in energy expenditure above rest (36). Exercise is usually described as a subcomponent of physical activity that is planned and/or structured (36). Whereas basal metabolic rate (BMR) and

dietary-induced thermogenesis (DIT) are broadly predictable components of total energy expenditure (TEE) (222), physical activity thermogenesis is highly variable between individuals. At the extremes, physical activity energy expenditure may be as low as just a few hundred kilocalories per day in sedentary individuals (e.g., 10–20% TEE), whereas very highly active athletes could easily expend several thousand kilocalories per day through physical activity (e.g., 60–70% TEE). This can be captured using the concept of physical activity level or PAL (TEE/BMR), with a low PAL being in the range 1.00–1.39 (sedentary) and a very active PAL being in the range 1.9–2.5 (23).

Total physical activity energy expenditure provides us with some information about one important characteristic of physical activity. While this is critical for energy balance, there are additional considerations that are important for other health-related outcomes. Physical activity (particularly during intervention studies) is often expressed using terms such as exercise intensity, duration, and frequency. The energy cost per minute (intensity) of physical activity ranges from activity just above rest (such as standing quietly, which is equal to ~ 0.2 – 0.3 kcal/min above rest) to energy expenditure more than 20 kcal/min above rest during activities such as running at ~ 14 km/h (4). In the United Kingdom, current physical activity recommendations state that adults should perform at least 30 min of moderate intensity activity on at least 5 days a week (50). Moderate intensity is defined as a threefold increase in metabolic rate above rest. Such recommendations are based on the amount of physical activity that is required for “general” health (50, 88), which may be different from the amount of activity that is required for long-term energy balance, although the interpretation of these recommendations is complex and sometimes a source of confusion (257).

The expression of exercise (physical activity) intensity presents a particularly challenging problem when designing experiments and interpreting results. For example, for an average 80 kg man with a $\dot{V}O_{2\max}$ of 30 ml·kg⁻¹·min⁻¹ (low aerobic capacity), then walking slowly at 4 km/h represents

35% $\dot{V}O_{2\max}$ and brisk walking is equivalent to $\sim 70\%$ $\dot{V}O_{2\max}$ (TABLE 1). In contrast, for a man with a higher aerobic capacity and a theoretical $\dot{V}O_{2\max}$ of 60 ml·kg⁻¹·min⁻¹ (assuming that they are identical in all other ways), brisk walking at the same absolute speed represents only 35% $\dot{V}O_{2\max}$ and running at 11.5 km/h would be required to elicit 70% $\dot{V}O_{2\max}$ (TABLE 1). So, in this example, the same activity (brisk walking) represents low-intensity exercise for one person and high-intensity exercise for another (for roughly the same absolute oxygen and energy cost).

To further illustrate the inherent complexity associated with the analysis of physical activity behavior, we have presented energy expenditure over a 24-h period in four different middle-aged men (FIGURE 1). The individual shown in FIGURE 1A shows a low level of activity using almost any metric (low PAL and little moderate intensity activity). FIGURE 1B shows two very clear and pronounced bouts of activity (structured exercise), with very little physical activity throughout the remainder of the day (overall, this individual has a high PAL and considerable moderate and vigorous intensity activity). The two other examples (FIGURE 1, C AND D) are much more difficult to interpret, since they both have a high PAL (and therefore energy expenditure), but there is no obvious bout of exercise and they have accumulated their activity in very different ways. We discuss this issue in more detail elsewhere (257) but, for the purpose of the current review, it is important to highlight that energy expenditure (e.g., PAL or TEE) and the pattern of physical activity (an obligatory part of most physical activity recommendations) are completely different parameters and outcomes. This is important because much of the past research has only sought (perhaps understandably) to capture or manipulate one defined dimension of physical activity behavior (usually structured exercise).

In most people, accumulated physical activity (rather than “exercise”) represents the most quantitatively important (and variable) subcomponent of physical activity energy expenditure (152). This has important implications. First, any exercise or physical activity intervention will inevitably

Table 1. Relative versus absolute exercise (physical activity) intensity

	Low Capacity ($\dot{V}O_{2\max}$ 30 ml·kg ⁻¹ ·min ⁻¹)		High Capacity ($\dot{V}O_{2\max}$ 60 ml·kg ⁻¹ ·min ⁻¹)		
	Slow walking (4 km/h)	Brisk walking (7.2 km/h)	Slow walking (4 km/h)	Brisk walking (7.2 km/h)	Running (11.5 km/h)
$\dot{V}O_{2\max}$, %	35.0	70.0	17.5	35.0	70.0
$\dot{V}O_2$, (ml·kg ⁻¹ ·min ⁻¹)	10.5	21	10.5	21	42
METs, *RMR	3	6	3	6	12
EE > rest, kcal/min	2.8	7.0	2.8	7.0	15.4

EE, energy expenditure; RMR, resting metabolic rate. For simplicity, we have assumed a body mass of 80 kg in both cases and that other factors such as body composition and gait are similar. Data are based on the oxygen cost of activities provided in Ref. 3. Estimated energy expenditure is only approximate and based on 5 kcal/liter oxygen consumed. One metabolic equivalent (MET) equals resting metabolic rate.

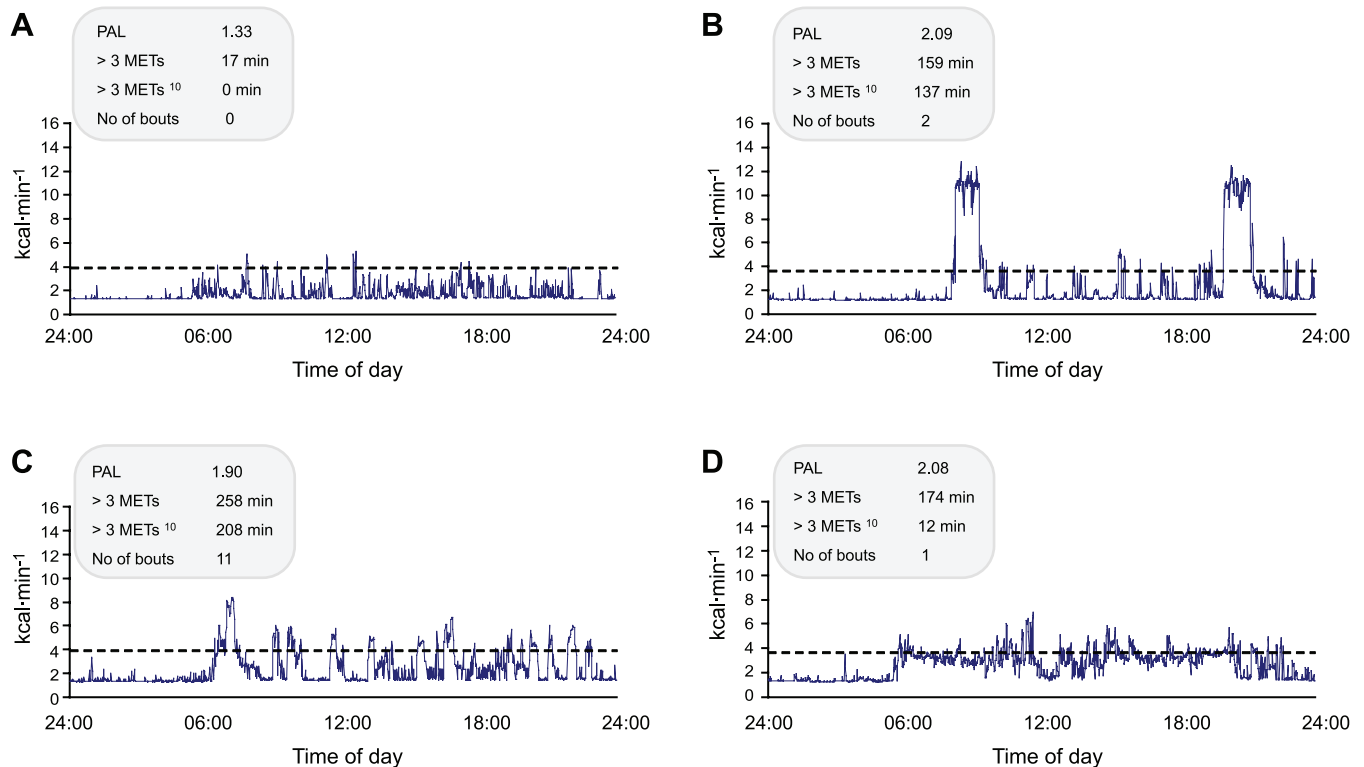


FIGURE 1. Physical activity energy expenditure (kcal/min) over a 24-h period in four different middle-aged men (A–D). One metabolic equivalent (MET) equals resting metabolic rate. The dashed line indicates the threshold for 3 METs, an intensity threshold often used in physical activity recommendations for general health. The text boxes show physical activity level (PAL), the amount of time engaged in activity above 3 METs (>3 METs); the amount of time engaged in activity above 3 METs but in bouts of at least 10 min (>3 METs¹⁰; a feature of many physical activity recommendations), and finally the number of bouts of activity above 3 METs that lasted at least 10 min (no. of bouts). Data captured using synchronised accelerometry and heart rate as described in (Ref. 256).

sit in the context of current physical activity behavior, and this can vary enormously from person to person (FIGURE 1). Notably, the removal of this activity will have a pronounced impact on metabolic control even in young healthy people within a remarkably short time frame (185). Second, even though an intervention may lead to an ostensibly large change in a given behavior, this may only have a modest impact on total physical activity energy expenditure (and therefore TEE). For example, a walking intervention in an average-sized man may lead to a considerable change in this behavior (i.e., walking), but this might only have a modest impact on physical activity energy expenditure (e.g., walking at 4.8 km/h for 45 min four times a week in an average man represents a large change in this behavior, but it will only increase energy expenditure by ~500 kcal/wk above rest, which might equate to a 3% increase in weekly TEE). Depending on a range of factors including existing physical activity behavior (e.g., FIGURE 1), the actual net energy deficit from an exercise-based intervention may be reduced, since structured exercise will inevitably substitute for other nonexercise physical activity energy expenditure unless it replaces a period of complete rest. It is not surprising that modest exercise interventions have no appreciable impact on total energy expenditure (264). Of course, energy bal-

ance is not the only consideration, and there may be other independent health-related benefits derived from the performance of sustained exercise or physical activity (even of a modest intensity).

IV. PHYSICAL ACTIVITY AND ADIPOSITY: OBSERVATIONAL EVIDENCE

The relationship between physical activity and adiposity from observational studies has been comprehensively reviewed and, in general, there appears to be the anticipated inverse relationship between measures of physical activity and measures of fat mass and distribution (271, 272). However, in spite of some large studies, the results are not entirely consistent, and the reported relationships tend to be only modest (271, 272). In one study of over 15,000 men and women across Europe, there was the expected inverse relationship between self-reported leisure-time physical activity and BMI (167). However, cross-sectional studies do not tell us whether increased adiposity is the consequence or cause of decreased levels of physical activity. The evidence from longitudinal studies is also rather mixed. Some studies have reported that self-reported physical activity at baseline

modestly predicts future weight gain. For example, in the Health Professionals' Study of more than 16,000 middle-aged men, self-reported physical activity at baseline was inversely related to the change in waist circumference 9 yr later (135). Similarly, in a retrospective assessment of self-reported weight gain and physical activity (FIGURE 2), women with higher physical activity tend to report lower weight gain over time (156). However, in contrast to these reports, some longitudinal studies found no relationship between baseline physical activity and weight gain. For example, in a study of more than 8,000 young women, there was no relationship between self-reported physical activity at baseline and the change in BMI 4 yr later (9).

Inevitably, the relationship between physical activity and measures of fat mass and distribution are limited by the same issues that affect any association study. However, for physical activity, the situation is further complicated by the multifaceted nature of physical activity behavior (142, 271, 272). Studies typically measure only one dimension of physical activity (e.g., leisure-time physical activity), usually by self-report. Since such behaviors are imperfect surrogate measures of overall physical activity energy expenditure (see sect. III), this almost certainly weakens the association between physical activity and the outcome measure (e.g., waist circumference). It has been argued that because the measurement of physical activity in observational studies is so much poorer than the measurement of obesity, this may not only attenuate the strength of the relationship but also lead to erroneous conclusions about the direction of causality (272).

Given the complexity of physical activity behavior and the limitations of self-report, it has been proposed that observational studies need to include more objective measures to better capture the relationship between physical activity and a given outcome measure (142, 272). Recent techno-

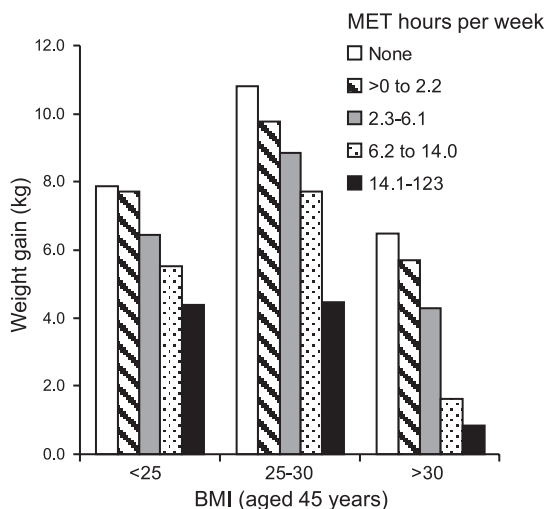


FIGURE 2. Estimated retrospective weight gain from age 45 over the following 8–12 yr in 7,944 women expressed relative to self-report physical activity in MET hours per week. [Redrawn from Littman et al. (156), with permission from Nature Publishing Group.]

logical progress has led to the development of better tools for the assessment of physical activity, and it is now possible to capture strong quantitative data on this component of energy balance (21, 256). However, even with objective measures, it may not be straightforward to form a clear opinion about physical activity status until we have a better idea about what constitutes appropriate physical activity behavior (257).

V. PHYSICAL ACTIVITY AND ADIPOSITY: INTERVENTION STUDIES

Cross-sectional comparisons, cohort studies, and other observational evidence with better measures of physical activity will improve our understanding of the relationship between a given aspect of physical activity behavior and adiposity. However, this will not overcome issues of causality, and in the following section we review the impact of physical activity on fat mass and distribution drawn from intervention studies and randomized controlled trials (RCTs).

A. Exercise-Induced Changes in Body Mass

An intervention that increases one type of physical activity behavior (such as walking or running) will induce a negative energy balance and consequently reduce fat mass as long as there is no compensation in other components of energy expenditure or energy intake. The magnitude of the subsequent reduction in fat mass will ultimately depend on the net energy deficit. As discussed in section III, it is noteworthy that even an ostensibly large change in only one aspect of physical activity behavior (e.g., the introduction of several defined “bouts” of activity per week) may create only a relatively small energy deficit.

Notwithstanding the above, systematic reviews show that physical activity interventions are generally effective at reducing body mass (226). The reported size of the effect for weight loss following physical activity intervention alone is relatively small (226), although this is probably because the prescribed dose of activity in many studies has been relatively low (111). Clearly, greater levels of prescribed physical activity in intervention studies will be required for greater weight loss. There is good evidence that, unlike dietary-induced caloric restriction, a negative energy balance from increased physical activity alone seems to reduce fat mass with little change (76, 113, 200, 211) or a modest increase in fat-free mass (275). However, the picture is complex because physical activity in the presence of marked caloric restriction does not always prevent the loss of fat-free mass (201), and readers are referred to a recent review for a more detailed overview of this subject (57). It is noteworthy that the actual mass lost as a result of exercise based on estimated energy expenditure, presumably because there is partial compensation in either energy intake or some other component of energy expenditure (128, 153, 212, 261, 275).

B. Effect of Exercise on Fat Mass and Distribution

A meaningful energy deficit created by increased physical activity generally leads to a loss of fat mass from the quantitatively significant depots (55, 211, 213, 223, 275). Although most of the change in total mass in response to exercise interventions is accounted for by changes in fat mass, using total fat mass alone may overlook potentially important and selective regional effects in functionally different adipose tissue depots. Indeed, it has been argued that too much emphasis has been put on weight and/or total fat loss as outcome measures in the past (210). With this in mind, it is noteworthy that a relatively large exercise-induced change in some of the key depots may take place in the context of only a small change in total fat mass (110, 180).

There has been considerable interest in whether physical activity interventions have the capacity to preferentially target visceral adipose tissue (VAT), especially compared with dietary-induced weight loss. This hypothesis is underpinned by a plausible mechanism, since visceral adipose tissue is more responsive to adrenergic activation (7, 168) and therefore may “benefit” most from physical activity-induced sympathetic activation. The greatest *absolute* change in fat mass in response to prolonged substantial energy deficit will normally be from subcutaneous adipose tissue (SCAT), since this is usually the largest fat depot (37, 223, 254). However, some studies have shown that VAT shows a greater *relative* change in response to exercise interventions (200, 211, 213, 223, 254), although this is not an entirely consistent finding (55). Some of the uncertainty may depend on the methodological difficulty in quantifying specific adipose tissue masses (227). There have been reports that exercise training reduces epicardial fat in obese men (127), although it is not clear whether this has particular ramifications or is simply representative of a general reduction in internal fat (216). Recent reviews have examined the impact of physical activity on visceral fat (37, 184, 210). Briefly, Ross and Bradshaw (210) found that out of 17 RCTs that reported only modest weight loss with an exercise intervention (<3%), the vast majority reported significantly reduced VAT. Ohkawara et al. (184) reviewed nine RCTs and seven non-RCT that examined the effect of exercise on visceral fat. They estimated energy expenditure during each intervention and found some evidence of a relationship between exercise dose (MET hours per week) and the rate of visceral fat loss when patients with metabolic disorders were excluded (184). It was suggested that at least 10 MET hours per week is required for significant VAT reduction. Importantly, this represents the dose of prescribed activity over and above baseline or background physical activity (see sect. III). It is likely that this threshold (10 MET hours per week) simply indicates that this increase in energy expenditure is sufficiently large to produce an energy deficit that leads to a measureable loss of fat from VAT (for a person with a mass of 90 kg, 10 MET hours per week is

equivalent to ~950 kcal/wk). Another recent review on visceral fat and weight loss included 20 studies that combined exercise with dietary intervention and 11 studies that used exercise alone (37). There was no evidence of a greater relative effect in VAT from interventions that included exercise and, instead, the authors suggested that this compartment is perhaps most responsive to early or modest weight loss partly because of its metabolic characteristics and unique position upstream from the liver (37). Several recent high-quality reports were not included in these reviews, and these studies tend to support the emerging view that exercise has no preferential or selective effect on VAT and/or SCAT mass over and above the effects of an energy deficit (38, 61, 146, 183, 200, 201). The results from one of these studies are shown in **FIGURE 3**. Therefore, the evidence clearly indicates that increasing PAEE and/or exercise is an effective strategy to reduce visceral fat (even in the absence of significant weight loss). However, an energy deficit from increased energy expenditure (physical activity) has no greater effect on VAT than a similar energy deficit from reduced energy intake. Further work is required in this area and especially in carefully defined populations that differ at

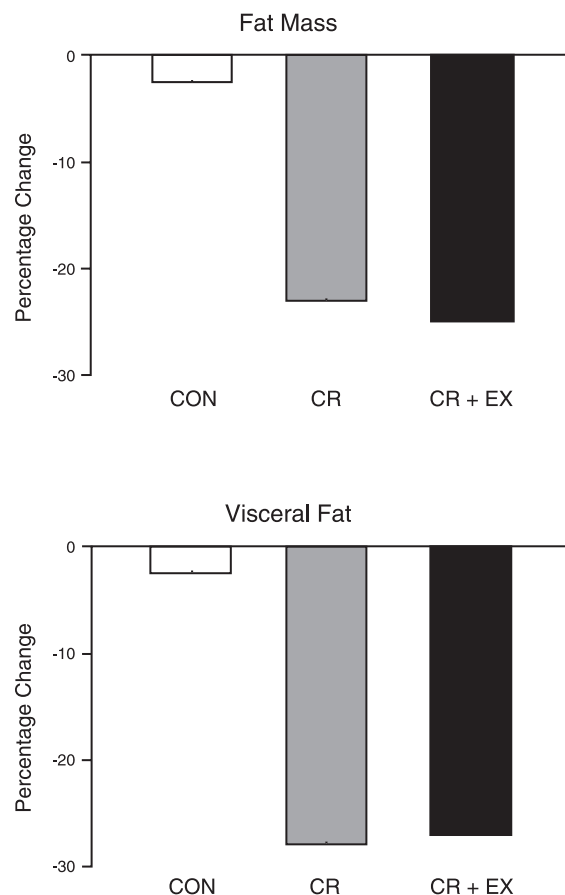


FIGURE 3. Changes in fat mass (determined with DEXA) and visceral fat mass (determined using a CT scan) in response to either -25% caloric restriction (CR) or energy-matched caloric restriction with exercise (CR + EX) or control group (CON). [Redrawn from Larson-Meyer et al. (146), with permission from Wolters Kluwer Health.]

baseline. For example, the changes in VAT in response to increased exercise are heterogeneous and not necessarily predicted by weight loss (210); thus some people may “benefit” more than others. Moreover, the small proportion of people who are TOFI represent a particularly interesting phenotype (255) that has been poorly explored.

Some studies have attempted to address the subtly different issue of exercise-induced changes in body composition without weight loss. Three investigations found that exercise may reduce VAT even when energy intake is increased to compensate for the energy expended through physical activity in an attempt to prevent weight loss (149, 211, 213). However, given the likelihood that VAT responds preferentially to a small energy deficit (37), and given the complexity underlying the energy balance equations that underpin these kinds of studies (109), it would be premature to state with any confidence that regular exercise has an independent impact on VAT over and above the role of physical activity in energy balance. In principle, if there is a remodeling of adipose tissue stores in the absence of an energy deficit, then we might expect a decrease in one depot (e.g., VAT) to be accompanied by an increase in another (e.g., SCAT). If this is not the case, then any reduction in VAT probably indicates some modest energy deficit as a result of the exercise intervention, since this depot appears to respond preferentially to such a deficit.

Independent of the ongoing debate about exercise and visceral adipose tissue, there is the separate question of whether physical activity-induced changes in the mass of SCAT are uniform across the different regional subcutaneous fat depots. While various forms of exercise training appear to reduce fat from all measured depots, in men the greatest loss of subcutaneous fat seems to be from the abdomen (55, 149, 214, 275). In one study, women showed the greatest loss of fat from the thigh (using skinfold measurements) in response to an exercise intervention (275). Interestingly, there is one report that while older overweight men lose more fat from abdominal subcutaneous depots in response to training, young overweight men showed a greater absolute and relative change in thigh fat (223).

C. Exercise-Induced Changes in Adipocyte Size and Number

A physical activity-induced reduction in fat mass could, in theory, be explained by either a reduction in adipocyte size and/or adipocyte number. Trained women have smaller adipocytes in both the abdominal and femoral region than age-matched sedentary controls (169). In support of these cross-sectional comparisons, the direct evidence showing that physical activity interventions reduce adipocyte cell size in humans is limited but generally consistent (15, 52, 53). For example, Despres et al. (53) conducted a 20-wk exercise training intervention and found that young men

lost ~3 kg body mass and showed a reduction in abdominal SCAT cell weight, whereas young women did not lose weight (or fat mass) and there was no change in abdominal SCAT cell weight (53). Exercise energy expenditure plus caloric restriction over a 6-mo period in obese postmenopausal women produced similar changes in abdominal and gluteal SCAT adipocyte diameter compared with isoenergetic caloric restriction alone (182, 282). More recent data from this group in obese postmenopausal women showed that the addition of high- or low-intensity exercise to diet-induced weight loss leads to a reduction in abdominal and gluteal adipocyte weight, whereas a similar energy deficit from diet alone reduced gluteal but not abdominal adipocyte weight (281). This contrasted with their earlier findings, and the authors explained this by the better control of energy intake through the provision of food in their later work. This led to the conclusion that regular exercise (low or high intensity) reduces subcutaneous abdominal adipocyte size, whereas similar caloric restriction does not. Interestingly, all groups (including diet-induced caloric restriction) showed similar reductions in waist circumference plus overall mass, so it is a little unclear which compartment responded to reduced energy intake. Presumably, this could only be explained by either the selective loss of fat from VAT or a loss of fat cells (number) with caloric restriction, both of which would be intriguing but perhaps unusual responses.

During modest weight gain it is generally assumed that there is hypertrophy of fat cells and hyperplasia is only significant once fat mass becomes considerably enlarged (97). Equally, during weight loss, it is believed that there is little change in adipocyte number but a decrease in adipocyte size (16, 236). In line with this perspective, it has been suggested that there is no change in abdominal adipocyte number in response to physical activity interventions even if there is a change in fat mass (15, 53). However, we should bear in mind that in these studies the estimated change in cell number was derived from estimated total body fat divided by average adipocyte size from a single location (53, 97, 236). Both of these measurements and therefore the calculated product (total adipocyte number) are associated with their own limitations. For example, adipocyte number varies with adiposity in a location-dependent manner that is also influenced by sex (250). Recent studies indicate that lower body adipose tissue responds to an energy surplus with the formation of new fat cells (251). Therefore, in terms of cell number, each adipose depot may respond differently to weight gain (and conceivably to weight loss), and this may be influenced by sex. Understanding whether changes in fat mass are explained by altered cell size or cell number is important since, independent of BMI, large adipocytes are associated with negative health outcomes (274), whereas small adipocytes appear to play a protective role (205). So, at the present time, it would be premature to conclude that all changes in adipose tissue

masses are accounted for by a change in adipocyte size alone. Nonetheless, this may ultimately turn out to be the primary mechanism. If so, it would be useful to know whether there is a reduction in the size of all adipocytes with increased physical activity energy expenditure or a shift in the distribution as a result of the selective reduction of certain cells (e.g., larger adipocytes). It is worth bearing in mind that most information on estimated changes in adipocyte number come from relatively short-term exercise training interventions over weeks and months. The turnover (half-life) of adipocytes is slow (see sect. II; Refs. 236, 247), and it would conceivably take a long time to see an effect from physical activity-induced weight loss on cell number that can be estimated with confidence.

D. Physical Activity and Adiposity: Summary

An energy deficit from increased physical activity energy expenditure will reduce fat mass in most of the important depots if there is a meaningful long-term net energy deficit. There is some evidence that early or modest weight loss will lead to the greatest relative loss in VAT, and this seems no different from the effects of energy-matched caloric restriction. More work is needed to examine whether particular groups or populations experience beneficial changes from increased exercise over and above that predicted from the energy deficit per se. It also appears that abdominal SCAT is more responsive than other subcutaneous sites (at least in men). Current evidence points towards a reduction in adipocyte size with exercise-induced weight loss (rather than a change in number), although the direct evidence to support this contention in humans is rather sparse. Physical activity has many independent metabolic effects over and above the effects of energy-matched caloric restriction alone. For example, the same energy deficit from regular exercise plus caloric restriction (**FIGURE 3**) had a greater positive impact on diastolic blood pressure, total cholesterol, LDL cholesterol, and insulin sensitivity than caloric restriction (146). Clearly, the additional benefits of regular physical activity over and above weight loss from caloric restriction are explained by mechanisms that go beyond a simply greater effect on either total fat mass or the mass of specific depots.

VI. ACUTE EXERCISE AND ADIPOSE TISSUE METABOLISM AND FUNCTION

The exercise-induced reduction in adipose tissue mass described in the previous section represents the accumulated net product of the changes derived from each bout of activity. So, from this perspective alone, it is important to understand the acute effects of exercise in adipose tissue. In addition, it is feasible that acute changes with exercise could play a role in broader aspects of adipose tissue function, and this could potentially explain some of the beneficial metabolic consequences of regular exercise over and above an energy deficit from caloric restriction alone.

A. During Exercise: Fatty Acid Mobilization

The reductions in fat mass described in section V ultimately rely on the breakdown of stored triacylglycerol (lipolysis) exceeding that of storage. Fat is an important metabolic substrate during prolonged exercise (3). Measurements at the whole body level show that fat oxidation increases profoundly in response to low-intensity exercise, with further modest increases up to intensities of $\sim 60\text{--}65\%$ $\dot{V}O_{2\max}$ (104, 115). The rate of appearance of nonesterified fatty acids (Ra NEFA) during exercise is typically two to three times that observed at rest and, with the exception of high-intensity exercise, there is a remarkably good coupling between the delivery of NEFA from adipose and oxidation by working skeletal muscle (65). A schematic view of this relationship is shown in **FIGURE 4**. It has been estimated that subcutaneous adipose tissue contributes the greatest proportion of fatty acids that are ultimately oxidized during moderate intensity exercise, with only a small contribution coming from intra-abdominal (visceral) fat (104). This may reflect the relatively small size of the visceral depot, but it should be noted that these estimates were mostly derived from studies in lean young men, and it is less clear if this is the case when the visceral depot is enlarged. There is also a contribution from intramuscular triacylglycerol, particularly during exercise of a moderate intensity (206, 266). It is appropriate to highlight at this stage that circulating NEFA concentrations represent the balance between release and uptake of NEFA and therefore will only provide a limited picture of fatty acid mobilization.

The release of fatty acids from adipose tissue during exercise is potentially influenced by adipose tissue lipolysis, the rate of fatty acid reesterification, and adipose tissue blood flow (ATBF). Measurements in vivo in a range of different subjects and exercise protocols using microdialysis (8, 176, 178, 242) and arteriovenous (a-v) difference (5, 100, 237, 240) provide direct evidence that fatty acids are mobilized from SCAT during exercise. At least part of the increase during exercise appears to be due to decreased rates of fatty acid reesterification (100, 206). According to direct measurements in abdominal SCAT, most of the increase in adipose tissue fatty acid mobilization requires only low-intensity exercise (5, 176, 238) with only modest (176, 238) or no additional increase when exercise intensity is increased further (5). Therefore, low-intensity physical activity provides a more than adequate stimulus for increased abdominal adipose tissue fatty acid mobilization. Interestingly, since whole body fat oxidation continues to increase up to $\sim 65\%$ $\dot{V}O_{2\max}$ (104), this indicates that alternative stores of fat are used as exercise intensity increases (e.g., other adipose sites or intramuscular fat). It should be noted that most research on exercise-induced fatty acid mobilization has been conducted using young lean (mostly active) subjects who have a relatively high $\dot{V}O_{2\max}$ and who were studied in the postabsorptive state. As discussed in section III and illustrated in **TABLE 1**, we should be cautious before auto-

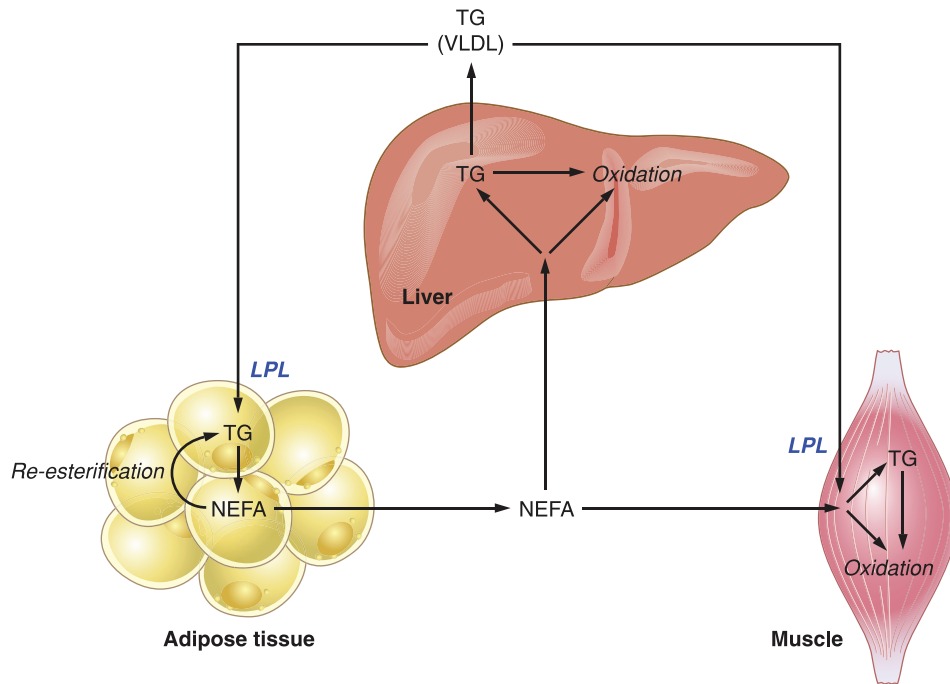


FIGURE 4. Pathways of fatty acid trafficking between tissues in the fasted state. Triacylglycerol (TG) stored in adipose tissue is mobilized to release nonesterified fatty acids (NEFA) into the circulation. The rate of NEFA release is also modulated by the reesterification of fatty acids within adipose tissue. NEFA are taken up by, among other tissues, skeletal muscle and liver. In each of these tissues, they may enter the pathway of β -oxidation, or they may be used for synthesis of TG. [There is some evidence that fatty acids for oxidation are drawn from the intracellular TG pool [44, 145].] The liver, in addition, may secrete fatty acids in the form of very-low-density lipoprotein (VLDL)-TG, from which fatty acids may be taken up for esterification in adipose tissue and for oxidation or esterification in muscle via the lipoprotein lipase (LPL) pathway.

matically extrapolating these results to different populations and scenarios. In a useful example of this problem, Ra NEFA in the circulation using tracers was greater in older women when they worked at the same absolute intensity as younger women but, as the authors pointed out, this was probably because this represented a greater relative exercise intensity (229). When these older women exercised at the same relative intensity as the younger women, then the Ra NEFA was lower, probably because the absolute work load was lower (229). Clearly, a better understanding of exercise intensity (absolute and relative) and fatty acid mobilization is required, since this plays an important role in the regulation of fat mass. For the purpose of the current review, it is important to highlight that in the fasted state an increase in fatty acid mobilization appears to require only a modest increase in physical activity above rest.

An exercise-induced increase in adipose tissue lipolysis has been classically attributed to elevated catecholamine concentrations and a small decrease in insulin concentration (8, 273). Even low-intensity exercise at 40–45% $\dot{V}O_{2\max}$ increases epinephrine concentration about threefold (92, 170). One study in paraplegic patients indicated that adipose tissue lipolysis during exercise is largely activated by circulating mediators and not sympathetic outflow (240), although other studies in similar patients indicate that neural activation of lipolysis can play an important role (129).

Selective blocking of β -adrenergic receptors in abdominal and gluteal subcutaneous adipose tissue at rest and during 30 min exercise at 66% $\dot{V}O_{2\max}$ in young lean men and women markedly reduced (but did not abolish) lipolysis during exercise (8). Several other studies have confirmed that while circulating epinephrine is primarily responsible for exercise-induced lipolysis, even after blocking the action of epinephrine, there is still an increase in lipid mobilization (47, 178). This suggests that other circulating mediators must play an important role in the stimulation of lipolysis during acute exercise. There is evidence that atrial natriuretic peptide (ANP) is secreted during exercise in an intensity-dependent manner, and this is a putative alternative candidate (176). Much less is known about other potential cardiac-derived mediators such as B-type natriuretic peptide. Interestingly, when β -adrenergic receptors are blocked during exercise in overweight men, the increase in lipid mobilization from abdominal SCAT during exercise remained unchanged, and this led to the conclusion that epinephrine is not the primary lipolytic stimulus in overweight men and that ANP might be more important (178). The same investigation showed that blocking β -adrenergic receptors in lean men produced a $\sim 50\%$ reduction in lipolysis during exercise, and it is therefore possible that ANP may be more important with increased adiposity (178). Recent work confirms the importance of this system (as well as the

importance of a fall in insulin concentrations) in both lean and obese men (136).

As the duration of fixed-intensity exercise increases, there is an increase in both whole body lipolytic rate (for a review, see Ref. 104) and also directly determined regional adipose tissue lipolysis (237, 240, 242). This may be the product of slow-acting hormones such as growth hormone and cortisol (56, 87, 90). The increase in hormones such as growth hormone is influenced by various factors including exercise intensity and duration (246), although it should be noted that a direct relationship between growth hormone-induced lipolysis and increased fat oxidation during exercise has been questioned (87). In young men, lipolysis is greater in a second bout of exercise performed 60 min after a first bout, and this raises the possibility that the system is perhaps “primed” in some way (242). There is support for this possibility since even a very short rest interval increases venous NEFA concentrations and fat oxidation during and after a second bout of exercise (85). Whether the low-level physical activity performed throughout a day (see sect. III) is a sufficient stimulus for the “priming” of the system is unclear. This may depend on numerous other factors such as age and sex. For example, there is an age-related decline in growth hormone secretion in response to exercise performed at the same relative intensity (77), and it is possible that this could carry over into different adipose tissue lipolytic response to prolonged exercise in older and younger people. This notwithstanding, it is an intriguing prospect that low-level physical activity early in the day primes the system so that the lipolytic response to subsequent physical activity is amplified, especially when viewed in the context of physical activity patterns and profiles discussed in section III (e.g., **FIGURE 1**).

Until now our discussion has perhaps underplayed the role of more vigorous intensity exercise. While vigorous intensity exercise appears to suppress NEFA mobilization from adipose tissue relative to moderate intensity exercise (207), we should not neglect the fact that the rate of energy expenditure would still be higher, and therefore, the potential net energy deficit would also be greater (all other things being equal). It is probably important to take into account postexercise metabolic changes following more vigorous intensity exercise before drawing conclusions about optimal exercise for fat mobilization (see below).

B. During and After Exercise: Fatty Acid Uptake

Low-level physical activity is a powerful stimulus for lipid mobilization in the fasted state, and the physical activity that accumulates throughout the day has considerable potential to mobilize large amounts of lipid over time (dependent on an individual’s physical activity profile; see sect. III). The consumption of food reduces fatty acid mobilization

from adipose tissue (59, 108) (see **FIGURE 5**). Of course, mobilization is only part of the picture, and fat mass is ultimately governed by the balance between the breakdown and storage (uptake) of fat. Lipoprotein lipase (LPL) is the gatekeeper for fatty acid uptake and reesterification in adipose tissue. A single bout of exercise in a fasted state leads to a small but significant increase in adipose tissue LPL activity (191, 221, 249). This is somewhat counterintuitive, since this would predispose to greater fat storage. However, this has to be viewed in the context of a much greater acute increase in skeletal muscle and systemic LPL activity with acute exercise (155, 217). This latter effect is so profound that a single bout of exercise has long-lived effects (12–18 h) on the postprandial response to feeding (79, 80, 162). As a consequence, the net delivery of dietary fat to adipose tissue (arterial triacylglycerol) is reduced by prior exercise (162). The modification of postprandial responses appears to be largely governed by the total energy expenditure of physical activity (163). Acute exercise has long-lived effects (10–20 h) on the oxidation of exogenous dietary fat (79, 268). So, in addition to enhanced lipolysis and fatty acid mobilization during and after acute physical activity in the fasted state, some of the regulation of adipose mass with regular physical activity is likely to be mediated through an acute exercise-meal interaction and a net reduction in adipose fat storage because fat has been removed by other tissues such as muscle.

C. During Exercise: Adipose Glucose and Lactate Metabolism

Glucose is necessary for triacylglycerol formation within adipocytes by provision of glycerol 3-phosphate and can act as a precursor for fatty acid synthesis via *de novo* lipogenesis (181). The release of glycerol during adipose tissue lipolysis could contribute to the generation of glucose via hepatic gluconeogenesis (181). There are few studies available that have examined glucose metabolism in human adipose tissue during and after acute exercise. One investigation reported that glucose uptake is reduced and becomes negligible across abdominal SCAT (a–v difference) during cycling, although the difference was not significant with the six subjects in this experiment (5). The same investigation also reported an increase in SCAT lactate output (a–v difference) during cycling at 40% $\dot{V}O_{2max}$ but a nonsignificant decrease in lactate output (and possibly lactate uptake) during cycling at 60% $\dot{V}O_{2max}$ (5). Similarly, Stallknecht et al. (240) showed a transient increase in adipose tissue lactate uptake at the start of arm cycling at 66% $\dot{V}O_{2max}$ (with no evidence of lactate release in clavicular or abdominal SCAT). Some other studies have shown an increase in lactate concentrations in microdialysis dialysate (91, 245), but it is difficult to know whether this reflects increased local production or contamination from increased arterial lactate concentrations. Lactate is potentially antilipolytic and appears to act via the GPR81 receptor (28). During demand-

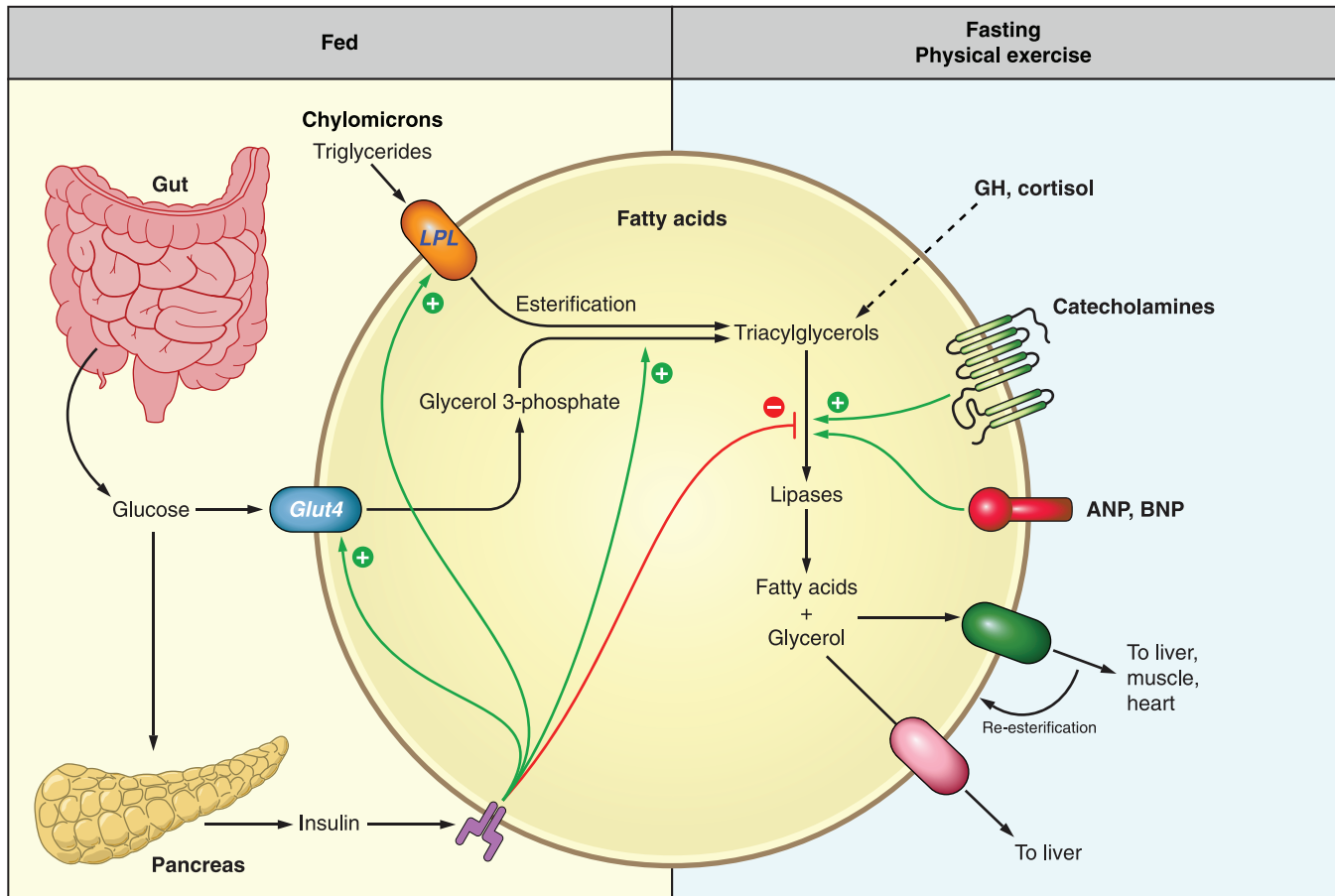


FIGURE 5. Metabolic pathways of adipose tissue fat storage and mobilization. Dietary fat reaches adipose tissue in the form of chylomicron-triacylglycerol and is taken up for storage via the lipoprotein lipase (LPL) pathway. This requires glycerol 3-phosphate produced from glucose metabolism. Stored triacylglycerol is hydrolyzed by a series of lipases [141] to liberate fatty acids, which are released into plasma as nonesterified fatty acids, and glycerol, which is exported, to be taken up by the liver where it may be used for glucose production. Lipolysis (fat mobilization) is stimulated by catecholamines acting through β -adrenoceptors and by natriuretic peptides [ANP, BNP] from the heart during exercise. Growth hormone (GH) and cortisol may reinforce increased lipolysis during and after prolonged exercise, probably through increased gene expression. Insulin is a master regulator, stimulating fat storage and suppressing fat mobilization. [Redrawn from Lafontan and Langin [141], with permission from Elsevier.]

ing exercise, arterial and interstitial lactate concentrations will be very high and, in principle, an increased delivery of lactate to SCAT could play a role in suppressing adipose tissue lipolysis during demanding exercise. However, lactate infused in microdialysis probes inserted into abdominal SCAT during exercise does not appear to affect lipolysis in this tissue (259).

D. During Exercise: Adipose Tissue Blood Flow

Fatty acid mobilization during exercise relies not only on an increased rate of lipolysis (assuming similar or reduced fatty acid reesterification) but also on adequate ATBF. In addition, the delivery of biologically relevant mediators to adipose tissue (e.g., circulating hormones) is a function of both concentration and blood flow (delivery = concentration \times

blood flow). Two main methods have been used to measure ATBF during exercise: washout of radioactive ^{133}Xe (Xe) and washout of an indicator (usually ethanol) from microdialysis. Most studies that have used ^{133}Xe washout indicate that ATBF increases during exercise, whereas most studies that have used microdialysis do not show a change (TABLE 2). There is no simple explanation for these differences, although ^{133}Xe washout captures a much larger area of tissue than the more localized microdialysis technique and is probably a more sensitive measure (121).

There is some evidence that this effect of exercise may be region-specific, with an increase in subcutaneous abdominal ATBF in response to cycling exercise but no change in femoral ATBF (106). However, other studies have shown that femoral ATBF does respond to a leg extension exercise model (237). Interestingly, one investigation showed that

Table 2. Adipose tissue blood flow during and after exercise

Reference	Subjects	Exercise	Technique	Site	Blood Flow	
					During	After†
Bulow and Madsen (27)	Young lean men	Cycling at ~50% $\dot{V}O_{2max}$ for 50 min	^{133}Xe washout	Abdominal (lumbar)	↑ (3- to 4-fold)	
				Perirenal	↑ (6- to 7-fold)	
Hellstrom et al. (91)	Young lean men and women	Cycling at 66% $\dot{V}O_{2max}$ for 30 min	Microdialysis	Abdominal	↔	
Almulla et al. (5)	Young lean men	Cycling at 40% (90 min) and 60% (60 min) $\dot{V}O_{2max}$	^{133}Xe washout	Abdominal	↑ (1.5- to 2-fold)	↑ (1.5- to 2-fold)
Stich et al. (242)	Young lean men	Cycling at 50% $\dot{V}O_{2max}$ for 60 min	^{133}Xe washout	Abdominal	↔	
			Microdialysis	Abdominal	↔	
Stich et al. (243)	Young lean and obese men	Cycling at 50% HR reserve for 60 min	Microdialysis	Abdominal	↔	↔
Stallknecht et al. (60)	Young lean men and women	Arm cycling at 60% $\dot{V}O_{2max}$ for 60 min	^{133}Xe washout	Clavicular	↑ (2- to 3-fold)	
				Abdominal	–	
Lyngso et al. (159)	Young lean men	Cycling at 60% $\dot{V}O_{2max}$ for 60 min	^{133}Xe washout	Abdominal	↑ (1- to 2-fold)	↑ (1.5-fold)
Van Hall et al. (265)	Young lean men	Cycling at 60% $\dot{V}O_{2max}$ for 60 min	^{133}Xe washout	Abdominal	↑ (3-fold)	↑ (1.5- to 2-fold)
Stich et al. (245)	Young obese women	Cycling at 50% HR reserve for 45 min	Microdialysis	Abdominal	↑	
Stallknecht et al. (238)	Young lean men	Leg extension exercise at 23% and 40% $\dot{V}O_2$ peak	^{133}Xe washout	Abdominal	↔	
			Microdialysis *		↔	
Simonsen et al. (231)	Older overweight men and women with type 2 diabetes	Cycling at 60% $\dot{V}O_{2max}$ for 60 min	^{133}Xe washout	Abdominal	↑ (~20%)	↔
Bulow et al. (26)	Young lean men and women	Cycling at 50% $\dot{V}O_{2max}$ for 60 min	^{133}Xe washout	Abdominal	↑ (2-fold)	
Moro et al. (176)	Young overweight men and women	Cycling at 30, 50, and 70% $\dot{V}O_{2max}$ (30 min each)	Microdialysis	Abdominal	↔	
Enevoldsen et al. (58)	Young lean men	Cycling at 50% $\dot{V}O_{2max}$ for 60 min [#]	^{133}Xe washout	Abdominal	↑ (2- to 3-fold)	
Stallknecht et al. (237)	Young lean men	Leg extension exercise at 13 W (30 min), 26 W (120 min), and 44 W (30 min)*	^{133}Xe washout	Femoral	↑ (2- to 4-fold)	
			Microdialysis	Femoral	↑	
Moro et al. (178)	Overweight young men	Cycling at 60% $\dot{V}O_{2max}$ for 35 min	Microdialysis	Abdominal	↔	

↑ represents an increase and ↔ indicates that there was no change (relative to rest). Where there is no symbol, this indicates that no measurement was taken. †Studies that have continued measurements in the postexercise period typically continue for 1–3 h postexercise. #Exercise was performed whilst octreotide (an inhibitor of growth hormone secretion) was infused. *No data for ^{133}Xe were included, but it was stated that this did not change. Fold change for microdialysis was not attempted, since this is a semi-quantitative measure that does not readily allow estimates of magnitude.

upper body (clavicular) ATBF increased two- to threefold during upper body (arm) cycling at 60% $\dot{V}O_{2max}$ in lean men and women, whereas abdominal ATBF did not change to upper-body exercise (240). It is plausible that there is a biological ceiling for abdominal ATBF during exercise because cycling at 40% $\dot{V}O_{2max}$ and 60% $\dot{V}O_{2max}$ similarly increased ATBF (5). On the other hand, Stallknecht et al. (237) showed a two- to threefold increase in femoral ATBF in response to a single-leg exercise bout performed at 25% work rate (WR) max in lean young men with a further

modest increase when participants exercised at 55% WR max. Importantly, this study found that there was a modest increase in ATBF of the contralateral resting leg during exercise (without any change in lipolysis) (237). Therefore, on the whole, it appears that there is an increase in ATBF during low- to moderate-intensity exercise even in adipose tissue that is distant from working skeletal muscle. It is unclear what causes an increase in ATBF during exercise. Some of the response may simply be a consequence of increased cardiac output, but other mediators such as epi-

nephrene and ANP increase during exercise and have active vasodilatory properties (22, 177, 218). Adenosine is a potent vasodilator in many tissues (68) and is present extracellularly in human adipose tissue (158). At least in swine, extracellular adenosine concentrations in adipose tissue increase markedly during exercise (35). It is also possible that the relative suppression of NEFA mobilization from adipose tissue during vigorous intensity exercise, discussed earlier, might reflect the antilipolytic effects of extracellular adenosine (136).

It is unclear whether ATBF can continue to increase in parallel with increases in exercise intensity and fatty acid mobilization. It has been hypothesized that vigorous intensity exercise leads to a catecholamine-induced vasoconstriction of adipose tissue and subsequent fall in ATBF and that this might explain the well-documented fall in fatty acid mobilization from adipose tissue at higher exercise intensities (100, 206, 207). This makes sense to preserve blood flow in working skeletal muscle. Unfortunately, these studies are technically challenging, and there have been few attempts to determine ATBF during demanding exercise. Stallknecht et al. (237) showed that femoral ATBF was similar during exercise at 85% WR max and at 55% WR max in a single-leg exercise model. There was a nonsignificant trend for ATBF to be lower during the 85% WR max trial, but ATBF was still approximately two- to threefold above resting levels (237). It is possible that when a more substantial muscle mass is involved in exercise, this might pose more of a challenge for the maintenance of ATBF. In this context, because this was a single-leg exercise model, even though the intensity was ~85% WR max, heart rate was only increased to 107 beats/min, and circulating epinephrine concentrations did not change (237). Therefore, it remains unclear whether very demanding exercise leads to a reduction of ATBF during exercise or whether ATBF simply fails to keep up with an intensity-related increase in adipose tissue lipolysis.

E. During Exercise: Site-Specific Variation in Lipolysis, ATBF, and Fatty Acid Uptake

Given the heterogeneity in the size of different adipose tissue depots, we might anticipate site-specific variation in lipolysis and ATBF. There is some evidence that exercise-induced lipolysis (using microdialysis) is greater in upper body (abdominal) subcutaneous adipose tissue compared with lower body (gluteal or femoral) subcutaneous adipose tissue, even if the mode of exercise involves primarily the lower body musculature (8, 106). Similarly, even in exercise that uses the arms (upper body cycling), lipolysis is greater in abdominal SCAT than in clavicular SCAT (240). It has been proposed that variation in the sensitivity to catecholamines underpins these regional differences in lipolysis during exercise (7, 168, 269). These observations support the finding that abdominal adipose tissue (SCAT and

VAT) tends to respond the most to an exercise-induced energy deficit, at least in young men (see sect. V), although, as noted earlier, the direct sympathetic outflow within adipose is not uniform and this could also play a role (11). Much less is known about the regional ATBF responses to exercise because so few studies have included measurements in different regions (TABLE 2).

It is unclear whether exercise exerts varied effects on the uptake of fatty acids in different regions of the body. It has been proposed that variable uptake could be a major factor in explaining regional differences in fat mass between individuals (219) and, along with regional differences in fatty acid mobilization, this could partly account for the heterogeneous regional change in fat mass with exercise interventions (see sects. II and IV).

F. Postexercise: Fatty Acid Metabolism and Adipose Tissue Blood Flow

In lean young men, fatty acid mobilization and ATBF remain elevated for several hours after moderate-intensity exercise (5, 58). Generally, it appears that immediately after exercise there is a transient decrease in fatty acid mobilization (determined directly in adipose tissue by a–v difference) followed by a steady increase over the following 3 h (5, 58). Interestingly, in these studies, values were still rising when observation ended 3 h postexercise. We know little about regional fatty acid metabolism or ATBF beyond 3 h postexercise. Recent evidence from tracer studies suggests that fatty acid mobilization (Ra NEFA) is maintained for 24 h after exercise but declines progressively until it is close to resting values at this time point (161). These authors suggested that higher fasting NEFA concentrations were inversely related to the magnitude of postexercise fatty acid mobilization (161). It appears that growth hormone plays an important role in postexercise lipolysis, since blocking the exercise-induced secretion of growth hormone (using octreotide infusion) suppresses postexercise lipolysis (a–v difference) and ATBF (^{133}Xe washout) in adipose tissue but does not affect these parameters during exercise (58). Interestingly, people with type 2 diabetes do not show this postexercise increase in abdominal lipolysis or ATBF in response to a similar exercise stimulus (231).

As discussed previously, during vigorous intensity exercise, fatty acid mobilization from adipose tissue may be suppressed and ATBF may fall or fail to increase with increased intensity. Fat oxidation during exercise appears to be maximal at around 60–65% $\dot{V}\text{O}_{2\text{max}}$ (1). Whether there is a subsequent increase in fat oxidation and fatty acid mobilization in the postexercise period after more vigorous intensity exercise remains unclear, but would make sense from a physiological perspective. One recent study found that there was a correlation between exercise intensity (absolute energy expenditure)

and postexercise fatty acid mobilization (Ra NEFA) (161), which supports a role for exercise intensity being an important determinant of fatty acid mobilization after exercise has ceased. Interestingly, this may be sex dependent, since men show an increase in lipolysis (Ra glycerol) in the hours after exercise whereas women do not (92). In support of a postexercise “correction” in fat utilization with high-intensity exercise, the total oxidation of fat over 24 h determined using a respiration chamber is similar when obese men perform high- or low-intensity exercise with equivalent energy expenditure (220). Clearly, fat balance ultimately depends on total fat oxidation, and this is the sum of fat oxidation both during and after a bout of exercise.

G. Fat Mass-Specific Variation in Lipolysis and ATBF During and After Exercise

Most of the information on adipose tissue lipolysis and ATBF during exercise comes from studies in young lean men. Given the enormous potential for phenotypic differences that accompany increased adiposity (see sect. II), we might anticipate that the responses to a bout of exercise would be different in overweight or obese individuals. This appears to be broadly the case. In obese young men, lipolysis during exercise is much lower than in lean young men, and this might be due to enhanced α_2 -adrenergic receptor responsiveness (FIGURE 6). It has also been shown that the Ra NEFA per unit fat mass during exercise is lower in obese men compared with lean men matched for physical capacity and work rate (173). The authors proposed that this was at

least partly explained by the lower circulating epinephrine concentrations seen in obese men during exercise (173), but other observations using microdialysis in situ support a local effect (178). A similar relationship might exist for ATBF and adiposity. There have been some reports that in overweight men and women there is no change in abdominal ATBF during exercise (176, 178). However, ATBF in these studies was assessed using microdialysis, and this might simply indicate a lack of sensitivity of this technique. Although definitive data are lacking, overweight middle-aged men and women with type 2 diabetes show a much smaller change in ATBF during exercise using ^{133}Xe washout compared with previous experiments by this group in young lean men (231). It is also noteworthy that men and women with type 2 diabetes do not show the same postexercise increase in fatty acid mobilization and ATBF as lean individuals (231). This might indicate a lack of secretion of and/or responsiveness to slow-acting hormones such as growth hormone (231). It is tempting to speculate that the failure to show a “normal” response to physical activity could set in motion some of the long-term negative consequences of expanded fat mass. This could be another symptom of the “metabolic inflexibility” often seen in obesity (70, 171). While this could be interpreted as a lack of responsiveness, it could also reflect a physiologically sensible counterregulation, since a reduction of adipose tissue lipolysis in the face of a greatly expanded fat mass might help to prevent excessive liberation of fatty acids and maintain relatively normal whole body NEFA delivery.

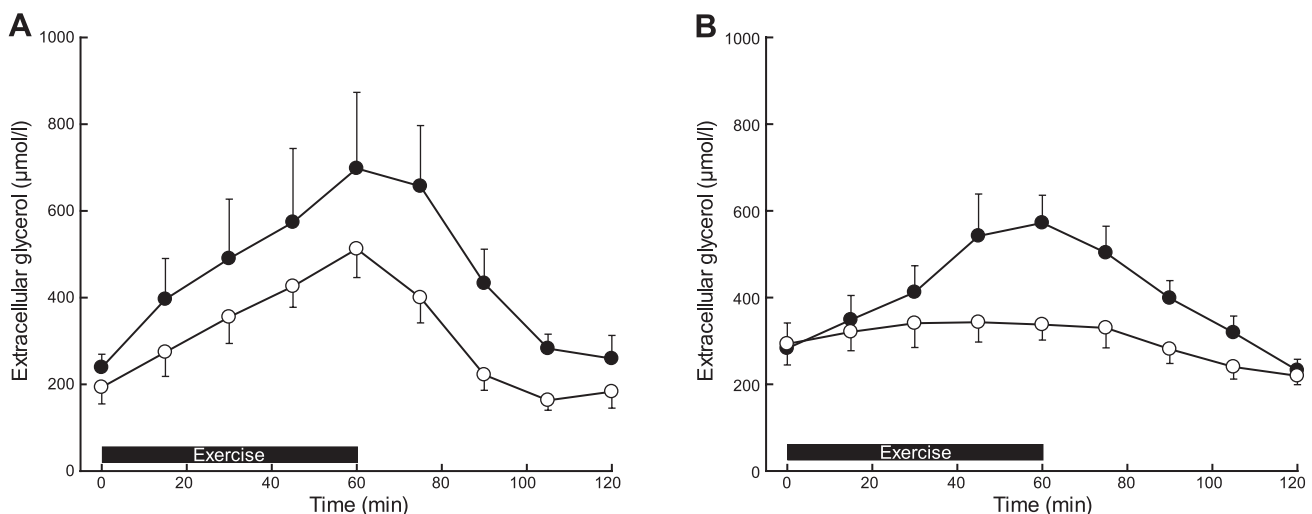


FIGURE 6. Many aspects of adipose tissue function are altered in obesity as illustrated in this example from Reference 243. Extracellular glycerol concentrations were determined in subcutaneous adipose tissue using microdialysis before, during, and after exercise in lean (A) and obese (B) young men. Microdialysis probes were infused with (●) or without (○) the α_2 -adrenergic receptor antagonist phentolamine. In control conditions (in the absence of α_2 -adrenergic receptor blockade), exercise-induced lipid mobilization is impaired in obese adipose tissue as indicated by a relatively modest increase in extracellular glycerol. The role of α_2 -adrenergic receptors in this effect was confirmed since blockade “normalized” the lipolytic response to exercise. Work rate and catecholamines were similar in lean and obese; insulin was higher in obese throughout. [Redrawn from Stich et al. (243).]

H. Sex-Specific Variation in Fatty Acid Mobilization During and After Acute Exercise

There appear to be sex-specific differences in lipolysis in response to exercise. At the whole body level (using tracers plus indirect calorimetry), young lean women show greater fatty acid mobilization during low- and moderate-intensity exercise than men (92). It has been proposed that this difference is partly because of the significantly greater fat stores found in women and that, when expressed for a given mass of adipose tissue, there is no such sex-related difference (26). However, there are other reports of inherent physiological differences in fatty acid metabolism between men and women. In overweight women, catecholamines make only a minor contribution to lipid mobilization from abdominal SCAT during exercise at low to moderate intensities (30–50% $\dot{V}O_{2max}$), whereas blocking α 2-adrenergic receptors potentiates lipolysis at all intensities in abdominal SCAT in young overweight men (176). This supports earlier observations that α 2-adrenergic activation is particularly important in men but not women (91). Interestingly, women show evidence of greater lipolysis during exercise at the same relative intensity in spite of the fact that they have lower concentrations of catecholamines in arterialized blood (45). These comparisons are complicated by the fact that men tend to have a higher $\dot{V}O_{2max}$ than women, so the absolute intensity of exercise will be different when relative intensity is controlled (see sect. III and **TABLE 1**). Furthermore, the well-documented regional differences in adipose tissue metabolism between men and women (sect. II) mean that information from multiple sites during exercise is needed to draw meaningful conclusions. As pointed out previously, greater lipolysis and oxidation of fat during physical activity in women is counterintuitive, since women tend to accumulate greater body fat (17). Observations made during exercise do not capture the full picture. Postexercise fat oxidation is greater than at rest in men but not in women, even the day after exercise (92). Therefore, at least at the whole body level, it appears that sex-related differences observed during exercise are reversed in the hours after exercise.

I. Acute Exercise and Adipokines

Adipose tissue is capable of secreting various products (adipokines) that play a role in the complications of increased adiposity (see sect. II). An acute bout of exercise leads to an increase in the concentration of some of these molecules in the blood, and many of these molecules can exert effects in other tissues (13). For example, leptin and adiponectin increase fatty acid oxidation and glucose uptake in skeletal muscle (13). In a recent review, it was concluded that acute exercise does not change circulating concentrations of adiponectin and that only acute exercise with a very considerable energy expenditure will have an impact on circulating

leptin (13). Changes in concentrations of tumor necrosis factor (TNF)- α in venous blood have been reported but these are inconsistent, whereas an increase in circulating interleukin (IL)-6 is a well-established response to demanding exercise (189). On the basis of plasma or serum concentrations alone, it is difficult to know whether a change represents an altered rate of secretion, a change in uptake, or both. For many molecules (e.g., IL-6), the source could be tissues other than adipose. As a result, in the current review, we will focus on direct observations in adipose tissue *in vivo* where possible.

One of the adipokines that has been most studied directly in adipose tissue in response to acute exercise is IL-6. There is consistent evidence that long-duration moderate-intensity exercise (3 h) leads to an increase in IL-6 mRNA in adipose tissue in young lean men (74, 103, 122). Interestingly, Lyngso et al. (159) showed that there was no increase in IL-6 secretion from abdominal SCAT during shorter duration (60 min) exercise at 60% $\dot{V}O_{2max}$ (using a–v difference), but that there was an increase in IL-6 secretion over 3 h postexercise so that it was 15-fold higher than in the control trial (159). In support of this delayed response, while 1 h of cycling at 55% $\dot{V}O_{2max}$ increased SCAT interstitial IL-6 and mRNA in both lean and overweight young men immediately after exercise, there was an even more marked increase postexercise (102). Therefore, it appears that while the increase in circulating IL-6 during exercise is primarily the result of release from skeletal muscle and probably not adipose tissue (189), adipose tissue may make a quantitatively significant contribution to systemic IL-6 concentrations in the postexercise period. In support of these findings, unlike muscle where the transcription of IL-6 mRNA is rapidly terminated at the end of exercise (189), adipose tissue IL-6 mRNA and interstitial concentration remain high for several hours postexercise (102, 122). This acute response is terminated by the following day, and by this point IL-6 expression in SCAT is lower than before exercise (49). Therefore, there is consistent evidence that long-duration moderate-intensity exercise has the capacity to transiently increase both adipose tissue IL-6 expression and secretion in the short term.

It is unclear what causes the increase in SCAT IL-6 mRNA during and after exercise. In the past, it was proposed that the increase in adipose tissue IL-6 expression was secondary to an increase in arterial IL-6 concentration due to increased release from muscle (122). However, this appears unlikely because the infusion of IL-6 does not change adipose tissue IL-6 mRNA (138). Interestingly, when lipolysis was reduced and systemic NEFA concentrations were low during exercise (through nicotinic acid administration), there was a 42-fold greater increase in the SCAT IL-6 mRNA response to exercise (103). Notably, the ingestion of carbohydrate during ex-

ercise (which blunts lipolysis and provides an alternative energy source) seems to reduce the normal increase in adipose IL-6 mRNA (122). Taken together, these results suggest that a substrate deficiency during exercise leads to increased IL-6 expression in adipose tissue, whereas low lipolysis in the presence of an alternative substrate does not. These differences in IL-6 in adipose tissue could be explained by different circulating concentrations of regulatory hormones. Nicotinic acid administration increases growth hormone, epinephrine, and cortisol concentrations (103), whereas carbohydrate administration has exactly the opposite effect (154). In support of this suggestion, epinephrine infusion increases the expression of IL-6mRNA in SCAT (123). Therefore, it appears that adipose tissue IL-6 expression during exercise is largely responsive to the concentration of certain hormones and that this is independent of lipolysis or NEFA mobilization per se.

There are some clues as to the physiological significance of an increase in adipose IL-6 during and after exercise. IL-6 may play a role in the regulation of liver metabolism to promote greater hepatic uptake of the fatty acids that are mobilized in the postexercise period (159, 160). Alternatively, IL-6 might be actively secreted by adipose in an attempt to increase fatty acid mobilization in the face of a significant metabolic challenge (103, 159, 160, 188, 192, 279), although a counterargument against this hypothesis is the fact that IL-6 infusion during low-intensity exercise has no effect on whole body lipolysis during exercise (98). Recent data indicate that acute changes in IL-6 concentration specifically target muscle fat metabolism (277), and it is tempting to speculate that the maintenance of IL-6 secretion by adipose tissue in the postexercise period is an attempt to maintain postexercise fat oxidation.

There have been a few isolated reports of other adipokines measured directly in SCAT before and after an acute bout of exercise. One investigation showed no change in SCAT leptin mRNA before or after 3 h of moderate-intensity exercise even though plasma concentration was lower over the 5 h postexercise observation period (124). The observation that carbohydrate ingestion countered the exercise-induced decrease in leptin prompted the authors to suggest that there was posttranscriptional regulation of leptin secretion (124), and this makes perfect sense based on other findings (148). Interestingly, as was the case for IL-6, it is possible that hormones such as epinephrine might be responsible for the fall in plasma leptin seen during sustained exercise (124). In support of this observation, β -adrenergic stimulation using local infusion of isoproterenol in subcutaneous adipose tissue reduces leptin concentration in microdialysate (186). We know very little about the effect of acute exercise on other adipokines. One hour of cycling at 55% $\dot{V}O_{2max}$ has been shown to generate a transient increase in

adipose tissue interstitial adiponectin concentration in both lean and overweight young men, although interestingly adiponectin SCAT mRNA actually fell during and after exercise (102). These authors reported no change in TNF- α in adipose tissue interstitial fluid, but there was an increase in TNF- α mRNA in both lean and overweight men which was most pronounced in the postexercise period (102). They also found that leptin mRNA was reduced in both lean and overweight men, whereas there was no change in resistin mRNA (102). There has been one report that 3 h of moderate-intensity exercise increases SCAT visfatin mRNA in young lean men (74), although the time course and the magnitude of the effect was highly variable between subjects. Visfatin is an insulin-mimetic peptide that is preferentially expressed in visceral fat (235). Finally, acute exercise in young lean women (2 h at 60% $\dot{V}O_{2max}$) or young lean men (1.5 h at 70% $\dot{V}O_{2max}$) did not change adipose tissue IL-18 mRNA (150).

Based on the preceding discussion, beyond the well-documented changes in adipose IL-6, we know very little about the acute effect of exercise on adipokine expression and/or secretion. There are multiple interesting molecules that could, depending on the extent and longevity of changes, have important implications in adipose tissue and beyond.

J. Acute Exercise and Adipose Tissue: Summary

Acute exercise has the capacity to induce numerous transient changes within adipose tissue, and the well-documented effects are summarized in **FIGURE 7**. If these changes take place with each exercise bout and the exercise is regular then, in addition to regulating fat mass, it is quite possible that some of these changes could have downstream consequences for adipose tissue phenotype. Equally, the absence of notable physical activity (e.g., **FIGURE 1A**) will not only favor fat accumulation (increased uptake and/or decreased mobilization) but will also deprive the tissue of these transient changes. For example, physical inactivity will mean that there is no activity-induced increase in the delivery of oxygen, and this could be important given the proposed role of tissue PO_2 in adipose tissue function (280). Equally, the absence of an activity-induced secretion of IL-6 by adipose tissue could have local effects on adipose tissue lipolysis and insulin sensitivity (101), as well as affecting fat oxidation and glucose uptake in other tissues such as skeletal muscle (34, 82, 277).

Most of the changes depicted in **FIGURE 7** are drawn from data obtained on lean young men and women. Increased fat accumulation is associated with lower lipolysis and ATBF at rest and in response to stimulation (70, 116). There is preliminary evidence that this persists into exercise, since overweight/obese individuals do not show the

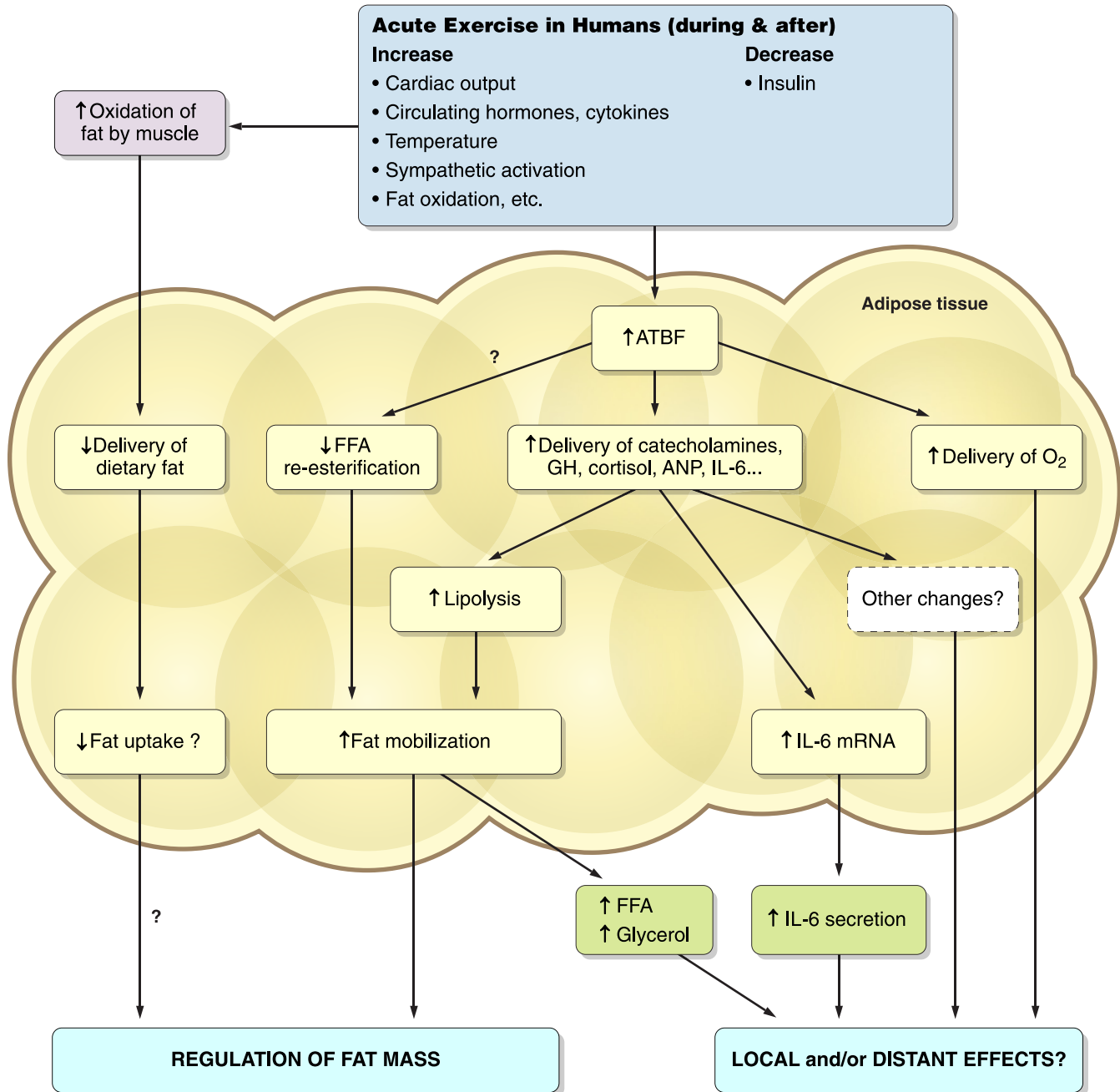


FIGURE 7. Dynamic changes in adipose tissue function during and after acute exercise. Adipose tissue responds to changes outside and within adipose tissue during and after acute exercise. For example, an increased concentration of catecholamines in arterial blood will increase ATBF (and the combination of increased flow and concentration will increase delivery of these hormones to adipose tissue). Altered delivery of these hormones affects lipolysis and therefore fat mobilization, as well as other changes such as expression and secretion of IL-6. An increase in ATBF will elicit other changes such as an increase in the delivery of oxygen and possibly decreased FFA reesterification. At the same time, for a period of 24 h or so after exercise, dietary fat is directed towards other tissues such as skeletal muscle, with a consequent reduced delivery of dietary fat to adipose tissue (and presumably reduced fat uptake by adipose). These results are drawn from studies on structured “exercise,” and little is known about other aspects of physical activity energy expenditure. Many of these results were obtained in fasted individuals and may be different in the postprandial state.

same adipose tissue metabolic or ATBF responses to acute exercise as their lean counterparts (173, 178, 243). It has been proposed that enlarged adipose tissue shows poor “metabolic flexibility” in response to nutrient intake (70). We may be able to make a similar argument for

enlarged adipose tissue and the lipolytic and ATBF responses to acute physical activity (FIGURE 7). More information on the acute effects of exercise in older overweight/obese men and women are needed as well as studies on the downstream consequences.

VII. CHRONIC EXERCISE (TRAINING) AND ADIPOSE TISSUE FUNCTION

Regular physical activity initiates changes and adaptations in almost every cell type and tissue studied to date (23). It might be reasonable to assume that adipose tissue would be no exception. One complication is that since increased physical activity leads to a reduction in fat mass (sect. V), it is difficult to tease out whether the long-term responses to physical activity and exercise are independent or dependent on changes in adiposity. Another major challenge is to establish to what extent the effects of regular physical activity represent sustained adaptations or are relatively short-lived changes induced by the last bout of acute physical activity (or perhaps recent energy imbalance).

The exercise-induced reductions in body fat described in section V must ultimately be accounted for by a negative fat balance. Equally, the maintenance of fat mass with regular physical activity must mean that fat intake and storage of dietary fat is balanced by oxidation if we assume that de novo lipogenesis is quantitatively unimportant. There are several ways in which regular exercise could increase net fat oxidation: 1) increased resting fat oxidation, 2) increased fat oxidation during activity/exercise, or 3) increased fat oxidation in the postactivity period. One notable caveat to the interpretation of results is worth mentioning at this stage. A decrease in BMR (e.g., because of weight loss) could, in theory, decrease resting fat oxidation (g/min) without necessarily changing respiratory exchange ratio (RER). Equally, an increase in BMR could increase fat oxidation without a change in RER and, of course, RER could change, but this might have no impact on absolute fat oxidation (g/min) because of a change in BMR.

A. Fat Oxidation at Rest After Training

The question of whether training affects fat oxidation at rest is complicated by the effects of recent energy deficit and/or altered substrate oxidation that is carried over from the last bout of exercise. Thus resting fasting whole body fat oxidation has been reported to be higher after a period of exercise training (130, 175, 177, 234), but other studies report no such effect (194, 199, 263). To complicate matters further, some studies have reported a reduction in fat oxidation with training (25, 117, 199). In general, when an exercise intervention leads to weight loss, then there is an increase in fat oxidation at rest (175, 177, 234); when there is no weight loss, then there is no such effect (194, 263) or possibly even a small increase in CHO oxidation (25, 117). However, one study reported meaningful weight loss in overweight men without an increase in fat oxidation (199). The explanation is probably that fat oxidation is increased in studies where follow up measures were taken during a period of negative energy balance or when they have captured some of the acute responses to the last bout of exer-

cise. There is good evidence that recent energy imbalance affects resting substrate utilization (215) and, conversely, overfeeding increases CHO oxidation and decreases fat oxidation at rest (29). Interestingly, this study showed that when energy balance was achieved by structured exercise to offset the energy intake from overfeeding, this still increased fat oxidation and decreased CHO oxidation at rest in the absence of an energy deficit (29). However, the last bout of exercise was performed 12–14 h before follow-up and, since fat metabolism is known to be increased in men the day after exercise (92), the reported increase in fat oxidation probably reflects part of the acute postexercise response.

B. Fat Oxidation During Exercise and Physical Activity After Training

In contrast to the ongoing debate about the impact of training on fat oxidation at rest, most studies at the whole body and local muscle level report that fat oxidation during exercise in a fasted state is higher after training at the same absolute or relative exercise intensity (71, 93, 106, 126, 166, 260, 263). Training-induced increases in fat oxidation of up to 41% during exercise at the same absolute intensity as pretraining have been reported (166). Achten and Jeukendrup (1) provide an excellent overview of this subject. This change is localized to muscle with no change in the oxidative capacity of adipose tissue with training in humans (30), and in any case, the oxidative capacity of human adipose tissue is very small (67). Notably, most existing data are derived from studies in lean individuals, and there has been some discussion of whether this is also true during exercise in obese individuals after training (18). There is sufficient evidence to indicate that fat oxidation during exercise is increased by exercise training in overweight and obese men and women (263, 283), even if weight is deliberately maintained (283). A comprehensive review of the molecular pathways underpinning lipid metabolism during exercise has recently been published in *Physiological Reviews* (125).

It would be reasonable to anticipate that a training-induced increase in fat oxidation during exercise will lead to an overall increase in fat oxidation over 24 h. Ultimately, this is the basis for an expenditure-induced loss of fat mass. Counterintuitively, one study reported that exercise training in weight-reduced (formerly obese) men increased 24-h carbohydrate and not fat oxidation (187). However, the men only undertook exercise training one to three times per week, and they actually gained ~7 kg in 12 mo in spite of the intervention (187). Clearly, the energy expenditure from this intervention was insufficient to balance energy intake let alone induce a deficit, and this inevitably favors the use of carbohydrate. A recent review highlighted the lack of training studies that have used a whole body calorimeter before and after training, so it is only possible to

speculate about how regular exercise contributes to fat balance (172). These authors proposed that people who are more active might consume less fat or, alternatively, that the depletion of glycogen during more demanding exercise will alter metabolism in favor of fat oxidation (172). These are possibilities although we would like to propose a complementary explanation. The unequivocal evidence that fat oxidation during activity is increased after training could have ramifications beyond fat oxidation during the training itself, since even a small shift in fat oxidation during daily physical activity after training will lead to an increase in total fat oxidation over the day (even in response to the same exercise). To illustrate this point, we have taken the physical activity trace shown in **FIGURE 1C** and worked through a theoretical example that assumes an identical physical activity pattern pre- and posttraining (**FIGURE 8**). According to our calculations, just a modest 5% increase in

fat oxidation during theoretically identical physical activity has the potential to generate an increase in fat oxidation equivalent to 83 kcal/day (equivalent to the loss of ~ 4.2 kg adipose tissue over 12 mo). It is noteworthy that this calculation assumes that there is no change in resting fat oxidation. We have also assumed that any interaction with meals remains the same before and after training; studies have shown that trained individuals have a greater capacity to increase fat oxidation during exercise at the same absolute intensity when given a glucose infusion (267) and in a fed state (14, 283). We also chose an arbitrary increase in fat oxidation during activity after training of just 5% when much larger increases have been reported (107, 166). All these factors may underestimate the impact of training on fat oxidation during daily physical activity. However, we have also ignored the fact that gross energy expenditure for a given movement before and after training could change,

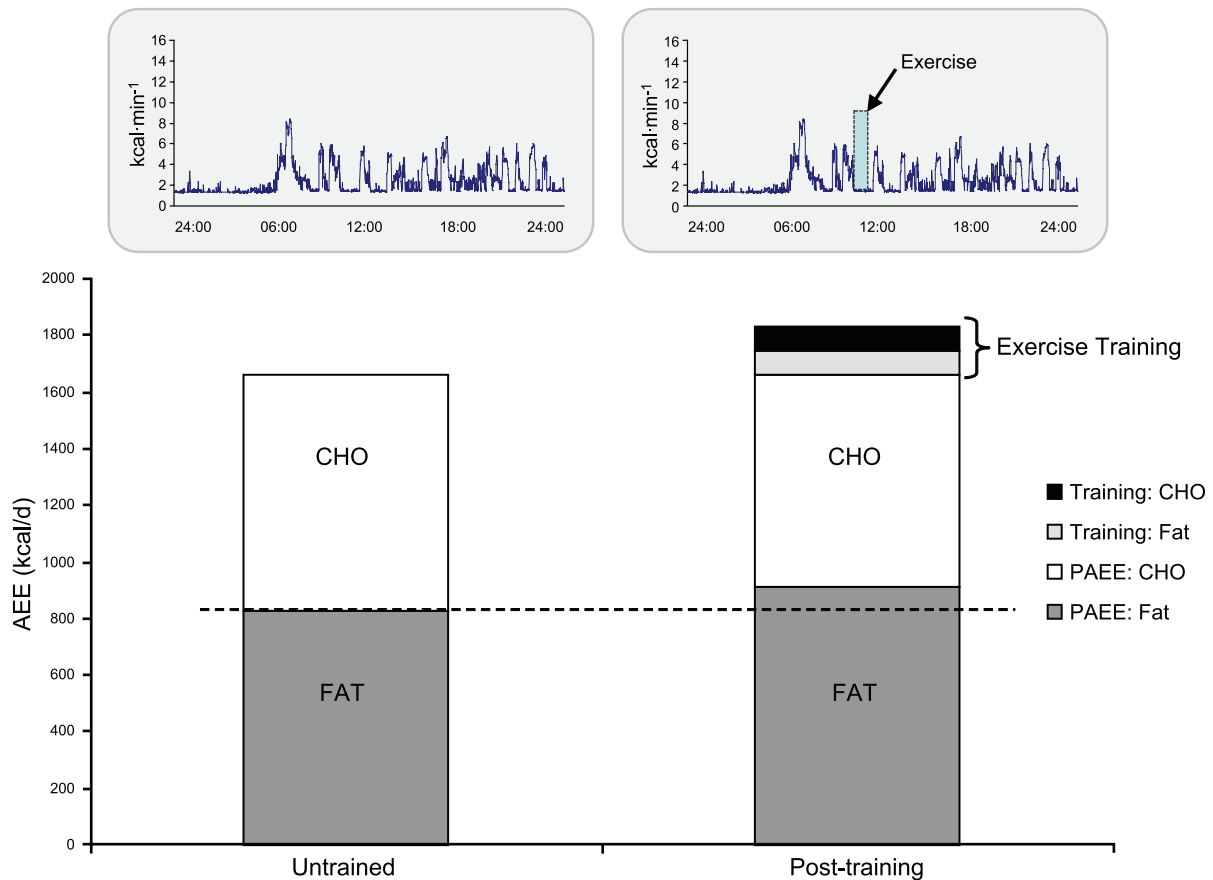


FIGURE 8. Theoretical impact of exercise training on components of energy expenditure during physical activity. This figure shows a theoretical calculation using the physical activity trace shown in **FIGURE 1C** for illustrative purposes. According to this hypothetical worked example (see text), if fat oxidation contributes 50% of energy expenditure above rest during activity before training and this increases by 5% after training, then over 24 h and in response to exactly the same physical activity, this modest increase in fat oxidation would equate to 83 kcal more energy coming from the oxidation of fat instead of other sources over 24 h. Over a year, this would translate to over 30,000 kcal ($83 \text{ kcal} \times 365 \text{ days}$) which would equate to ~ 4.2 kg adipose tissue (assuming 1 g adipose equals 7.1 kcal) and assuming that there were no other compensatory changes. For comparison, we have included the impact of exercise training per se (3 times per week $\div 7$) using an assumed exercise energy expenditure of 400 kcal above rest, with 50% of this being derived from the oxidation of fat. This hypothetical illustration highlights that adaptations to exercise training have the capacity to “spill over” and affect fat oxidation during all other physical activity.

especially if there is substantial weight loss, and therefore absolute activity energy expenditure might not remain the same even if a person has identical physical activity behavior. Taking all of this into account, it seems reasonable to assume that a modest training-induced shift in fat oxidation during daily physical activity has the capacity to generate a meaningful increase in daily fat oxidation. To put this into context, if the exercise training in this example yielded an energy expenditure of 400 kcal above rest, with approximately half of this coming from the oxidation of fat and this was performed three times a week, then this equates to an increase in fat oxidation equivalent to 85 kcal/day from training alone (50% of 1,200 kcal ÷ 7 days). Therefore, in this example, the predicted amount of fat that would be oxidized during (unchanged) physical activity after training is actually similar to the predicted amount of fat that would be oxidized during exercise training. Clearly, this is only a theoretical example, but it serves to illustrate that the adaptations to exercise training will “spill over” and affect fat oxidation during all other physical activity.

One implication is that studies using a whole body calorimeter should ensure that physical activity inside the chamber reflects “normal” levels of physical activity to avoid an underestimation of the impact of training on overall fat oxidation. Of course, another implication is that if there is an increase in training and fitness, this only increases the *capacity* for fat oxidation, which will only be realized if overall physical activity is at least maintained.

C. Basal Fatty Acid Mobilization and Lipolysis After Training

As outlined in the preceding section, the evidence that regular training per se causes a shift in phenotype towards an increased oxidation of fat in basal conditions at rest is inconsistent and complicated by confounding factors such as recent energy balance. It is perhaps inevitable that observations using direct measures of basal adipose tissue lipolysis and fatty acid mobilization are complicated by the same issues.

Basal (nonstimulated) lipolysis in adipocytes studied *ex vivo* has been found to be similar (43), lower (204), and higher (169) in trained men and women compared with sedentary controls. Likewise, exercise intervention (training) studies have reported similar, higher, and lower basal lipolysis in isolated adipocytes examined *ex vivo* before and after training (TABLES 3 and 4). There has been one report that weight loss from caloric restriction alone reduces basal lipolysis in adipocytes from obese postmenopausal women, whereas the same energy deficit and weight loss from combined caloric restriction and exercise maintains basal lipolysis (182). Subsequent work from this group showed no effect of weight loss through caloric restriction on basal lipolysis in obese postmenopausal women, whereas the

same energy deficit and weight loss from caloric restriction and exercise actually increased basal lipolysis (282).

Various investigators have measured intercellular glycerol with microdialysis to examine training-induced changes in regional lipolysis *in situ*. One cross-sectional study reported that basal adipose tissue lipolysis is similar in trained young men compared with sedentary controls when this was corrected for differences in adipose tissue blood flow (241). However, in a follow-up investigation, these authors reported no difference in basal adipose tissue intercellular glycerol concentrations between trained and sedentary young men in spite of large differences in adipose tissue blood flow (239), which presumably indicates greater basal lipolysis in trained individuals. Most intervention (training) studies that have used adipose tissue microdialysis show no change in basal regional lipolysis with training (TABLES 3 and 4). Two studies reported a training-induced decrease in basal regional lipolysis in abdominal SCAT but, as pointed out in one of these studies and mentioned above, the decrease in glycerol in microdialysate may actually reflect an increase in adipose tissue blood flow with training (177).

Stable isotopes have been used to examine lipid metabolism at the whole body level in trained versus untrained individuals and before and after a period of training. In a cross-sectional comparison, markedly higher Ra of glycerol and NEFA were found in athletes at rest in a fasted state compared with untrained controls (208). These authors also showed higher rates of fatty acid reesterification in athletes at rest and proposed that a reduction in reesterification could make a large contribution to the mobilization of fatty acids at the start of exercise in trained individuals. To what extent this reflects a long-lived difference between athletes and controls is difficult to determine because the athletes performed exercise ~24 h before investigation, and fat metabolism can be affected at this time postexercise (92). Training intervention studies that have used stable isotopes have reported lipolysis at rest to increase (263), decrease (228), and not change (262, 263). Body mass did not change in any of these studies; diet was not deliberately manipulated, and follow-up measures were taken between 36–64 h (262, 263) and 72 h after the last exercise bout (228). It is possible that the different intensity of exercise and perhaps poorer fitness and baseline activity in some study participants (228) may play a role in explaining these variable findings. Alternatively, this study (228) also reported improved insulin sensitivity, whereas the others did not (262, 263), and this could be particularly important.

On the basis of the preceding discussion, there is no consistent evidence from studies in isolated adipocytes, using microdialysis or at the whole body level to support the idea that there is a uniform shift in spontaneous fatty acid mobilization at rest with training. The picture is complex because in obesity there is a suppression of fatty acid mobili-

Table 3. *Ex vivo lipolysis in response to exercise training (intervention) studies*

Reference	Subjects	Training Intervention	Last Bout of Training	Site	Weight Loss	Basal Lipolysis	Basal Lipolysis Expressed Per	Stimulated Lipolysis (Stimulant)
Despres et al. (54)	Young lean men	Cycling at 60–85% HR _{max} for 40–45 min 4–5 times per week for 20 wk	?	Abdominal	↔	↔	Adipocyte	↑ (Epinephrine)
	Young lean women		?	Abdominal	↔	↔	Adipocyte	↔ (Epinephrine)
Despres et al. (53)	Young lean men	Cycling at ~80% HR _{max} for 40 min 4–5 times per week for 20 wk	60 h	Abdominal	~3 kg	↔	Adipocyte	↑ (Epinephrine)
	Young lean women		60 h	Abdominal	↔	↔	Adipocyte	↑ (Epinephrine)
Despres et al. (51)	Young lean men and women (twins)	Cycling at ~80% HR _{max} for 40 min 4–5 times per week for 20 wk	60 h	Abdominal	↔	↑	Adipocyte	↑ (Epinephrine)
Wirth et al. (276)	Overweight middle-aged men	Jogging/games activities 3 times per week for ~1 h for 4 mo	48–72 h	Abdominal	↔	↔	Per g adipose	
Krotkiewski et al. (139)	Obese men and women with type 2 diabetes	Walking/jogging at 80–90% V _{O₂max} for 50 min 3 times per week for 12 wk	96 h (?)	Abdominal	↔	↔	Adipocyte	↔ (Norepinephrine)
Poehlman et al. (195)	Young lean male twins	Cycling at 58% V _{O₂max} for 116 min per day for 22 days	?	Abdominal	~1.5 kg	↔	Adipocyte	↔ (Epinephrine)
De Glisezinski et al. (46)	Obese middle-aged men	Cycling at 50–65% HR reserve for 30–45 min 4 times per week for 12 wk	48 h	Abdominal	↔	↓	Per g lipid	↑ (Epinephrine)

↑ ↓ represents an increase/decrease in response to training, and ↔ indicates that there was no change. Where there is no symbol this indicates that no measurement was taken, and a question mark indicates that this information was not provided.

zation (per unit mass) to avoid an excessive increase in the liberation of fatty acids from adipose (171, 174). In this situation, if there was an increase in fatty acid mobilization with training in the absence of an increase in fat oxidation at rest, then this would potentially have adverse consequences in terms of elevated systemic concentrations of NEFA; so arguably, the lack of change in resting fatty acid mobilization makes perfect sense. Equally, however, in other situations a very different response might be anticipated. For example, if there was a greatly expanded fat mass at baseline, then whole body fatty acid mobilization is still generally higher than in lean counterparts probably since the downregulation of fatty acid mobilization per unit mass is not sufficient to offset the expanded fat mass (171, 174). In this situation, we might expect a *reduction* in fatty acid mobilization at rest with exercise training if weight loss was considerable (although it does not appear that any interventions have achieved such weight loss using exercise alone). Clearly, the impact of exercise training on resting

fatty acid mobilization is context specific and not readily generalized.

D. Stimulated and Exercise-Induced Fatty Acid Mobilization and Lipolysis After Training

In contrast to the uncertainty regarding basal lipolysis after exercise training, there is better (but still inconsistent) evidence that the lipolytic response to stimulation is increased after training. Cross-sectional studies indicate that isolated adipocytes from active men and women examined *ex vivo* have a greater response to lipolytic agents per cell or per gram of lipid than sedentary controls (42, 43, 169, 204). In support of these observations, most exercise intervention (training) studies report an increase in the response to lipolytic agents in isolated adipocytes even with little or only modest weight loss (TABLES 3 and 4). However, as dis-

Table 4. *In situ lipolysis in response to exercise training (intervention) studies*

Reference	Subjects	Training Intervention	Last Bout of Training	Site	Weight Loss	Basal Lipolysis ([glycerol] in SCAT)	Stimulated Lipolysis ([glycerol] in SCAT)	Notes
Stich et al. (244)	Obese middle-aged men	Cycling at 50–70 HR reserve for 30–45 min 4 times per week for 12 wk	48 h	Abdominal	↔	↔	↑	↑ Lipolysis in response to β -adrenergic agonist in dialysate
Hickner et al. (96)	Obese young women	30 min exercise at 70% $\dot{V}O_{2max}$ plus 30 min interval training per day for 10 days	24 h	Abdominal	↔	↔	↔	↔ Lipolysis during an insulin clamp
Horowitz et al. (106)	Lean young women	Cycling for 35–45 min at 70–85% HRmax 4 times per week for 12–14 wk	72 h	Abdominal Femoral	↔	↔ ↔	↔ ↔	↔ Lipolysis during a bout of exercise in either region
Lange et al. (143)	Older women	Cycling for 60 min at 65–70% $\dot{V}O_{2max}$ 3 times per week for 12 wk	40–48 h	Abdominal	↔	↔	↔	↔ Lipolysis during a bout of exercise
De Glisezinski et al. (48)	Young overweight men	Cycling or running at 50–85% $\dot{V}O_{2max}$ for 60 min 5 times per week for 16 wk	36–48 h	Abdominal	~2 kg	↔	↑	↑ Lipolysis during a bout of exercise ↔ Lipolysis in response to α 2-adrenergic antagonist
Richterova et al. (203)	Obese young women	Cycling and aerobics at 50% $\dot{V}O_{2max}$ for 45 min 5 times per week for 12 wk	?	Abdominal	~4 kg	↔	↑ ↔	↑ Lipolysis during a bout of exercise ↔ Lipolysis in response to α 2-adrenergic antagonist
Polak et al. (198)	Obese middle-aged men	Dynamic strength training for 60 min 3 times per week for 12 wk	47–72 h	Abdominal	↔	↓	↑/↔	↑ Relative anti-lipolytic effect of insulin clamp. Baseline but no absolute effect?
Moro et al. (177)	Overweight young men	Cycling or running at 50–85% $\dot{V}O_{2max}$ for 45 min 5 times per week for 16 wk	?	Abdominal	~3 kg	↓	↑	↑ Lipolysis in response to β -adrenergic agonist ↑ Lipolysis in response to ANP

↑ ↓ Represents an increase/decrease in response to training, and ↔ indicates that there was no change. Where there is no symbol this indicates that no measurement was taken, and a question mark indicates that this information was not provided.

cussed previously (238), it should be noted that these lipolytic assays tend to use very high (supraphysiological) concentrations of lipolytic agents such as epinephrine. This shows an increased *capacity* for lipolysis at a cellular level after training, although it is less clear to what extent this capacity is relevant in vivo.

Studies using microdialysis have reported that regional epinephrine-stimulated lipolysis is similar in trained and sedentary young men (241), whereas the suppression of lipolysis by insulin is greater than sedentary controls (239). As

shown in TABLES 3 and 4, some intervention studies have reported a training-induced increase in regional lipolysis during an acute bout of exercise (48, 203), whereas other studies have reported no change in regional lipolysis during exercise after training (106, 143). It is noteworthy that an increase in lipolysis during exercise was observed in overweight and obese men and women who lost weight as a result of training (48, 203). This increase in regional lipolysis during exercise could be coupled to a training-induced increase in fat oxidation during exercise (FIGURE 4 and sect. VI). Alternatively, since overweight subjects often show

suppressed lipolysis preintervention as a result of their expanded fat mass (see sect. II), it is possible that exercise interventions will only change regional lipolysis when this is not “normal” at baseline. While microdialysis allows the regional investigation of adipose tissue function, there are inevitably some limitations to the technique. Microdialysis does not take into account reesterification of fatty acids, which could change after training (71, 206). Also, changes in ATBF could potentially confound interpretation of observed glycerol concentrations in dialysate (177). Microdialysis is perhaps most useful to understand the mechanisms involved in lipolysis (see below).

Cross-sectional studies using stable isotopes have reported no difference in Ra glycerol between trained and sedentary subjects when exercising at the same absolute work load, even though there were large differences in total fat oxidation (130). In contrast, the Ra glycerol is higher in endurance-trained men compared with untrained controls during exercise at the same relative intensity of 70% $\dot{V}O_{2\max}$ (132). Since the absolute work rate and energy expenditure in trained men at this intensity would also have been much higher (see sect. II), this probably indicates that trained individuals have a greater ability to increase (and maintain) lipolysis at higher absolute work loads. Intervention (training) studies using stable isotopes are less consistent than these cross-sectional comparisons. Friedlander and co-workers (71, 72) showed that 10–12 wk of training in young lean men and women increased the Ra NEFA during exercise at a given relative or absolute intensity (but not Ra glycerol). In contrast, 12 wk of training in lean (106) and obese women did not change the Ra NEFA during exercise at the same absolute intensity (262), although whole body fat oxidation increased ~20%. [Interestingly, lower-body obese women did not show an increase in fat oxidation (262).] Notably, in the studies by Friedlander and colleagues (71, 72), baseline and follow-up measures were taken 1–4 h after a meal, whereas other observations were in a fasted state (106, 262). Horowitz et al. (105) also found that 16 wk of training in five young lean men did not change the Ra glycerol or NEFA in response to epinephrine infusion. In most of these intervention studies, participants were given the energy expended during exercise training to avoid weight loss (71, 72, 105, 106). The strength of this decision is that it seeks to eliminate the confounding effect of fat loss. From a different perspective, this could be seen as a weakness, since a negative energy balance and/or fat loss may be a mediator of the effect (a parallel would be to decrease energy expenditure in caloric restriction studies to eliminate the effect of fat loss per se). In the study that did not deliberately manipulate energy intake, this seemed to happen spontaneously or there was compensation in other aspects of energy expenditure because there was no weight loss in spite of exercise training (262). So, the picture from isotope studies is only partially complete, and what we know is influenced by subtle differences in experimental design (e.g., fed versus fasted observations, replacement of the energy cost of training).

Although the evidence is not clear cut, it appears that there is an increase in the *capacity* for fatty acid mobilization with training. There is some (inconsistent) evidence that there is an increase in stimulated or exercise-induced regional lipolysis with training (and possibly greater whole body lipolysis). This makes sense because exercise training increases fat oxidation and the demand for fatty acid from working skeletal muscle (73) and increased delivery of NEFA to muscle is important in facilitating fat utilization (65, 129, 260). The intriguing observation that adipose tissue achieves similar or greater lipolysis in spite of lower circulating concentrations of lipolytic agents during exercise (106, 203, 263) points towards an increase in the sensitivity of the regulation of adipose tissue lipolysis (although blood flow is a consideration; see below).

E. Regulation of Fatty Acid Mobilization After Training

Adipose tissue seems to maintain fatty acid mobilization during exercise in the face of reduced lipolytic signals such as epinephrine after training. This is where the microdialysis technique has been most useful and, in general, there appears to be a heightened sensitivity to regulatory signals posttraining. Probes infused with specific agents have revealed some of the mechanisms involved in the local (regional) regulation of lipolysis before and after training (TABLES 3 and 4). Many of these studies have been discussed in recent reviews (141, 196). Briefly, microdialysis studies show that adipose tissue is more responsive to local infusion of β -agonists after training, which may indicate better β -adrenergic responsiveness (177, 244). In one investigation, blocking the action of α 2-adrenergic receptors removed the training-induced increase in lipolysis during a standardized bout of exercise in young overweight men, and it was proposed that this indicated a less pronounced antilipolytic effect from α 2-adrenergic activation as a result of training (48). In contrast, 12 wk of training in obese women did not improve α 2-adrenergic activity (203). This apparent discrepancy could be explained by the different sex, adiposity, location of probe placement, or training stimulus used in these investigations (TABLES 3 and 4), as these could all influence the relative importance of α 2-adrenergic activity. Microdialysis also shows a greater lipolytic response to ANP infusion after 16 wk training in overweight men (177). Taken collectively, these results indicate that after exercise training, adipose tissue is more sensitive to lipolytic agents at a local level (e.g., postreceptor events affecting lipase expression and/or activity).

F. Fatty Acid Uptake After Training

As reviewed recently, exercise and physical activity have a profound effect on postprandial lipid metabolism (163). At the whole body level, this seems to be a relatively short-lived

response rather than a chronic effect from training (94), since it is lost after 60 h of detraining. There is an approximate twofold increase in skeletal muscle LPL activity as well as LPL gene expression in response to exercise training (224) which is manifest within 8 h of the training bout (225), with a similar decrease for detraining (232); although the responses in muscle can be subtle, variable, and/or intensity dependent (95). The response appears to be independent of adrenergic stimulation (86) and involves increased transcription (225). Moderate-intensity exercise seems an insufficient stimulus to increase resting postprandial skeletal muscle fat uptake the following day but still has a powerful effect on systemic triacylglycerol concentrations (162), possibly because of reduced hepatic very-low-density lipoprotein (VLDL) production (163). Adipose tissue LPL seems to be either reduced with training (169, 232, 252), or remain unchanged (224). Therefore, the tissue-specific response of LPL favors the view that long-term exercise training diverts dietary fat to other tissues such as muscle for oxidation rather than being stored in adipose tissue, although ultimately much of this is a short-lived (up to 3 days) response to recent exercise rather than a sustained (persistent) effect of training per se. This is supported by the observation that trained individuals tend to have greater intramuscular lipid than their lean counterparts (83).

G. Basal, Stimulated, and Exercise-Induced Adipose Tissue Blood Flow After Training

An integrated view of training-induced changes within adipose tissue necessitates an understanding of the adipose tissue blood flow responses to training. For example, a lower concentration of a given hormone in the blood plus greater adipose blood flow could actually mean that the tissue receives the same or greater stimulus posttraining (i.e., a lower concentration with increased flow could equal the same delivery).

With the use of the ^{133}Xe washout technique, basal abdominal ATBF for a given mass of adipose tissue has been reported to be up to twofold higher in trained compared with sedentary young men (238, 239, 241). In addition, there is a larger increase in ATBF in response to physiological epinephrine infusion in cross-sectional comparisons of young trained versus sedentary men (241).

The results from intervention studies are less consistent. Using microdialysis, one study reported a modest nonsignificant increase in ATBF (~5% reduction in ethanol ratio) after 12 wk of training in middle-aged obese men who did not lose weight (244). Other studies using microdialysis (48, 198, 203) showed no change in ATBF after 12–16 wk training in overweight/obese men and women (see TABLES 3 and 4 for details of the interventions). However, given the poor ability of microdialysis to determine potentially large changes in ATBF in response to acute exercise (TABLE 2) and

other metabolic challenges such as feeding (121), it might be expecting too much from this technique to determine subtle differences in basal ATBF before and after short-term training regimes. This notwithstanding, one microdialysis study reported an increase in fasted resting ATBF after 16 wk training in overweight young men (177). Interestingly, in this study (177), there was also a greater increase in ATBF in response to isoproterenol infusion (a β -receptor agonist), whereas an earlier investigation showed no such improvement with training (244). It is unclear whether this reflects a subtly greater exercise stimulus (Moro and colleagues trained their participants at a higher intensity, more often per week, and for a longer period) or differences in subjects (overweight versus obese) between these studies (177, 244).

Two studies have used ^{133}Xe washout to determine basal ATBF in response to training. Horowitz et al. (105) examined the impact of 16 wk of training in five young lean men. Follow-up measures were taken 3 days after the last bout of exercise, and subjects were given the energy expended during exercise to prevent weight loss. Training had no effect on basal ATBF or ATBF in response to epinephrine infusion. It is possible that the young lean phenotype of the study participants, the relatively short duration of the intervention, the decision to replace expended energy, or the delay in follow-up measures could all have influenced the outcome of this investigation. Lange et al. (143) trained 17 healthy older women (75 yr) for 12 wk. Follow-up measures were taken 40–48 h after the last training session. There was no change in fasted basal ATBF or ATBF during exercise at the same absolute work load after training. There was no change in body mass or fat mass, which is not surprising given the low exercise prescription superimposed on the low exercise capacity of these older participants (143).

Based on the preceding discussion, we clearly know very little about the impact of training on ATBF. An exercise-induced increase in ATBF would mean that more of a given molecule or compound is delivered to the tissue for the same circulating concentration (hormones, nutrients, oxygen, etc.). For example, adipose tissue hypoxia may be important in the pathogenesis of the complications of obesity, and it has been hypothesized that exercise could play a role in mitigating these effects because of its ability to change ATBF (280). In principle, an increase in basal ATBF could reflect long-term vascular remodeling in response to chronic training presumably over a period of months and years. However, detection of such a response might be technically challenging, since an increase in vascularity might lead to a lower flow in each vessel but the same ATBF per 100 g tissue. A more straightforward explanation for differences in basal ATBF might be that this reflects reduced fat mass with no change in adipose vasculature or flow in a given vessel (because ATBF is expressed relative to a given mass of tissue). In addition to basal ATBF, it is noteworthy that

there has been no attempt to make dynamic assessments of ATBF before and after training (e.g., in response to a standardized meal or another known stimulus of ATBF such as epinephrine infusion). Whereas basal ATBF is largely NO dependent, the response of ATBF to nutrient intake is largely adrenergically mediated (6). There is also transcriptional regulation (190): postprandial ATBF in subcutaneous adipose tissue was related to the postprandial expression of two genes (endothelial nitric oxide synthase and natriuretic peptide receptor A). Interestingly, a role for ANP in the regulation of ATBF is supported by previous investigations (179), and the sensitivity of adipose tissue to ANP (at least in terms of lipid mobilization) increases with training (177). Therefore, in addition to the examination of basal ATBF with training, it may be informative to determine whether exercise training alters regulated (e.g., exercising or postprandial) blood flow in adipose tissue. If basal and stimulated ATBF does not change in response to training, and if ATBF plays a role in adipose tissue “health,” then the transient changes induced by acute physical activity and the amount of daily physical activity would arguably become more important (TABLE 2).

H. Adipokines and Related Changes After Training

Physical activity-induced regulation of fat mass and/or acute changes associated with each exercise bout (see sect. VI) could influence the secretion of adipokines. At present, there is little information on this subject. One small 12-wk training intervention in eight obese postmenopausal women reported that in spite of training-induced weight loss of ~5 kg, there was no change in leptin, adiponectin, IL-6, or TNF- α mRNA in abdominal SCAT (197). Follow-up adipose tissue biopsies were taken 72 h after the last bout of exercise. Twelve weeks of resistance training in 12 obese middle-aged men did not lead to weight loss, and there was no change in SCAT mRNA for adiponectin, leptin, IL-1 β , IL-6, and TNF- α (134). Samples were collected 48–72 h after the last exercise bout. In contrast, Bluher et al. (19) found that 4 wk of exercise training in 60 men and women (ranging from young lean to obese glucose intolerant) increased the expression of adiponectin receptors in abdominal SCAT. Body mass decreased 1–3 kg during the intervention, and samples were collected 48 h after the last exercise bout. In support of this finding, 12 wk of exercise training and 3.5 kg weight loss in obese men and women increased the expression of adiponectin and adiponectin receptors in abdominal SCAT (mRNA), although serum concentrations of adiponectin were unchanged (40). In a separate report from this investigation (39), there was no change in abdominal SCAT gene expression (mRNA) for various adipokines (IL-6, MCP-1, MIP-1 α , TNF- α , leptin) and no change in markers of macrophage accumulation (CD68 and CD14) with regular exercise training (samples collected 24–48 h after the last bout of exercise). Finally,

Leick et al. (150) reported that 8 wk of training in 12 obese men and women decreased the expression of IL-18 mRNA in abdominal SCAT and also decreased plasma IL-18. There was a reduction in BMI, but no data were reported. Adipose tissue samples and blood were collected 48 h after the last bout. Based on these isolated observations, it is difficult to draw meaningful conclusions at the present time. The interventions were conducted over 4–12 wk, and none employed a control group to account for possible seasonal variation. All outcome measures are at mRNA level alone. Observations were made in crude adipose extracts, when the expression of many adipokines is specific to certain cell types (20). Furthermore, each study carefully controlled when samples were taken relative to the last bout of exercise (waiting 48–72 h) but, as discussed below, this is both a strength and a weakness.

One 15-wk combined diet and exercise intervention in severely obese men and women (BMI >45 kg/m²) reported very pronounced weight loss (~18 kg) and a reduction in the expression of inflammatory mediators within abdominal SCAT (IL-6, IL-8, and TNF- α mRNA), a reduction in markers of macrophage infiltration (CD68 and CD14 mRNA), and an increase in adiponectin expression (24). Energy intake was reduced, and participants were asked to perform 2–3 h of moderate-intensity physical activity on 5 days of the week. Normalization of results against the change in macrophage markers removed the effect of the intervention on IL-8 and TNF- α , and this led the authors to conclude that changes in IL-8 and TNF α were secondary to a reduction in adipose tissue macrophage content. In this study there was no control group, and it is not clear when measures were taken relative to the last exercise bout. Interestingly, the authors chose to take follow-up measures after a relatively short fast of ~6 h. This was a demanding intervention with marked weight loss (physical activity was a considerable but minority component). It is noteworthy that 10 wk of energy restriction and weight loss changes the expression of ~1,000 genes in subcutaneous adipose tissue (33). In a recent review, it was concluded that weight loss in the order of 5–10% is required to change the expression of many adipokines in human subcutaneous adipose tissue (133). Therefore, it seems reasonable to suggest that if exercise-induced weight loss is considerable (i.e., >5%), then this will be sufficient to change the expression of various adipokines in subcutaneous adipose tissue in the same way as reduced energy intake (this does not preclude specific changes in response to exercise training, but such evidence is lacking at the present time). The picture is complex because the responses to an energy deficit vary with cell type (e.g., adipocyte versus adipose tissue macrophages) and, moreover, this is affected by whether weight loss is current and ongoing or whether people are in energy balance and weight stable after a period of weight loss (32). A further complication is that adipokine expression and secretion are heavily influenced by adiposity, and thus changes in re-

sponse to exercise (and weight loss) may depend to some degree on baseline phenotype.

One study of twins who had differing levels of physical activity found that numerous genes in subcutaneous adipose tissue were differentially expressed (fatty acid biosynthesis, branched chain amino acid degradation, T cytotoxic pathways), but the inactive twins inevitably had significantly greater fat mass (151). Teasing out the relative importance of physical activity and physical activity-induced changes in fat mass is always going to be a challenge. In addition, the timing of follow-up measures following exercise interventions will be an important consideration. An argument for a central role for adipocytes in the sensing and control of energy balance has been proposed (209). Within this context, it has been suggested that many of the changes in circulating concentrations of TNF- α , IL-6, leptin, and adiponectin induced by weight loss might reflect recent negative energy balance rather than weight loss per se (63), and the expression of many adipokines in human adipose tissue depends on whether samples are taken during a period of energy deficit or energy balance (32). This possibility serves as a reminder for two interrelated considerations. First, the measures and controls that are put into place prior to follow-up measures (e.g., energy balance, time after last bout of exercise) will influence the information that is obtained from exercise intervention studies (especially using measures at mRNA level). Second, if we only undertake assessments in resting conditions, then we might overlook dynamic changes, and these could potentially be important. For example, much of the effect of exercise on a diverse range of physiological parameters (e.g., postprandial lipemia and lipid metabolism, insulin sensitivity, and blood pressure) are labile and short-lived phenomena (258).

I. Chronic Exercise Training and Adipose Tissue: Summary

Regular exercise (i.e., training) has the capacity to increase total energy expenditure and fat oxidation and therefore maintain fat balance and/or generate an energy (fat) deficit. This will reflect the combination of fat oxidized during and after “training” as well as an increase in fat oxidized during all other physical activity energy expenditure. At the present time, the evidence in support of an increase in fat oxidation at rest is not convincing and confounded by issues such as recent exercise behavior and energy balance. The impact of regular exercise training on basal fatty acid mobilization is complicated by many of the same issues that affect assessments of resting fat oxidation. As might be expected, if there has been a recent prior energy deficit, then fatty acid mobilization will be increased, but there appears to be no chronic shift in phenotype towards greater fatty acid mobilization at rest. If resting whole body fatty acid mobilization is raised (perhaps secondary to obesity), then we might

anticipate a reduction in resting whole body fatty acid mobilization with training-induced weight loss (although there is no direct evidence from training studies to support this assertion).

As highlighted in section V, exercise is similar to caloric restriction in terms of the ability to change the masses of various adipose tissue depots as long as the “dose” of exercise is high enough to create the same energy deficit (111), and there is no compensatory change in energy intake or expenditure (128, 153, 212, 261, 275). From the perspective of adipose tissue function observed in resting conditions, many of the consequences of exercise training may be mediated by an exercise-induced energy deficit. For example, an energy deficit through caloric restriction leads to an increased sensitivity of adipose tissue to hormones such as norepinephrine and insulin (157, 202, 245). Importantly, the creation of an energy deficit seems to be important because surgical removal of fat does not have the same effect (131). An energy deficit from caloric restriction and/or exercise will create smaller adipocytes that are more metabolically flexible (205, 274). While we know relatively little about the impact of exercise on the expression/secretion of adipokines, it seems reasonable to assume that altered expression/secretion of adipokines with exercise-induced weight loss will be at least equivalent to reports from other forms of weight loss (31–33, 41, 133). So, from an adipose tissue perspective observed in basal resting conditions, this places arguably the greatest emphasis on energy balance and weight loss rather than exercise or caloric restriction per se.

The preceding discussion is reasonable in the context of resting measurements, but this ignores a unique aspect to physical activity physiology. Superimposed over and above a chronic impact of training on fat mass are a diverse set of transient acute changes induced by each bout of exercise, and these also form part of the training “response.” As discussed in section VI (FIGURE 7), each bout of exercise initiates acute changes within and beyond adipose tissue, and many of these persist for hours. As discussed in section VI, if exercise is sufficiently regular, then a given individual will spend much of their time in a “postexercise” state (e.g., if they trained on alternate days). During these periods, transient dynamic perturbations in adipose tissue function could play a critical role in processes in other tissues (e.g., liver and muscle). For example, the mobilization of fat, the increase in ATBF, and the secretion of IL-6 appear to be sustained events that continue long after exercise has ceased. Perhaps coupled to these changes it is noteworthy that (even in obesity) skeletal muscle continues to oxidize more fat the day after the last bout of exercise, whereas even massive weight loss has no impact on muscle fat oxidation (12). The consequence of fat being diverted to muscle is that there is less fat for adipose to take up, with physical activity acting as a “buffer” for dietary fat and thus contributing to

the regulation of fat mass. Linked to this, it is noteworthy that the postprandial responses to feeding are affected by recent acute exercise, whereas there is no such effect from a recent energy-matched deficit from caloric restriction (78). Collectively, these acute responses to regular exercise could have downstream consequences and partly explain the additional metabolic gains over and above equivalent weight loss derived from caloric restriction (146). Undoubtedly, the net benefit of exercise training is ultimately a reflection of chronic sustained changes that will be readily observed at rest but also the accumulated net product of transient acute changes induced by each bout. The “last bout effect” is often seen as an inconvenience that investigators seek to remove from their experimental designs, but of course these

are also critical physiological events that we need to better understand.

VIII. PERSPECTIVES AND CONCLUSIONS

Exercise-induced weight loss seems just as effective as caloric restriction for changes in adipose tissue function that are secondary to a reduction in fat mass per se. Broadly, if assessments are taken a few days after the last exercise bout, then the effects of exercise-induced weight loss seem similar to the effects of weight loss from energy-matched caloric restriction. Notably, fat loss from exercise interventions is often modest because the dose of prescribed exercise is

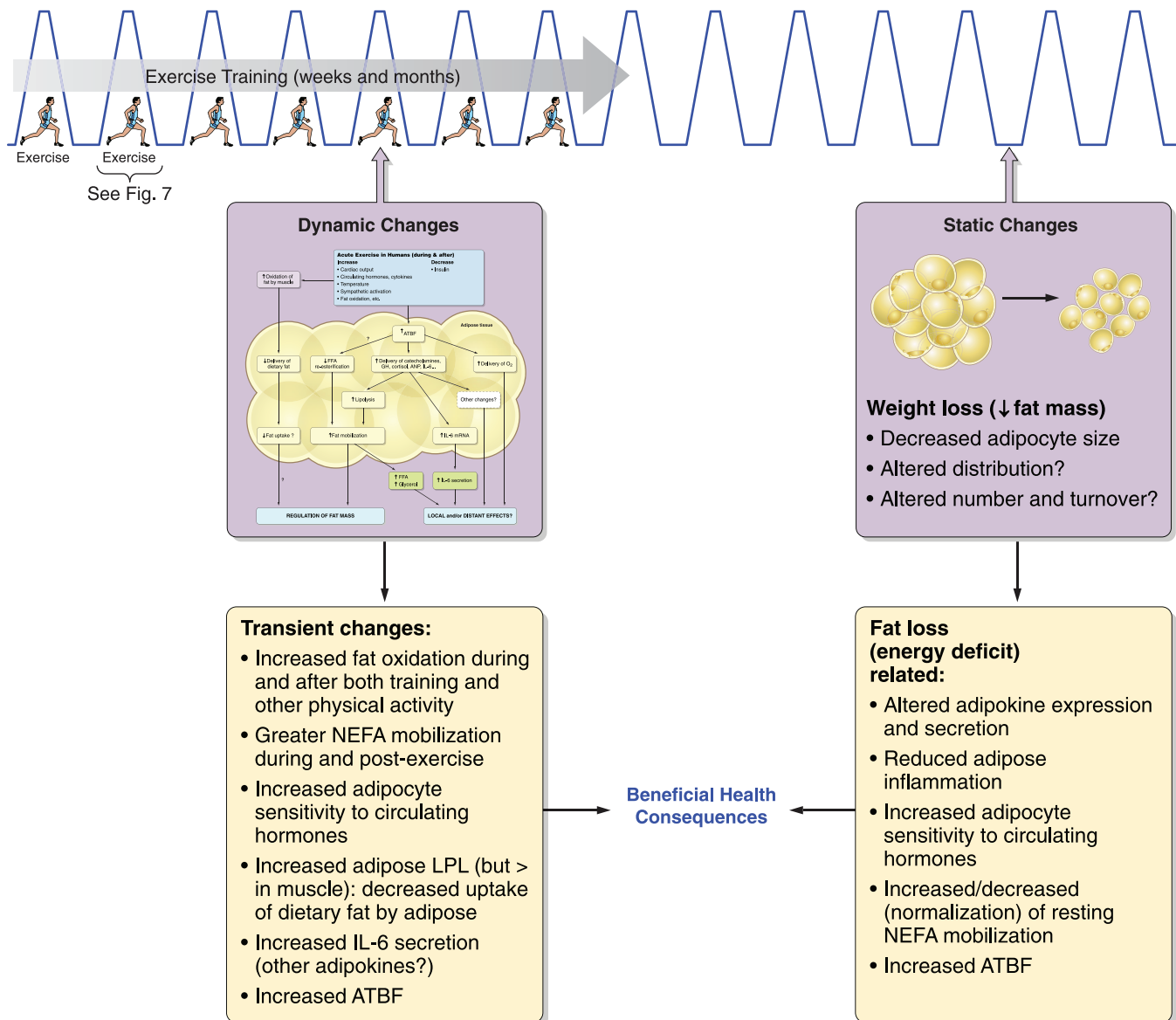


FIGURE 9. Acute (dynamic) and sustained (static) changes in adipose tissue both contribute to the overall response to exercise training or increased physical activity. While many changes appear to be secondary to fat loss (and are presumably no different from the effects of caloric restriction), some changes are only evident during and after acute exercise and/or physical activity. If exercise/physical activity is sufficiently regular, these acute changes persist for hours after each bout and form part of the training response.

equally modest and/or because there is partial compensation in terms of energy intake. This is an adipose-centric view, and we should not overlook the fact that regular exercise has numerous other benefits not observed from caloric restriction (e.g., maintenance of muscle mass and RMR, acute effects on insulin sensitivity, skeletal health, and so on).

Another key point of difference between exercise and caloric restriction is the episodic nature of physical activity and the dynamic changes that are elicited through each exercise bout. Adipose tissue may be a bystander in some of these responses, but there is sufficient evidence to indicate that adipose plays at least some active role (FIGURE 9). Adipose tissue is called upon to mobilize fatty acids to provide for increased fat oxidation during and after each exercise bout. The coupling of mobilization to oxidation is generally very good (FIGURE 4). The postexercise secretion of IL-6 by adipose may play a role in other processes such as postexercise fat oxidation. Adipose tissue blood flow is upregulated for several hours following each bout (at least in “healthy” adipose). Even an acute change in adipose tissue blood flow has potentially important implications. Acute exercise influences the responses to subsequent stimulation (e.g., the lipolytic response to subsequent exercise), and in some ways this reflects a more “flexible” metabolic phenotype. Whether this carries over into a more flexible response to other stimuli (e.g., food consumption) is an open question. A more fundamental issue is to what extent any of the dynamic changes observed in adipose tissue during and after acute exercise drive positive changes in other tissues and whether this contributes to the benefits of regular exercise over and above energy-matched caloric restriction. At the present time, with the exception of NEFA and IL-6, we know very little about the various products of adipose tissue that might change with acute exercise and therefore might play an important downstream role. Lee et al. (147) provide an excellent overview of the ways in which adipose tissue might communicate with and influence other tissues. From an adipose-centric perspective, the challenge is to examine whether any of the established independent effects of exercise over and above an energy deficit are due to changes within adipose tissue or whether adipose tissue is merely a spectator while key players elsewhere drive these changes. For instance, it is attractive to speculate that exercise training might lead to a remodeling of adipose tissue, with increased adipocyte turnover and appearance of a population of newer, more active adipocytes. Potentially also, there could be a reduction in the inflammatory phenotype with loss of inflammatory M1 macrophages from the tissue, or maybe a switch to the more benign M2 macrophage phenotype. Of course, from a more integrated perspective, it is already clear that adipose tissue is able to respond to exercise training and not just because of a reduced fat mass. The fact that many of these changes are acute dynamic responses to recent exercise emphasizes the importance of the totality

of accumulated daily physical activity and the need to better understand the implications of these episodic and transient events.

ACKNOWLEDGMENTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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