Adipose Tissue Insulin Action and IL-6 Signaling after Exercise in Obese Mice

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ABSTRACT

MACPHERSON, R. E. K., J. S. HUBER, S. FRENDO-CUMBO, J. A. SIMPSON, and D. C. WRIGHT. Adipose Tissue Insulin Action and IL-6 Signaling after Exercise in Obese Mice. Med. Sci. Sports Exerc., Vol. 47, No. 10, pp. 2034–2042, 2015. Introduction: Adipose tissue insulin action is impaired in obesity and is associated with inflammation, macrophage infiltration, and polarization toward a proinflammatory phenotype. Acute exercise can reduce markers of adipose inflammation, including interleukin (IL) 6, in parallel with improvements in insulin action; however, others have provided evidence that IL-6 has anti-inflammatory properties. Purpose: This study aimed to examine the relation between IL-6 signaling, macrophage infiltration, and polarization and insulin action in inguinal fat after acute exercise in obese, insulin-resistant mice. Methods: Male C57BL/6 mice were fed a low-fat diet (10% kcal lard) or a high-fat diet (HFD, 60% kcal lard) for 7 wk and then underwent an acute bout of exercise (2-h treadmill running: 15 m min⁻¹, 5% incline). Results: The HFD resulted in increased body mass, glucose intolerance, and attenuated insulin-induced AKT Thr308 phosphorylation in inguinal fat. This was accompanied by increases in indices of macrophage infiltration (F4/80, CD68, and monocyte chemoattractant protein-1 expression) and polarization toward an M1 phenotype (increased expression of CD11c, CD11c/galactose-type C-type lectin 1, and inducible nitric oxide synthase). Immunofluorescence imaging demonstrated increased F4/80- and CD11c-positive cells with the HFD. Two hours after exercise, the insulin-induced activation of AKT Thr308 phosphorylation was recovered in HFD mice. This was accompanied by an upregulation of IL-6 and IL-10 signaling, as demonstrated by increased expression of IL-6, IL-10, and SOCS3 as well as STAT3 phosphorylation. Furthermore, acute exercise resulted in a shift toward reduction in M1 polarization indicated by a decrease in the ratio of CD11c to galactose-type C-type lectin 1 mRNA as well as a decline in F4/80- and CD11c-positive cells. Conclusions: The results suggest a link between exercise-induced increases in IL-6, reductions in indices of M1 macrophages, and increased IL-10, a reputed anti-inflammatory cytokine with insulin-sensitizing properties. Key Words: INFLAMMATION, MACROPHAGE, ACUTE EXERCISE, ADIPOSE TISSUE

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An acute bout of exercise has previously been reported to induce markers of inflammation in adipose tissue from lean healthy rats (27). The underlying cause of this inflammation may be the rapid increase in adipose tissue lipolysis and fatty acid release that occur with exercise (10). In agreement with this supposition, recent work has demonstrated that the beta-3 adrenergic agonist (CL 316,243) rapidly induces markers of inflammation in mouse adipose tissue in vivo parallel with large increases in adipose tissue lipolysis (3,23). Moreover, the induction of proinflammatory genes after CL 316,243 treatment is abrogated when fatty acid release is attenuated (23). Together, these studies reveal an important role of exercise-induced lipolysis in initiating inflammatory response in adipose tissues of lean mice.

In contrast to exercise in lean rats, it has recently been reported that markers of inflammation such as IL-6, IL-1 beta, and TNFα as well as markers of M1 macrophage polarization were reduced in epididymal adipose tissues of obese rats 2 h after 6 h of swimming exercise (24,25). The decrease in adipose tissue IL-6 expression after exercise in obese rats, despite a shift in macrophage polarization and improvements in adipose tissue insulin action, is particularly interesting, as it has been proposed that IL-6 plays a crucial role in the alternative activation of macrophages in obesity (22).

Given these apparent discrepancies in the role of IL-6 after exercise, the purpose of the current study was to re-examine the effects of an acute bout of exercise on markers of inflammation and insulin action in the setting of preexisting obesity and insulin resistance. To examine this question, we used treadmill running, instead of swimming, because we viewed this as a more clinically relevant mode of exercise. Indices of inflammation, macrophage infiltration/polarization, and insulin signaling were examined in inguinal subcutaneous adipose tissue, a fat depot proven to play a significant role in the regulation of whole body glucose homeostasis (33,35) and which responds more robustly to exercise than visceral adipose tissue depots (2). We hypothesized that an acute bout of exercise would induce IL-6, and this would be associated with reductions in markers of M1 macrophages and improvements in insulin signaling.

METHODS

Materials. Molecular weight marker, reagents, and nitrocellulose membranes for SDS-PAGE were purchased from Bio-Rad (Mississauga, Ontario, Canada). ECL Plus was a product of Amersham Pharmacia Biotech (Arlington Heights, IL). Horseradish peroxidase-conjugated donkey anti-rabbit and goat anti-mouse IgG secondary antibodies were from Jackson ImmunoResearch Laboratories (West Grove, PA). Antibodies against total AKT (CAT# 4685), phosphothreonine AKT (CAT# 8582), total JNK (CAT# 9252S), phospho-JNK (CAT# 4671S), total ERK (CAT# 4695S), phospho-ERK (CAT# 9101S), total STAT3 (CAT# 8768S), phospho-308 AKT (CAT# 4056), total STAT3 (CAT# 9138S), phospho-STAT3 (CAT# 9138S), total p38 (CAT# 9212S), and phospho-p38 (CAT# 9211S) were purchased from Cell Signaling (Danvers, MA); F4/80 (60343, 2 µg·mL⁻¹, FITC conjugated), CD11c (33483, 2 µg·mL⁻¹), and Alexa Fluor 568 (175716, 2 µg·mL⁻¹) were from Abcam (Toronto, Ontario, Canada). Random primers, SuperScript II Reverse Transcriptase, and dNTP were from Invitrogen (Burlington, Ontario, Canada). Taqman gene expression assays for mouse IL-6 (Mm00446190_m1), SOCS-3 (Mm00545913_s1), TNFα (Mm00443258_m1), MCP-1 (Mm00441242_m1), IL-10 (Mm00439614_m1), CD68 (Mm03047340_m1), INOS (Mm00440502_m1), and GAPDH (4352932E) were from Applied Biosystems (Foster City, CA). All other reagents were from Sigma-Aldrich.

Animals and diet. Male C57BL/6 mice (Charles River) were fed a low-fat diet (LFD) (10% kcal from lard; Research Diets D12450J; n = 9) or an HFD (60% kcal from lard; Research Diets D12492; n = 18) ad libitum for 7 wk. In preliminary experiments, we found that this duration of high-fat feeding induced adipose tissue insulin resistance and markers of macrophage infiltration. Animals were housed individually, had free access to water, and were maintained on a 12/12-h light cycle. All protocols were approved by the University of Guelph Animal Care Committee and met the guidelines of the Canadian Council on Animal Care.

Glucose tolerance. Intraperitoneal glucose tolerance tests were performed on fasted (6 h), nonanesthetized mice during the last week of feeding. Glucose measures were obtained from tail vein blood using an automated glucometer at baseline and at 15, 30, 45, 60, 90, and 120 min after intraperitoneal injection of glucose (2 g·kg⁻¹ body mass).

Acute exercise protocol. To minimize differences between groups and in stress, both LFD and HFD mice were acclimated to motorized treadmill running during a 3-d period consisting of 15 min·d⁻¹ of running at 15 m·min⁻¹ and 5% grade. Mice were maintained on their respective diets during this time. Mice were assigned into one of the following three groups: sedentary LFD (LFD, n = 9), sedentary HFD (HFD, n = 9), and exercised HFD (HFD + ex, n = 9). Seventy-two hours after the last day of acclimation, mice ran for 120 min at 15 m·min⁻¹, with an incline of 5%. The acute bout of exercise started at approximately 10:00 a.m., which is the beginning of the light cycle. From a previous work in our laboratory (38), we have found that this duration and intensity of exercise are well tolerated; all mice in the exercise treatment group completed the 2-h treadmill running without issue. After the exercise bout, mice were placed back in their cages to recover for 2 h without food. Sedentary low- and high-fat-fed mice had their food removed at the same time as the high-fat-fed mice that exercised.

Insulin stimulation. Two hours after exercise, mice were anesthetized with a weight-adjusted bolus injection of sodium pentobarbital (5 mg per 100-g body weight). The left inguinal fat depot was dissected and immediately frozen in liquid nitrogen and stored at −80°C until further analysis. Mice were then injected in the peritoneal cavity with a weight-adjusted bolus of insulin (10.0 U·kg⁻¹ BW). This dosage of insulin is typically used to measure responsiveness.
of the insulin signaling pathway in vivo (17). Fifteen minutes after injection, the contralateral fat depot was rapidly excised and immediately frozen in liquid nitrogen and stored at −80°C. Sedentary LFD and HFD mice underwent the same manipulations.

Real-time polymerase chain reaction. Total RNA was extracted via Trizol reagent and reverse-transcribed into cDNA. Changes in mRNA expression were determined using real-time quantitative polymerase chain reaction (PCR), as described in detail previously by our laboratory (3). Briefly, RNA was isolated from inguinal adipose tissue using an RNeasy kit according to the manufacturer’s instructions (RNeasy Kit, 74104;Quiagen). Quantity and purity were assessed using a NanoDrop system (NanoDrop 2000 Spectrophotometer; Thermo Scientific). cDNA was synthesized from total RNA (1 µg) using SuperScript II Reverse Transcriptase, dNTP, and random primers (Invitrogen, Burlington, Ontario, Canada). Real-time PCR was carried out using a 7500 fast real-time PCR system (Applied Biosystems). Samples were loaded in triplicate using a 96-well plate layout. Each well contained a total volume of 20 µL comprised of 1-µL gene expression assay, 1-µL cDNA template, 10-µL Taqman fast universal PCR master mix, and 8-µL RNase-free water. GAPDH was used as our housekeeping gene, and relative differences in gene expression between groups were determined using the 2-ΔΔCT method (18). PCR efficiency was similar between GAPDH and our genes of interest. Similarly, our experimental manipulations did not alter the expression of our housekeeping gene (GAPDH).

Western blotting. Samples were homogenized (FastPrep®-24; MP Biomedicals, Santa Ana, CA) in cell lysis buffer (three volumes) supplemented with phenylmethylsulfonyl fluoride and protease inhibitor cocktail (Sigma-Aldrich). Homogenized samples were centrifuged at 4°C (10 min at 5000g), the infranatant was collected, and protein content was determined using a bicinchoninic acid assay (32). Samples were prepared to contain equal concentrations of protein that were then separated on 10% SDS-PAGE gels. Protein was wet-transferred onto nitrocellulose membranes at 100 V per transfer unit. Membranes were blocked in Tris-buffered saline/0.1% tween 20 (TBST) prepared with 5% nonfat dry milk for 1 h followed by overnight incubation at 4°C with the appropriate primary antibody. After primary incubation, membranes were rinsed with TBST and incubated with the appropriate horseradish peroxidase-conjugated secondary antibodies for 1 h at room temperature (Jackson ImmunoResearch Laboratories, West Grove, PA). Phospho and total blots were run on duplicate gels. Signals were detected using enhanced chemiluminescence and were subsequently quantified by densitometry using a FluorChem HD imaging system (Alpha Innotech, Santa Clara, CA). Phosphorylated proteins were expressed relative to total.

Histological analysis. Inguinal adipose tissue was fixed in 10% neutral-buffered formalin (VWR, Mississauga, Ontario, Canada) dehydrated in xylene (Fisher Scientific) and embedded in paraffin. Five-micrometer sections were mounted on 1.2-mm Superfrost slides stained with modified Harris hematoxylin and eosin stock with phloxine (Fisher Scientific) and imaged (Olympus FSX 100 light microscope; Olympus, Tokyo, Japan). Cells (approximately 100) from were sampled in each image to determine cross-sectional area (ImageJ software; National Institute of Mental Health, Bethesda, MD).

Immunofluorescence. Inguinal adipose tissue was embedded in Tissue-Tek optimal cutting temperature compound at −80°C. The adipose tissue was then cut into 30-µm sections at −35°C and mounted on charged 1.2-mm Superfrost slides (Fisher Scientific). Frozen sections were then fixed in acetone at −20°C. The slides were then incubated with anti-F4/80 overnight at +4°C for the identification of macrophages, washed, then incubated with primary anti-CD11c and secondary Alexa Fluor 568 to identify CD11c-positive cells. Images were acquired using Olympus FSX 100 light microscope and analyzed using Cell Sense software (Olympus, Tokyo, Japan). As sections were 30-µm thick, macrophages were present at different focal planes when using light microscopy, resulting in varying intensities of fluorescence signal for macrophages. Cells that were F4/80+ and F4/80+CD11c+ were counted per square centimeter in two images per animal. Image analysis was completed in a blinded fashion by an individual experienced with this technique.

Statistics. Comparisons between LFD and HFD groups were made using unpaired, two-tailed Student’s t-tests. Differences in insulin-induced Akt phosphorylation were determined with a two-way repeated-measures ANOVA followed by least significant difference post hoc analysis. Differences in protein content, gene expression, and glucose over time were determined using one-way ANOVA followed by least significant difference post hoc analysis. In cases where data were not normally distributed, data were logarithmically transformed. Data are expressed as means ± SEM with significance set at P < 0.05.

RESULTS

High-fat feeding increased body and adipose tissue mass and induced glucose intolerance. Mice fed with the HFD for 7 wk gained more weight than the mice fed the LFD (P < 0.05) (Fig. 1A and B). Similar to differences in body mass, inguinal adipose tissue mass of the mice fed with the HFD was greater than that of the LFD mice (P < 0.05) (Fig. 1C). HFD mice cleared glucose less effectively after an intraperitoneal glucose injection and had a higher glucose area under the curve compared with that of LFD mice (P < 0.05) (Fig. 1D and E). These results demonstrate that 7 wk of HFD resulted in obese, glucose-intolerant mice.

Acute exercise improved insulin signaling independent of reductions in MAPK signaling. To examine the effects of an acute bout of exercise on adipose tissue insulin action, we measured insulin-induced AKT phosphorylation 2 h after an acute bout of exercise. This time point was chosen because others have shown improvements in adipose tissue insulin signaling at this point after acute exercise in...
obese rats (24). In LFD mice, insulin resulted in approximately fourfold increase in AKT phosphorylation that was absent in sedentary HFD mice (Fig. 2A). Two hours after an acute bout of exercise, insulin-stimulated AKT phosphorylation in inguinal adipose tissue was restored in HFD mice. No changes in basal phosphorylation or total AKT protein levels were observed in any group. The ERK, p38, and JNK MAPK are involved in the cellular response to inflammatory cytokines (5), thus linking them to insulin resistance. Diet had no effect on the phosphorylation of JNK, ERK, or p38. However, 2 h after exercise, p38 phosphorylation was significantly increased \((P < 0.05)\) (Fig. 2B).

**Acute exercise decreases indices of M1 macrophages.** Markers of macrophage infiltration, F4/80 and CD68, were significantly increased in inguinal adipose tissue after HFD. Exercise had no effect on the expression of these macrophage markers (Fig. 4A). M1 macrophages can be characterized by increased expression of iNOS (31). High-fat feeding resulted in increased iNOS expression, and this was reduced 2 h after exercise (Fig. 4B). M1 and M2 macrophages can further be distinguished by the presence or absence of the M1 marker, CD11c, and the M2 marker, MGL-1 (19). The ratio of CD11c to MGL-1 gene expression is a useful measure of the relative polarization of macrophages (19). HFD led to marked increase in the mRNA expression of CD11c, whereas MGL-1 expression was unaffected. Two hours after exercise, the expression of CD11c and the ratio of CD11c to MGL-1 were significantly reduced in comparison with HFD sedentary samples (Fig. 4B). To confirm the changes in gene expression, we measured F4/80 and CD11c protein using immunofluorescence. As shown in Figure 5, the consumption of an HFD for 7 wk led to increases in inguinal adipose tissue fat cell size and F4/80-positive cells and an acute bout of exercise did not alter these endpoints. F4/80- and CD11c-positive cells were increased in inguinal adipose tissue from mice fed with an HFD. In keeping with our gene expression data, the percentages of F4/80- and CD11c-positive cells were reduced 2 h after an acute bout of exercise.

**Acute exercise increases the expression IL-10.** Anti-inflammatory cytokines are expressed to a higher degree in adipose tissue from lean healthy mice in comparison with that in obese mice, and previous work has demonstrated that a bout of acute exercise increases IL-10 and IL-4 expression in adipose tissues of rats fed with an HFD (24). Furthermore,
both IL-4 and IL-10 have been demonstrated to induce alternative macrophage phenotype (12,19). In inguinal adipose tissue, IL-4 and IL-10 were not altered in sedentary HFD mice. However, 2 h after exercise, IL-10 was increased approximately fivefold (Fig. 6).

**DISCUSSION**

Adipose tissue macrophages are known to be significant contributors to inflammation in obesity and mediators of insulin resistance (11,19). Exercise training provides a potential therapeutic treatment to resolve adipose tissue inflammation and M1 macrophage activation; however, these results typically happen with declines in adipose tissue mass occurring with the training (1,13–15) and the effects of exercise per se remain relatively unstudied. The current investigation used an acute bout of exercise to characterize changes in the expression of proinflammatory cytokines and markers of macrophage infiltration as well as activation in mice with diet-induced obesity and insulin resistance mice. Novel results from this study indicate that the recovery of insulin signaling in inguinal adipose tissue after an acute bout of exercise in obese mice is associated with increases in markers of IL-6 and IL-10 signaling and decreases in M1 macrophages.

Seven weeks of high-fat feeding resulted in attenuation of insulin-stimulated AKT phosphorylation in inguinal adipose tissue. This was associated with increases in macrophage infiltration (increased F4/80 protein and mRNA expression of F4/80 and CD68), M1 polarization (increased F4/80- and CD11c-positive cells as well as mRNA expression of iNOS and CD11c), and expression of MCP-1, a chemotaxic factor thought to play a role in macrophage infiltration (11,30). Insulin signaling was recovered after the acute bout of exercise; however, this was accompanied by an increase in IL-6 signaling (SOCS3 expression (4) and STAT3 phosphorylation (7)). The specific mechanisms driving the increase in IL-6 expression in adipose tissue with exercise are not known. However, recent evidence suggests that increases in fatty acid

![Graph A](image1.png)

**FIGURE 2**—Acute exercise improved insulin signaling independent of reductions in MAPK signaling. A. HFD-induced reductions in AKT phosphorylation are rescued by an acute bout of exercise. B. Diet had no effect on the phosphorylation of JNK, ERK, or p38. Two hours after exercise, p38 phosphorylation was significantly increased. Representative blots are shown beside (A) or below (B) the quantified data (LFD, n = 9; HFD, n = 9; HFD+ ex 2 h after exercise, n = 9; + indicates insulin stimulated conditions). Data are presented as means ± SEM. *P < 0.05.
release (23) and sphingosine kinase expression/activity (39) are involved in the regulation of IL-6 expression in adipocytes. Although we do not have direct evidence demonstrating exercise-induced increases in adipose tissue lipolysis with our exercise model, the previously mentioned mechanisms could likely be involved in regulating the effects of exercise on induction of IL-6.

The increase in IL-6 is an interesting finding, as IL-6 is generally viewed as a proinflammatory cytokine with increased expression in adipose tissue from obese, insulin-resistant animals (16). However, the inflammatory role of IL-6 remains controversial and studies indicate that IL-6 may instead have positive immunometabolic effects (22). In support of this, IL-6–deficient mice develop late-onset obesity and resistance to insulin (37). Moreover, when fed an HFD, IL-6–deficient mice develop enhanced inflammation and deteriorations in glucose metabolism when compared with wild-type controls (21). Similarly, the myeloid-specific ablation of the IL-6 receptor leads to greater development of glucose intolerance in mice fed with an HFD when compared with that in wild-type controls, and this is associated with increases in markers of M1 macrophages in insulin-sensitive tissues.

**FIGURE 3**—Acute exercise increases IL-6 signaling in inguinal adipose tissue from obese mice. A. No effect of diet was observed on the expression of IL-6, TNFα, or SOCS3, whereas MCP-1 expression was increased. Two hours after exercise, IL-6, SOCS3, and MCP-1 expression was increased. B. Acute exercise resulted in increased STAT3 phosphorylation two hours after exercise. Representative blots are shown beside the quantified data (B) (LFD, n = 9; HFD, n = 9; HFD+ ex 2 h after exercise, n = 9). Data are presented as means ± SEM. * and # indicate significantly different values from those in other groups at P < 0.05.

**FIGURE 4**—Effects of diet and acute exercise on the expression of markers of macrophage infiltration and polarization. A. The HFD led to increases in F4/80 and CD68 gene expression. B. High-fat feeding increased the expression of iNOS, CD11c, and the ratio of CD11c to MGL-1, with acute exercise resulting in a decline in these endpoints (LFD, n = 9; HFD, n = 9; HFD+ ex 2 h after exercise, n = 9). Data are presented as means ± SEM. * and # indicate significantly different values from those in other groups at P < 0.05.
In keeping with these findings in the present study, we found that an acute bout of exercise, parallel with increases in reputed markers of IL-6 signaling, i.e., SOCS3 and p-STAT3 (4,7), led to reductions in F4/80- and CD11c-positive cells as well as the ratio of CD11c to MGL-1 mRNA, providing evidence of a reduction in M1 macrophage polarization. Although the results from our immunohistological staining do not evaluate the absolute number of infiltrated macrophages,

(22). In keeping with these findings in the present study, we found that an acute bout of exercise, parallel with increases in reputed markers of IL-6 signaling, i.e., SOCS3 and p-STAT3 (4,7), led to reductions in F4/80- and CD11c-positive cells as well as the ratio of CD11c to MGL-1 mRNA, providing evidence of a reduction in M1 macrophage polarization. Although the results from our immunohistological staining do not evaluate the absolute number of infiltrated macrophages,
as can be done with flow cytometry, we believe that our results provide sufficient evidence of relative changes in macrophage polarization.

In contrast to our findings, Oliveira et al. (24,25) found that the insulin-induced activation of AKT in epididymal adipose tissue was increased in obese rats 2 h after a single bout of exercise; however, these changes were associated with reductions in the mRNA expression of inflammatory factors such as TNFα, IL-1β, and IL-6. The discrepancy between the present study and that by Oliveira et al. may be due to the mode of acute exercise (24,25). Oliveira et al. (24,25) used a strenuous 6-h swimming protocol, whereas we used a 2-h treadmill running protocol that may be considered more physiologically relevant. Although the adipose tissue depot examined could also play a role in the differences between studies, we find this to be unlikely because IL-6, TNFα, and MCP-1 were also increased in the epididymal adipose tissue from mice fed an HFD after exercise (MacPherson et al. 2014; Effect of acute exercise on epididymal adipose tissue from mice fed a high fat diet, unpublished findings).

In addition to the increased markers of IL-6 signaling, our findings demonstrate reductions in indices of M1 macrophages, as demonstrated by the decline in the F4/80- and CD11c-positive cells after exercise. M1 macrophages are known to be central mediators of obesity-induced inflammation and insulin resistance (19). Therefore, if an increased M1 macrophage population leads to disruption of glucose homeostasis, the ratio of M1 to M2 macrophages is likely important for metabolic control. The significance of this ratio for insulin sensitivity was previously demonstrated in a study in which mice deficient in M2 macrophages displayed increased white adipose tissue inflammation and insulin resistance (8). Furthermore, ablation of CD11c-positive cells results in normalization of insulin sensitivity (26).

M2 macrophages express and secrete IL-10 to a greater degree than M1 macrophages (6). In cultured L6 myoblasts, IL-10 potentiates insulin action, as demonstrated by increases in insulin-stimulated AKT phosphorylation, glucose transport, and GLUT4 translocation (28). Moreover, it has previously been demonstrated that IL-10 improves glucose uptake in 3T3-L1 adipocytes (9) and can activate PI3K-dependent pathways (40). In the current study, we have shown increases in IL-10 expression that were paralleled by increases in the phosphorylation of p38 MAPK, a signaling enzyme previously shown to control the expression of IL-10 (as reviewed by Saraiva and Garra [29]). Along with increased IL-10 expression, the present study also found increases in the phosphorylation of STAT3, a marker of IL-10, in addition to IL-6 signaling. Based on these findings, it is our current working hypothesis that the exercise-induced increases in IL-6 may serve as a trigger to mediate a switch in macrophage polarization, leading to a more anti-inflammatory phenotype including increases in IL-10 expression and secretion. These changes could be linked to improved adipose tissue insulin action.

In summary, we have provided novel data demonstrating improvements in inguinal adipose tissue insulin action in obese mice after a single bout of exercise that is paralleled by apparent increases in IL-6 and/or IL-10 signaling and decreased M1 macrophages. These findings speak of the powerful effects of exercise as a means of modulating adipose tissue immunometabolism independent of weight loss and further suggest that targeted interventions to stimulate these pathways could be an effective approach to improve adipose tissue insulin action.

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There are no conflicts of interest to disclose.

The results of the present study do constitute endorsement by the American College of Sports Medicine.

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