Exercise and Estrogen Make Fat Cells “Fit”

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VIEIRA-POTTER, V.J., T.M. ZIDON, and J. PADILLA. Exercise and estrogen make fat cells “fit”. Exerc. Sport Sci. Rev., Vol. 43, No. 3, pp. 172–178, 2015. Adipose tissue inflammation links obesity and metabolic disease. Both exercise and estrogen improve metabolic health, enhance mitochondrial function, and have antiinflammatory effects. We hypothesize that there is an inverse relationship between mitochondrial function and inflammation in adipose tissue and that exercise acts as an estrogen “mimetic.” Explicitly, exercise may improve adipose tissue “immunometabolism” by improving mitochondrial function and reducing inflammation. Key Words: adipose tissue, inflammation, mitochondria, estrogen, exercise, immunometabolism

INTRODUCTION

Obesity and its comorbidities continue to increase in the United States and abroad in large part because of an increasingly sedentary lifestyle combined with excess energy intake. Work conducted during the past two decades has illustrated the important role played by adipose tissue in mechanistically relating obesity to disease. Beginning with the discoveries of the hormone leptin (12) and the cytokine tumor necrosis factor-α (TNF-α) (14), both secreted by adipose tissue, the realization that the adipose tissue is much more than an inert storage depot evolved. Now, the adipose tissue is known to produce and secrete a rapidly expanding list of hormones and immune factors collectively referred to as “adipokines.” Moreover, the adipose tissue becomes infiltrated with recruited immune cells such as macrophages (M) and T lymphocytes that cross-activate one another and perform various immunomodulatory and metabolic functions (37). The study of these interrelationships in adipose tissue has been referred to as “immunometabolism.” Moreover, the recent appreciation of the relevance in adult humans of brown adipose tissue (BAT), an adipose tissue depot present in small amounts whose major role is in thermoregulation rather than energy storage, highlights the metabolic importance of the adipose organ. A rapidly evolving body of research in this new area has demonstrated that BAT may play an important role in metabolic health and has the potential to be “activated” by various stimuli including cold exposure and exercise. In addition, positive relationships exist between energy expenditure and BAT across species, whereas an inverse relationship has been documented in humans between BAT mass and obesity (1).

White adipose tissue (WAT) becomes inflamed with the progression of obesity, and the inflammatory profile in WAT associates strongly with increased adipocyte size and systemic insulin resistance. In fact, animal studies have illustrated that WAT inflammation per se, even in the absence of obesity, contributes to system metabolic dysfunction. Early studies elucidated a mechanistic role of specific immune factors released from WAT in whole-body insulin resistance. The most notable example is the pathway by which TNF-α inhibits insulin signaling by interfering directly with phosphorylation of the insulin receptor (14). However, at the present time, dozens of such examples exist. It is now understood that much of the inflammatory processes that occur in WAT are the result of the resident and infiltrating M. Classical obesity-associated WAT inflammation that correlates strongly with insulin resistance is predominated by M1 “inflammatory” M, which secrete proinflammatory cytokines such as TNF-α. However, lean, healthy, insulin-sensitive adipose tissue is classified by a predominance of alternatively activated “M2” M. However, it is important to emphasize that this model of M polarization is oversimplified, and it is now known that M lie on a wide continuum and may display characteristics of both M1 and M2. While the mechanisms underlying WAT inflammation in obesity are not elucidated fully, one current view is that WAT expansion per se results in adipocyte stress that triggers inflammation (37). Emerging evidence indicates that specific behavioral factors may impact adipose tissue immunometabolism. Exercise training is perhaps the most important among these factors.
A growing body of work performed across species, with only few exceptions, has illustrated an antiinflammatory role of exercise training in the WAT. Before the realization of such an exercise-mediated effect in WAT, it was established that exercise training results in a reduction in circulating inflammatory markers (33). This effect has been shown in obese populations as well as other populations with elevated inflammation, such as older sedentary individuals. Because there is a strong link between WAT inflammation, particularly in the intra-abdominal area (i.e., visceral fat), and systemic inflammation, it is reasonable to hypothesize that exercise may affect the inflammatory state of WAT directly.

Exercise Reduces WAT Inflammation

Several studies examining obese individuals with chronic low-grade inflammation demonstrate that exercise training lowers systemic inflammation. The mechanism by which exercise reduces systemic inflammation may involve exercise-mediated reductions in WAT inflammation. In support of this notion, we conducted a 10-month training intervention on previously sedentary older men and women and found that the reduction we observed in circulating C-reactive protein (CRP), an important clinical marker of systemic inflammation, correlated strongly with a reduction in visceral adipose tissue, measured indirectly via dual-energy x-ray absorptiometry (33). To test this idea more directly, human studies have examined inflammatory gene expression in subcutaneous WAT (SQAT) biopsy samples after exercise training. Some, but not all, of these studies have shown reductions in SQAT gene expression of common markers of WAT inflammation. In a study of obese but otherwise healthy premenopausal females, the 12-wk exercise protocol resulted in significant weight loss but no changes in SQAT inflammatory gene expression (23). Similarly, another study using a similar exercise intervention, also with a healthy female population, reported a significant reduction in adiposity and circulating CRP but no improvements in SQAT inflammation (e.g., adiponectin, interleukin-β (IL-β), IL-6, IL-10) (31). Interestingly, the antiinflammatory marker IL-10 was higher initially in those female participants and remained so after exercise. It is probable that the absence of changes in SQAT inflammation in those subjects was attributed to their relatively healthy state (i.e., lack of WAT inflammation at the outset of the trial) and/or the fact that those subjects were female. Interestingly, exercise intensity also may play a role in whether or not exercise reduces SQAT inflammation in humans because at least one study investigating both sexes and using a high-intensity training protocol reported significant reductions in adiposity and circulating inflammatory markers, as well as increases in SQAT adiponectin; no other inflammatory genes were altered, however (8).

It is interesting to note that, of the human studies that do show reductions in SQAT inflammation with exercise, the vast majority were conducted in both men and women. Although most studies show concomitant effects of weight loss and improved WAT inflammation (6), some demonstrate that exercise may exert antiinflammatory effects in WAT in the absence of weight loss (2,18). Taken together, the human data show a modest antiinflammatory effect of exercise on SQAT in some but not all studies. The effect does not appear to be exclusively dependent on body weight reduction or even exercise intensity but rather the metabolic state of the population. There are insufficient data comparing the effects of caloric restriction to exercise while controlling other important variables such as total fat loss and/or comparing responses by men and women. However, the antiinflammatory effects of exercise seem most notable in subject groups with inflamed WAT and/or preexistent metabolic conditions before the onset of the exercise intervention. Importantly, women seem to present with protection against WAT inflammation, which may explain the lack of effect specifically in this population. Another important consideration is that the body of literature assessing the potential antiinflammatory role of exercise on WAT in humans has evaluated only SQAT, whereas a preponderance of research implicates the visceral WAT as the major source of inflammation. This is an important area of future investigation.

Our group and others have conducted animal studies to assess the effect of exercise on WAT inflammation more comprehensively by investigating inflammation across several depots and controlling the duration and intensity of exercise. Early work from our group (33,35) and others (4) demonstrated that exercise reduces WAT inflammation, and this finding has been replicated several times using many different animal models in many different laboratories. In the vast majority of cases, the antiinflammatory effect of exercise is stronger in visceral WAT compared with SQAT, suggesting that exercise may have depot-specific effects on WAT immunometabolism. This contention is supported by depot comparisons in response to exercise training (9). We recently conducted a study comparing voluntary wheel running, which may be considered a model of habitual physical activity rather than structured exercise training, with caloric restriction (30% caloric restriction) in a male obesity-prone rat model, Otsuka Long-Evans Tokushima Fatty (OLETF). Part of what made that study unique was an in-depth adipose tissue depot comparison that included traditional SQAT and visceral WAT depots as well as periaortic adipose tissue (PAT) and BAT. Although both interventions reduced most inflammatory markers across depots (with BAT being the one exception), the extent of the antiinflammatory effects appeared most pronounced in visceral compared with the SQAT and PAT. And, in a recent study by Castellani et al. (7) where trained versus untrained mice were exposed to an inflammatory stimulus, exercise mitigated the inflammatory response in trained animals in the perigonadal WAT (PGAT) only and not SQAT (7). The fact that exercise/enhanced physical activity has been demonstrated to primarily reduce visceral but not SQAT inflammation in animal studies supports the possibility that the negative findings reported in human literature may be attributed to the lack of evaluation in visceral WAT.

Interestingly, in animal studies that examined SQAT inflammation (e.g., TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), leptin) after either voluntary wheel running (9) or treadmill training (5), reductions in inflammatory gene expression have been reported. Still, in cases where SQAT and a visceral depot were investigated, the inflammatory changes were more robust in visceral WAT (9). The most common species used to assess the antiinflammatory
Effect of exercise in WAT has been the mouse. Of the training studies using mice, most show reductions in at least one or more inflammatory markers, independent of the type of exercise or chronicity. Importantly, the vast majority of animal studies have used only males and virtually all used C57BL/6 mice, the strain most commonly used in diet-induced obesity studies. We conducted a study using a different strain, Balb/c (36), and did show exercise-mediated reduction in WAT inflammation, hence indicating that the antiinflammatory effect of exercise is not specific to the C57BL/6 mouse. Only one rat study used females (using a model of polycystic ovary syndrome (PCOS)) and demonstrated exercise-related improvements in adiposity and reductions in mesenteric WAT inflammatory adipokines including IL-6 and leptin (19). It is important to note that PCOS associates with dysregulated female ovarian hormones and insulin resistance.

Another factor that may affect whether or not exercise training reduces WAT inflammation in animal studies is the dietary means by which obesity was initiated. For example, two studies using very similar protocols of moderate-intensity treadmill training both reported no exercise-mediated weight loss yet only one found a reduction in WAT inflammation. Baynard et al. (3) found a significant reduction of F4/80, a nonspecific M marker, in PGAT but no reductions in proinflammatory adipokines such as TNF-α, MCP-1, and leptin, whereas Kawanishi et al. (15) showed significant reductions in TNF-α, IL-6, and MCP-1. The only difference between those two studies was the fat composition of the diet, 45% versus 60%, respectively. Commercial high-fat diets (HFD), such as those used in the aforementioned studies, are particularly high in saturated fatty acids, which are known to activate inflammatory pathways directly, thus, potently triggering WAT inflammation. Similarly, rodent HFD studies often use a commercial low-fat diet (LFD) control, which is very low in fat; this may amplify the between-group differences assessed via gene expression. That is, the difference between groups in a study using 60% HFD and the standard LFD would be more robust than one using a 45% HFD and the same standard LFD. Thus, similar to the human studies, the effect of exercise on reducing WAT inflammation seems dependent largely on the initial inflammatory state of the tissue. In summary, human and animal studies support the contention that there is an antiinflammatory effect of exercise training in WAT. The effect may be most pronounced in visceral WAT but seems not to be dependent exclusively on fat loss and is conserved across species.

Potential Mechanisms Behind the Antiinflammatory Effect of Exercise

Although the role of adipose tissue as an endocrine organ has been appreciated only recently, it has long been known that exercise, especially endurance exercise, profoundly affects WAT metabolism. As blood glucose levels become limited during exercise, catecholamine-mediated lipolysis increases to provide free fatty acids (FFA) for utilization by skeletal muscle cells. Indeed, adipocyte lipolysis and skeletal muscle FFA oxidation are linked tightly during exercise. Together, these events create a negative energy balance with exercise training to facilitate fat loss presumably caused by reduced adipocyte size. Smaller adipocytes are more insulin sensitive; this likely contributes to the powerful insulin-sensitizing effects of exercise on WAT. On the other hand, a hallmark feature of adipocyte insulin resistance, which occurs in metabolically disturbed states such as obesity and diabetes, is impaired insulin-mediated suppression of lipolysis and larger insulin-resistant adipocytes. Moreover, dysfunctional adipocyte lipolysis is associated with inflammation caused by the inflammatory nature of the mobilized FFA. In fact, in the study by Castellani et al. (7) previously described, the drug used to trigger WAT inflammation was a known stimulator of lipolysis; the trained mice in that study had a lessened inflammatory response to the increase in lipolysis. Thus, one mechanism by which exercise may reduce WAT inflammation is via an increase in adipocyte insulin sensitivity and a corresponding decrease in dysregulated lipolysis. The Figure 1 summarizes this hypothesis. This idea is supported by another recent study in mice that demonstrated enhanced stimulation of lipolysis and insulin sensitivity after exercise training, which correlated with increased FFA oxidation and lower lipid storage in WAT (13). That study examined male diet-induced obese C57BL/6 mice and found that exercise attenuated gains in adiposity, prevented insulin resistance, reduced expression of glucose 6-phosphate dehydrogenase, an enzyme involved in fatty acid synthesis, and increased citrate synthase activity, a marker of mitochondrial function, in WAT (13).

Relationship Between Adipose Tissue Inflammation and Mitochondrial Function

Enhancement of adipocyte mitochondrial function may play a major role in exercise training–mediated improvements in adipose tissue immunometabolism. The effects of exercise training on the capacity of skeletal muscle cells to use FFA efficiently is well known and supported by evidence of muscle fiber type switching and enhanced mitochondrial function and density in skeletal muscle. The role of FFA oxidation and mitochondrial function in adipocytes with exercise training is much less studied; however, recent evidence implicates adipocyte mitochondria as having a role in training adaptations (29), albeit not to the degree of skeletal muscle mitochondria. This exercise-mediated effect on adipocyte mitochondria was first shown by Stallknecht and colleagues (28) in 1991. We recently highlighted literature demonstrating the interrelationships between adipocytes, their mitochondria, and adipocyte inflammation (37). Briefly, “healthy” adipocytes are characterized by highly functional mitochondria (e.g., sufficient capacity to oxidize FFA), a resident M phenotype characterized as “M2” with highly efficient lipid-handling capabilities and less proinflammatory cytokine production, and high insulin sensitivity. In contrast, “unhealthy” adipocytes are characterized as having dysfunctional mitochondria that produce reactive oxygen species (ROS), undergo dysregulated lipolysis because of insulin insensitivity, and contain “M1” M, which are recruited to the tissue and perpetuate the inflammatory situation by secreting proinflammatory cytokines.

Greater mitochondrial density is characteristic of BAT. Exercise increases mitochondrial biogenesis and brown adipocyte–specific gene expression and may even induce a phenotypic switch from WAT to BAT (22). Slocum et al. (27) showed that, even with low-intensity exercise training, there was increased mitochondrial content mainly because of increased
uncoupling protein-1 (UCP-1) and peroxisome proliferator–activated receptor-γ (PPARγ) expression in BAT suggestive of enhanced BAT activation. Another study found that exercise increased UCP-1 and PPARγ expression in PGAT, suggesting that exercise enhances brown adipocyte progenitor cells in WAT (39). Importantly, BAT activation and/or regeneration in animal models has been associated with enhanced metabolic function, including obesity reduction and increased insulin sensitivity (1). Although the mechanisms by which exercise training may increase mitochondrial function in WAT and/or BAT are not understood completely, a new hormone recently recognized to be induced in muscle with exercise training, meteorin-like (24), increases energy expenditure and improves insulin sensitivity. Interestingly, it also upregulates antiinflammatory cytokines and alternative (M2) M activation in WAT, suggesting an inverse relationship between inflammation and mitochondrial function perhaps caused by an alternative M activation (Fig. 1).

Interestingly, recent data suggest that the type of M present in WAT determines not only the local inflammatory state but also lipid dynamics within the adipocyte, and this relationship seems to involve adipocyte mitochondria (37). In a recent cell culture study using the adipocyte cell line 3T3L1, Hahn et al. (11) revealed a direct relationship between the inflammatory cytokine TNF-α (but not other cytokines investigated such as IL-6 and IL-1β), produced by adipose tissue M, and adipocyte mitochondrial function. Exposure of the mitochondria to TNF-α decreased their function as indicated by reductions in regulators of mitochondrial biogenesis, PGC1α, and endothelial nitric oxide synthase (eNOS). Moreover, the mitochondria showed other signs of dysfunction including fragmentation and dysregulated fusion causing them to produce more ROS and perpetuate the inflammatory situation. Meanwhile, activation of the important cellular fuel gauge associated with greater FFA oxidation and mitochondrial function, AMP kinase (AMPK), is

Figure 1. Proposed mechanism by which exercise reduces adipose tissue inflammation. Depicted in (A), adipocyte hypertrophy, as occurs in obesity, leads to dysregulated adipocyte lipolysis and insulin resistance. Insulin’s ability to suppress lipolysis becomes impaired, leading to increased free fatty acid (FFA) mobilization, even in the presence of insulin. In the absence of FFA utilization, FFA trigger adipocyte inflammation and an increase in inflammatory (M1) M, which also produce tumor necrosis factor-α (TNF-α), a cytokine that inhibits insulin signaling and impairs mitochondrial function (12), leading to increased reactive oxygen species (ROS) production; ROS further contribute to inflammation, leading to a vicious cycle. Depicted in (B), exercise stimulates adipocyte lipolysis via catecholamine activation while stimulating FFA oxidation in skeletal muscle. Exercise training also reduces adipocyte size, enhances adipocyte insulin sensitivity, and also may stimulate mitochondrial function in adipocytes, thereby further limiting the inflammatory effects of FFA within the adipocyte. In addition, exercise triggers the release of myokines, which are cytokines and other peptides released by skeletal muscle. One such recently discovered myokine, meteorin-like, enhances adipocyte insulin sensitivity and reduces adipocyte inflammation (24). Meteorin-like also promotes alternative (M2) M activation, which is characteristic of healthy insulin-sensitive adipocytes. Similar to exercise, estrogen improves adipocyte metabolism by facilitating FFA oxidation and mitochondrial biogenesis and also via activation of M2 M, which increases local catecholamine production. Dashed lines, inactive processes; solid lines, active processes. ATP, adenosine triphosphate.
activated potently by exercise in both skeletal muscle and adipose tissue and has been shown to associate with reduced cellular inflammation. On the other hand, M2 M, which release antiinflammatory cytokines, associate with increased FFA oxidation and decreased availability of potentially toxic lipid species. Importantly, exercise increases M2 M activation, which has been proposed as a potential mechanism by which exercise reduces inflammation in adipose tissue. In a study by Kawanishi et al. (16), C57BL/6 mice fed HFD and exercise trained did not experience a reduction in fat mass, yet marked reductions in proinflammatory cytokines in WAT were observed. Those changes were associated with both a suppression of M infiltration as well as a M phenotype switch from M1 to M2 (16). Unfortunately, that study did not assess WAT mitochondrial function. The link between M2 M activation and mitochondrial function recently was illustrated by the finding that M2 M activation and associated local catecholamine production are related mechanistically to the “browning” of WAT (17). What occurs metabolically to adipocytes when they undergo the browning process is an increase in mitochondrial density, function, and uncoupling of oxidative phosphorylation caused by the increase in expression of the uncoupling protein UCP-1 (11). Interestingly, another factor that has been shown recently to increase M2 M activation in WAT is the hormone estrogen (E2) (30). Furthermore, studies have implicated E2 in increasing mitochondrial biogenesis and activating AMPK and BAT (20).

What Can We Learn About the Immunoregulatory Role of Exercise on Adipose Tissue Through Sex Comparison Studies?

There is growing appreciation for the fact that premenopausal females are protected from metabolic dysfunction compared with age-matched males. Senthil Kumar et al. (26) compared male and female mice for their metabolic responses to HFD and found that, despite similar body composition changes, females were protected against the development of inflammation and insulin resistance observed in the males. This sex difference in metabolic response also has been observed in other species such as sheep and rats. There is good evidence that E2 is a key player in mediating this sex difference. Senthil Kumar and colleagues (26) demonstrated that, unlike sham-operated mice, female ovariectomized (OVX) mice developed WAT inflammation and insulin resistance on HFD. In addition, these detrimental metabolic effects were rescued with E2 replacement, even while the OVX-E2-HFD mice developed WAT inflammation and insulin resistance on HFD. However, this “protection” disappears when ovarian hormone levels are depleted in young females. In this study, using female OVX mice, we found that OVX significantly increased WAT inflammation, which was associated with the development of insulin resistance (32). Importantly, this effect was independent of adiposity, suggesting that ovarian hormone loss, and not the associated increase in adiposity per se, caused the changes. That study suggests that the protection against WAT inflammation and systemic insulin resistance in young females largely is caused by the presence of ovarian hormones, the leading contender among them being E2.

Although sex differences in the metabolic response to HFD are not understood completely, convincing data implicate E2 and signaling through estrogen receptor-α (ERα) as playing important roles. ER are present in adipocytes, within the cell membrane, in the nucleus, and within the mitochondrial membrane. There is evidence of both ERα- and ERβ-mediated increases in mitochondrial biogenesis, which likely plays a role in the increased fat oxidation capacity among females. More recently, it has been discovered that E2 also stimulates intracellular signaling pathways via binding to membrane-associated ERs and this rapid signaling pathway results in, among other end points, nitric oxide production via activation of eNOS, which is associated with improved mitochondrial function. Estrogen also is a known regulator of the transcription of nuclear respiratory factor 1, which promotes transcription of mitochondrial transcription factor (Tfam), which transcribes many mitochondrial genes. Studies also have shown that estrogens activate mitochondrial respiration (10). And, E2 increases transcription of genes associated with protection against mitochondrial damage, such as glutathione peroxidase (Gpx3) and superoxide dismutase (MnSOD). Taken together, those lines of evidence suggest that females are protected against mitochondrial damage, which presents with less inflammation compared with that from equally obese males, likely also contains more or better-functioning mitochondria. In fact, adipocytes from female mice have been shown to have more mitochondria, and the mitochondria take on a different phenotype consisting of more densely packed cristae (25). Moreover, the higher fat oxidation rates among females compared with males diminish after menopause. Interestingly, ER-knockout studies have shown that ablation of ERα leads to not only increased total adiposity but also reduced energy expenditure, whereas E2 replacement increases energy expenditure and reduces adiposity in males and females.
controls, low aerobically fit female rats (with reduced metabolic protection compared with ovary-intact specifics) play a role in adipose tissue inflammation. This idea, ongoing work by our group attempts to identify the role of intrinsic aerobic fitness on adipose tissue metabolism, reduce inflammation via this mechanism? The emergence of research studies on the metabolic importance of BAT underscores the potential utility of exercise on improving adipose tissue immunometabolism, as exercise increases BAT activity and may increase “browning” of WAT. Although mechanisms are not elucidated fully, mitochondrial function in adipose tissue seems to be related intimately to inflammation, lipid metabolism, and overall metabolic function; thus, exercise improves adipocyte immunometabolism. The similarities between the metabolic protection imparted by exercise and estrogen are striking; thus, sex comparison studies may offer important insight about the antiinflammatory role of exercise.

Nonetheless, it should not be understated that both exercise and E2 represent master regulatory factors. That is, the effects of both exercise and E2 are multifactorial, suggesting that they both work in virtually the same manner to improve adipocyte immunometabolism would be a grossly simplistic model. It is intriguing nonetheless that major mechanisms by which exercise has been postulated to have antiinflammatory effects in adipose tissue (e.g., increased catecholamine secretion, alternative M activation, AMPK activation) also are stimulated by E2 via either direct signaling pathways or E2-mediated genomic effects. In addition, there are numerous indirect potential mechanisms by which exercise improves adipose tissue inflammation, including increased angiogenesis and enhanced antioxidant defenses; similarly, E2 activates angiogenesis in models of tumor progression and increases antioxidant defenses via genomic mechanisms. It also is possible that other newly recognized strategies to improve immunometabolism such as cold exposure may be working via similar mechanisms (e.g., increased catecholamine secretion, enhanced mitochondrial function). In conclusion, exercise training, similar to E2 signaling, improves the metabolic health of the adipose tissue, and this effect likely contributes to the global metabolic health benefits of exercise.

SUMMARY

Exercise is one of the most powerful behavioral strategies to improve metabolic health. Even when body weight or adiposity is not reduced, exercise training has significant cardiometabolic benefits for reasons that are not completely understood. Exercise has been postulated to have antiinflammatory and antioxidant effects, specifically in the WAT, whereas WAT inflammation plays a major role in the development of metabolic diseases. Although it is difficult to dissociate exercise training and WAT reduction, convincing new evidence suggests that the effects of exercise are not explained fully by its fat-reducing effects. For example, recent important data demonstrated that training imparts protection against an acute inflammatory stimulus, thereby supporting a fat loss-independent antiinflammatory effect. In that study, the protection observed in trained animals was associated with a reduction in a cation channel protein (TRPV4), suggesting a molecular mechanism by which training reduces WAT inflammation (7).

The body of work illustrating the joint mitochondria-enhancing and antiinflammatory effects of E2 lends support to the idea that exercise may serve as an E2 “mimetic.” That is, exercise and E2 seem to improve adipocyte health similarly: by enhancing mitochondrial function and reducing inflammation. The “protection” among females against insulin resistance and inflammation and the loss of this protection after OVX or menopause, along with the data highlighting the metabolically important role of ERα, support the contention that E2 is a “protective factor.” Thus, emerging evidence suggests that exercise makes fat “fit” and that adipocyte “fitness” (i.e., greater mitochondrial function) may be related mechanistically to its antiinflammatory effect. It should be noted that the idea that exercise makes fat “fit” is not new; this exercise-mediated effect on adipocyte mitochondria was first shown by Stallknecht and colleagues (28) in 1991 and, in 2009, Sutherland et al. (29) elegantly showed that one mechanism involves exercise-mediated catecholamine production. The emergence of research studies on the metabolic importance of BAT underscores the potential utility of exercise on improving adipose tissue immunometabolism, as exercise increases BAT activity and may increase “browning” of WAT. Although mechanisms are not elucidated fully, mitochondrial function in adipose tissue seems to be related intimately to inflammation, lipid metabolism, and overall metabolic function; thus, exercise improves adipocyte immunometabolism. The similarities between the metabolic protection imparted by exercise training and estrogen are striking; thus, sex comparison studies may offer important insight about the antiinflammatory role of exercise.

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References


