



# Sexual dimorphism in the effects of exercise on metabolism of lipids to support resting metabolism

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Exercise training is generally a healthful activity and an effective intervention for reducing the risk of numerous chronic diseases including cardiovascular disease and diabetes. This is likely both a result of prevention of weight gain over time and direct effects of exercise on metabolism of lipids and the other macronutrient classes. Importantly, a single bout of exercise can alter lipid metabolism and metabolic rate for hours and even into the day following exercise, so individuals who regularly exercise, even if not performed every single day, overall could experience a substantial change in their resting metabolism that would reduce risk for metabolic diseases. However, resting metabolism does not respond similarly in all individuals to exercise participation, and indeed gender or sex is a major determinant of the response of resting lipid metabolism to prior exercise. In order to fully appreciate the metabolic effects and health benefits of exercise, the differences between men and women must be considered. In this article, the differences in the effects of exercise on resting metabolic rate, fuel selection after exercise, as well as the shuttling of triglyceride and fatty acids between tissues are discussed. Furthermore, concepts related to sex differences in the precision of homeostatic control and sex differences in the integration of metabolism between various organs are considered.

**Keywords:** post-exercise recovery, physical activity, fat oxidation, RMR, EPOC

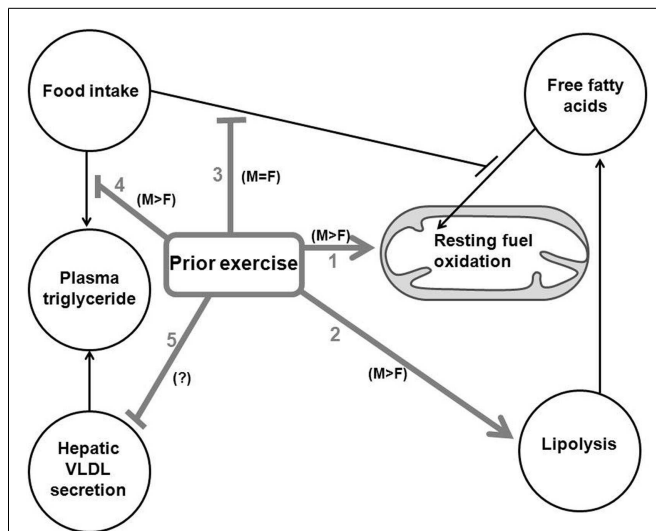
## BACKGROUND

Chronic exercise training reduces all-cause mortality risk (1–4) and specifically shows a major beneficial impact on the risk for cardiovascular disease (CVD) (1–4) and diabetes (5–8). These risk-reducing effects in people who regularly exercise are likely a result of the prevention of future weight gain (9) as well as changes in lipid metabolism (10–14) and in metabolism of other nutrient classes such as carbohydrate (15–17). Many of the apparent benefits of chronic exercise participation may be a result of acute effects of the most recent exercise bout(s). For example, chronic exercise training increases resting fat oxidation (18), but even a single bout of exercise can lead to increased fat oxidation for hours or even on the following day (12, 19). Chronic exercise can also reduce hepatic triglyceride (TG) secretion or increase plasma TG clearance (20–23), but again, these results can be achieved even following a single exercise bout (14, 24, 25). It is critically important to understand physiological differences between populations in order to appreciate the complexity of physiology and responses to environmental stresses, and particularly it is clear that there are significant differences between men and women in response to exercise. Sex differences in the exercise response are exemplified by relatively greater reliance of women than men upon fat as an energy substrate during exercise (12, 26–35), and thus women are better able to spare carbohydrate and amino acids (36–38). Though still less explored than the responses during the exercise sessions, there are also numerous sex differences in metabolism during resting periods after exercise. Recent findings have described sexual dimorphism in substrate metabolism during the post-exercise recovery period and the role of lipid kinetics to support resting

metabolism during this time period (Figure 1). Here, these aspects of sexual dimorphism after exercise are reviewed.

## EFFECTS OF EXERCISE ON THE SUBSEQUENT RESTING METABOLIC RATE

A single bout of exercise can lead to a modest but potentially significant elevation of the resting metabolic rate (RMR) for many hours afterward (9, 19, 39). This increase in RMR after exercise has been assessed through elevations in oxygen consumption ( $\text{VO}_2$ ). Historically, the phenomenon of elevated  $\text{VO}_2$  after exercise had been referred to as oxygen debt, but the term “excess post-exercise oxygen consumption” (EPOC) was proposed as a more reasonable description of the phenomenon (39) and EPOC has now become a well-accepted term. Resting  $\text{VO}_2$  changes alone have been used by many investigators in attempts to study this phenomenon of altered RMR after exercise without consideration of the corresponding carbon dioxide production ( $\text{VCO}_2$ ). However, the caloric equivalence of  $\text{VO}_2$  depends upon relative fuel selection as indicated by the respiratory exchange ratio (RER) or as also referred to as the respiratory quotient (RQ). Indeed, the RER is altered after exercise (11, 12, 19), and thus the caloric equivalence of  $\text{VO}_2$  is altered (40). If the RER were 0.7, then the caloric equivalence of a liter of  $\text{VO}_2$  would be 4.7 kcal, while if the RER were 1.0, a liter of  $\text{VO}_2$  would correspond to an energy expenditure of 5.05 kcal (40). Thus, assessments of the acceleration of metabolism after exercise are flawed unless a true metabolic rate is calculated (e.g., in kilocalories/minute rather than simply in liters of oxygen). This variability in the metabolic energy equivalence of  $\text{VO}_2$  of slightly <10% is indeed modest, but certainly



**FIGURE 1 | Summary of the effects of an acute endurance exercise bout on subsequent metabolism of lipids in the support of the resting metabolic rate is shown.** M > F, response of males greater than that of females to a recent exercise bout. M = F, responses similar between males and females to a recent exercise bout. ?, Results for investigations of sex differences not yet reported. 1, recent exercise increases subsequent RMR (total substrate oxidation) in men but not significantly in women. 2, Exercise increases subsequent post-absorptive whole-body lipolysis in men but not in women. This higher lipolysis in men increases availability of FFA, which causes greater accentuation of post-absorptive fat oxidation in men than women. 3, Food intake generally inhibits subsequent fat oxidation, such that postprandial lipid oxidation is lower than post-absorptive lipid oxidation, but prior exercise blunts this inhibition of fat oxidation; thus, postprandial fat oxidation is enhanced by a recent exercise bout (similarly in men and women). 4, Food intake leads to transient elevation of plasma TG concentration (postprandial lipemia), but recent exercise blunts postprandial lipemia, likely to a greater extent in men than women. 5, Prior exercise blunts hepatic VLDL-TG secretion, but the sex difference is not yet clearly defined in the literature.

the EPOC phenomenon is very modest [e.g., an elevation of RMR of 0.1 kcal/min would be reasonably common (19)], so precision in assessment is essential. An additional methodological factor to consider is timing of assessments. In numerous studies of the EPOC phenomenon, post-exercise RMR (or simply  $\text{VO}_2$ ) was compared to pre-exercise values. However, RMR could drift throughout the day as a result of circadian changes in metabolism as well as reduced thermic effect of feeding (TEF) as time passes since the most recent meal. Furthermore, as the RER would drift downward across a day in the absence of multiple meals, then the caloric equivalence of  $\text{VO}_2$  would also decline across the day. Thus, it is important to conduct separate time-of-day matched sedentary control trials when attempting to perform a rigorous study of the effects of prior exercise on RMR.

Recently, we conducted a meta-analysis on post-exercise RMR (19). We expected that there could be sex differences in the degree to which RMR is accentuated by a recent exercise bout, so we were unable to interpret studies where men and women were combined into a single group in the analysis. For reasons explained above, we also only included studies in the analysis in which investigators

performed time-of-day matched sedentary control trials. The results of this meta-analysis indicated that men experience a more robust increase in RMR than women after an endurance exercise bout (19). Furthermore, it appeared that the smaller increase in fat oxidation in women vs. men after exercise, discussed in the subsequent section of this article, is largely driven by this sex difference in the RMR response. It is not yet known why women exhibit less increase in RMR after exercise. However, this could be viewed as a higher level of precision in metabolic control in women than men, as discussed in greater detail later in this report. It appears that women are better able to resume normal resting metabolic parameters after exercise, whereas in men metabolism remains more significantly perturbed. It is possible that men experience a higher degree of respiratory uncoupling or a higher metabolic burden from processes such as lipolysis and gluconeogenesis after exercise. Indeed, as discussed below in detail, it is known that women reach resting rates of lipolysis (12) and hepatic glucose production (41) after exercise much more rapidly than men, and these observations correspond to the precise resumption of RMR after exercise (19).

### EFFECTS OF EXERCISE ON THE SUBSEQUENT USE OF LIPID AS A FUEL DURING REST

Compared with rest, during exercise, the relative contribution of carbohydrate to fuel oxidation increases and the relative contribution of lipid decreases compared with rest (42–44). Thus, generally carbohydrate is the predominant fuel during exercise, especially if the intensity of exercise is vigorous (42–44), but after exercise there can be a shift toward lipid oxidation predominating in the support of the RMR for many hours (11, 12, 32, 45) and even into the next day (12, 14, 46, 47). As stores of glycogen are limited in the body, it could reasonably be expected that lipid oxidation would be elevated after exercise in proportion to the degree of glycogen depletion that occurred during exercise. After glycogen-depleting exercise, glycogen synthase activity is elevated in skeletal muscle (15), and this activation is associated with an accentuated lipid oxidation rate (48). This would likely be a result of the channeling of glucose toward storage, so it competes less with fatty acids (FAs) as a substrate for mitochondrial respiration.

During exercise, women rely more heavily upon lipid for fuel than do men, and thus women are better-equipped to spare carbohydrate (12, 26–35). Consistent with this finding of carbohydrate sparing in women during exercise, initial observations were that the increase in lipid oxidation after exercise was more pronounced in men than women when studied in the post-absorptive state (12, 32). Subsequently, a meta-analysis confirmed that in the post-absorptive state, the increase in lipid oxidation after endurance exercise was more robust in men than women (higher effect size in men) (19). However, this meta-analysis also indicated that the sex difference is abolished when men and women took a post-exercise meal and thus were in the postprandial state during assessments (19). Therefore, the sexual dimorphism is dependent upon nutritional status. The sex difference during exercise (higher reliance on carbohydrate in men) could theoretically explain the sex differences in fuel selection after exercise in men and women through effects of glycogen depletion on lipid oxidation. However, glycogen depletion actually does not appear to sufficiently predict patterns

in post-exercise fuel selection, so it appears that other undiscovered cellular factors may be relevant. From a glycogen-centered viewpoint, one might predict that the higher carbohydrate use during exercise in men would lead to greater reduction in the RER after exercise in men than women, but a quantitative literature review (meta-analysis) indicated no sexual dimorphism in humans for the effect size of RER depression after exercise (19). Sex differences in post-exercise lipid oxidation appeared to be more closely related to the RMR than the RER. Further support for a glycogen-independent determinant of post-exercise lipid oxidation comes from the effects of nutritional state (postprandial vs. post-absorptive) on the sex difference in post-exercise lipid oxidation. The sex difference in post-exercise lipid oxidation is only present in the post-absorptive state (not in the postprandial state) (19). If the sex difference in lipid oxidation were the result of a need for glycogen replenishment, then one would expect a sizable difference in the postprandial state during net glycogen deposition. Thus, when searching for potential mechanisms for sex differences in post-exercise lipid oxidation, higher metabolic efficiency in women than men after exercise should be considered (19). Additionally, accentuation of lipolysis in men but not women after acute bouts of endurance exercise likely contributes to sex differences in post-exercise substrate oxidation through supply of FAs to  $\beta$ -oxidation (12). In summary, carbohydrate use during exercise might have some effect on post-exercise lipid oxidation, but the regulation of post-exercise substrate oxidation is far more complex, and the sexual dimorphism in post-exercise lipid oxidation is a result of factors that go beyond that of glycogen stores.

### EFFECTS OF EXERCISE ON THE SUBSEQUENT SHUTTLING OF TRIGLYCERIDE AND FATTY ACIDS BETWEEN TISSUES LIPOLYSIS AND FREE FATTY ACID MOBILIZATION

In order to become available for inter-organ shuttling (e.g., from adipose tissue to muscle), the FAs from TG must be liberated by lipolysis. During complete lipolysis of a TG molecule, three FAs and one glycerol are released. However, despite this theoretical stoichiometry, the rate of appearance (Ra) of free fatty acid (FFA) in plasma remains lower than three times the glycerol Ra (12, 29, 30, 49–51). Therefore, FFA mobilization is less than the lipolytic rate, and this is believed to be a result of intracellular FA reesterification in adipose tissue, because this tissue can recycle FAs but cannot utilize free glycerol for TG synthesis *in vivo* (49). Glycerol Ra measures lipolysis but FFA Ra represents the true mobilization rate of FFA for distribution between tissues. These processes are measured by the use of stable isotope tracer methodology (12, 52). Glycerol and FFA mobilization are generally expected to follow similar patterns of change in response to stimuli, but FFA mobilization could also be effected by a change in intracellular metabolism of FA following lipolytic stimulation. In response to fasting for several days, lipolysis (53–55) and FFA mobilization (53–57) are increased. Lipolysis increases even over the duration of just a single day when meals are not consumed (58) and increases during exercise (12, 59, 60). Thus, it appears that lipolysis and related FFA mobilization are quite responsive to the energetic needs and fuel availability in the body. In men for hours after exercise, glycerol and FFA Ra remain substantially

elevated above those of a sedentary control condition (12) and it was shown that men can exhibit this elevation even the day after exercise (61). However, the elevations of glycerol and FFA mobilization after exercise were substantially lower in women than men even after performing similar exercise sessions (12). These results for lipid mobilization, collected in the post-absorptive state, are believed to provide a mechanism for the lesser accentuation of lipid oxidation in women than men after exercise under these nutritional conditions through substrate supply to  $\beta$ -oxidation (12). The sex difference for resting lipolysis after exercise was most striking, as men exhibited approximately a 50% elevation for hours after endurance exercise, but women displayed absolutely no apparent elevation in lipolysis and instead very rapidly regained the resting lipolytic rate after exercise (12). This intensely homeostatic control of metabolism after exercise in women is discussed in more detail below under the section on homeostatic precision. Norepinephrine levels after exercise and the greater growth hormone response in men during exercise may have played a role in post-exercise sexual dimorphism in whole-body lipolysis, but these endocrine differences are not expected to be of an adequate magnitude to fully explain the sex difference in post-exercise lipolysis. Thus, while the predominant signal for post-exercise lipolytic control is not entirely clear, enhanced lipolysis in men is a likely explanation for sexual dimorphism in substrate oxidation in the post-absorptive state after exercise (12).

### POSTPRANDIAL LIPEMIA

Though plasma FFA are a major contributor to total fat oxidation in the post-absorptive state, in the fed state, the concentration of FFA in plasma drops while the availability of plasma TG increases, indicating a relative shift in the availability of different shuttling forms of FA (11). During the postprandial period, after taking a high-fat or even a mixed meal, this rise in the concentration of TG in circulation for hours is referred to as postprandial lipemia. During this period, plasma TG in the very low-density lipoprotein (VLDL) pool rises (hepatic TG secretion) in addition to that in the chylomicron pool (intestinal TG secretion) (46, 62), and FAs from the recent meal are rapidly recycled from initial appearance in chylomicrons into VLDL particles (63–65). In this process of postprandial TG shuttling, mild fluctuations in plasma TG concentration may be metabolically appropriate, but excessive postprandial lipemia increases risk of CVD (66–70); thus, regulation of the postprandial plasma TG excursion is important for health. A single bout of exercise, immediately before or even a day before a meal can profoundly blunt the response of postprandial lipemia (11, 13, 14, 46, 71–84). However, the excursion of postprandial plasma TG concentration (i.e., postprandial lipemia) is drastically lower in premenopausal women than men (64, 85–87), so the need to manage this aspect of metabolism is far lesser in young, lean women than men. This is a fundamental sexual dimorphism in the need for physical activity to manage a metabolic parameter. However, because of the effect of obesity in exaggerating postprandial lipemia (88, 89), despite the very low plasma TG excursion in lean women, in obese women postprandial lipemia can be sizable (11), and in that case exercise can be quite efficacious in blunting the response to that which would be typically observed in a lean

woman (11). Post-menopausal women also exhibit elevated postprandial lipemia (90), so ovarian hormones may be involved in the control of postprandial lipemia. In summary, exercise can blunt postprandial lipemia appreciably, but lean, premenopausal women are unique from men and unique from obese or post-menopausal women, in that they have very little room for improvement in postprandial lipemia. Young women would likely exhibit minimal capacity to benefit from a recent exercise bout for postprandial lipemia.

### HEPATIC TG SECRETION

An additional aspect of TG shuttling through plasma is that of hepatic TG secretion, which contributes to postprandial lipemia (46, 62) but that is the sole source of plasma TG during the fasted state. Generally, this VLDL-TG secretion is studied in the post-absorptive state such that a steady state is present and such that chylomicrons do not contribute to plasma TG. It has been shown that VLDL-TG secretion rates are higher in women than men (91, 92), though it is not yet firmly established whether or not there is sexual dimorphism in the response to exercise. Chronic running wheel exercise vastly reduces the VLDL-TG secretion rate in rats (20, 21), so the rate of TG shuttling from the liver to other tissues appears to be modifiable by exercise. In men, VLDL-TG secretion rate was not reduced by a single recent bout of endurance exercise (14, 61), but in women, in a different study, a single session of a high volume of endurance exercise did indeed reduce subsequent resting VLDL-TG secretion (25). It is possible that there is sexual dimorphism in the response of resting VLDL-TG secretion to recent exercise, but this idea will need to be tested in a carefully controlled study in which the sexes are compared directly within a single study. Additionally, an animal model of this aspect of sexual dimorphism is needed in order to identify mechanisms, and this work is underway in our laboratory. In addition to the secretion rate of VLDL-TG from the liver, clearance of plasma TG can also be altered during the post-exercise recovery period (14, 25, 93–95); however, sexual dimorphism in the response of plasma TG clearance to exercise is not apparent. When exercise reduces hepatic TG secretion, the potential consequences of this reduction in TG export from the liver ought to be considered. Though this would reduce the supply of FAs to adipose tissue, which could be beneficial for managing the size of adipose depots, in the absence of any other changes, such as compensatory changes in FA uptake from plasma or changes in FA oxidation rates, then the reduced hepatic TG secretion would theoretically lead to an accumulation of hepatic TG. Thus, it is the balance of each of these processes that must be regulated, and likely appropriate compensation occurs eventually in response to reductions in hepatic TG secretion in healthy individuals. For example, increased hepatic mitochondrial density and capacity for FA oxidation in the liver were reported to be a response to chronic exercise training in rats (96–99), and this could provide compensatory FA disposal in response to the reduced VLDL secretion that has been observed under certain chronic exercise conditions (20–22).

### PRECISION OF HOMEOSTATIC CONTROL

In considering the variety of changes in resting metabolism to the stress of a recent exercise session, a pattern from the variety of

sexual dimorphisms begins to emerge. Generally, women appear to be more precisely homeostatic than men. As discussed above, after exercise women rapidly regain euglycemia whereas men remain in a state of reduced blood glucose concentration for hours (41). Perhaps as part of a counter-regulatory response to the challenge to glycemia, men display a substantial elevation in lipolysis after exercise, while on the contrary, women quickly resume their normal resting rate of whole-body lipolysis (12). Furthermore, RMR is elevated significantly after exercise in men but to a negligible extent in women (19). The ability to spare energy expenditure and to retain rather than mobilize body fat stores would likely be a desirable trait for mammals, including humans, during the course of our evolutionary past. It is unclear why this trait of homeostatic precision has been of greater selective advantage in females than males, but one could speculate that metabolic precision is paramount in women because of the expected stresses on the body's energy stores that are imposed by pregnancy and lactation. Furthermore, when considering other sex differences in homeostatic control, particularly those related to regulation of energy balance, it becomes apparent that female sex hormones play a role in the precision of homeostatic control of metabolic processes. For example, when challenged with a high-fat diet, female mice gain less body weight than male mice, but when the ovaries are surgically removed (ovariectomy), then this tight homeostatic control over energy balance is lost (100). It also appears that female rats (101–105) and possibly female humans (106, 107) are less prone to negative energy balance (weight loss or fat loss) when challenged with chronic exercise training, and indeed estrogen is known to generally act on neural control of behavior and metabolism for precise regulation of energy balance (108). Analogously, female rats also appear to demonstrate a better ability to cope with the metabolic stress of starvation compared with their male counterparts (109). Furthermore, in humans, even when controlling for the effect of age *per se*, there is an accelerated gain of weight and body fat after menopause (110–112), further implicating ovarian hormones in the control of energy metabolism. This concept of a sex difference in the precision of homeostatic control could provide an important context for past as well as future discoveries in the sexually dimorphic responses to single exercise bouts, chronic exercise training, and even sex differences in the tolerance of other physiological stressors. It appears that the tight regulation of lipid metabolism after exercise in women (**Figure 1**) fits into a general pattern in biology for sexual dimorphism in energy metabolism.

### SUMMARY AND FUTURE DIRECTIONS

The vast majority of the work on metabolic responses to exercise has addressed the changes in physiology and metabolism during the actual exercise bouts, but the majority of even an avid exerciser's life is not spent exercising and rather is spent at rest. Thus, because of importance for developing a view of the overall impact of exercise on metabolism, the discoveries on resting metabolism in the post-exercise recovery period have been reviewed here. Indeed, continued work on this important aspect of exercise-related metabolism is needed to fully understand how exercise participation can change the integration of metabolism during the many hours of rest in the day. The majority of work

on exercise has been conducted on males, so additional work on women and female laboratory animals is needed to further extend our understanding of sexual dimorphism in the future. Finally, in order to understand hormonal mechanisms, and relevance to post-menopausal women, additional work is needed on the post-menopausal human population and on ovariectomized (OVX) laboratory animals.

In summary, there are numerous changes in resting metabolism for hours or even a day after exercise (Figure 1). However, many of these changes in lipid metabolism and the metabolic energy demand are different between men and women after exercise. In isolation, each example of sexual dimorphism lacks a context. However, when viewed within the general pattern that emerges from the list of sex differences that have been reported, one can understand that females display a more precise defense of homeostasis during the post-exercise recovery period, including the control of the RMR, fasting lipolytic rate, postprandial TG concentration, blood glucose concentration, and fuel selection. The supply of lipid-based fuels to support mitochondrial respiration and to spare carbohydrate is depicted by a complex orchestration of flux of multiple metabolites between multiple tissues. This integration of lipolysis, FFA mobilization, lipoprotein kinetics, and fat oxidation with the RMR is clearly impacted by recent participation in an exercise bout, but generally to a lesser extent in women because of superior homeostatic control of metabolism and thus less perturbation of metabolism after exercise. In the future, it may be of benefit to discover ways to alter the response of resting metabolism to prior exercise, including the changes, which currently appear to be sex-dependent, in order to manipulate lipid metabolism in ways that will be ideal for the prevention of chronic disease as well as for the recovery from the energetic demands of exercise participation.

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