Review Article

The Effects of Exercise Training on Obesity-Induced Dysregulated Expression of Adipokines in White Adipose Tissue

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Obesity is recognized as a risk factor for lifestyle-related diseases such as type 2 diabetes and cardiovascular disease. White adipose tissue (WAT) is not only a static storage site for energy; it is also a dynamic tissue that is actively involved in metabolic reactions and produces humoral factors, such as leptin and adiponectin, which are collectively referred to as adipokines. Additionally, because there is much evidence that obesity-induced inflammatory changes in WAT, which is caused by dysregulated expression of inflammation-related adipokines involving tumor necrosis factor-α and monocyte chemoattractant protein 1, contribute to the development of insulin resistance, WAT has attracted special attention as an organ that causes diabetes and other lifestyle-related diseases. Exercise training (TR) not only leads to a decrease in WAT mass but also attenuates obesity-induced dysregulated expression of the inflammation-related adipokines in WAT. Therefore, TR is widely used as a tool for preventing and improving lifestyle-related diseases. This review outlines the impact of TR on the expression and secretory response of adipokines in WAT.

1. Introduction

In recent years, obesity caused by the hypertrophy of white adipose tissue (WAT) has steadily increased worldwide, and has become a serious social problem [1]. In 2010, the Organization for Economic Cooperation and Development (OECD) released a report on the current state of obesity and the cost-effectiveness of preventive measures [2, 3]. That report states that obesity rates have risen in many countries, and that one in two individuals is either obese or overweight in about half of OECD countries. It is widely known that obesity is a risk factor for various “lifestyle-related diseases” such as type 2 diabetes and hypertension, and that obesity and diabetes cause increases in atherosclerotic disease. Therefore, there is an urgent need to establish strategies for the prevention and improvement of obesity and diabetes.

Epidemiological studies have shown that exercise is effective for preventing and improving obesity and diabetes...
[4, 5]. For example, a study by Helmrich et al. [6] followed 5,990 male graduates of the University of Pennsylvania over 14 years and found that the risk of developing diabetes is reduced by 6% for every 500 kcal increase in weekly exercise. Furthermore, a study that followed 21,271 male U.S. doctors over five years revealed that even a once-weekly bout of exercise at an intensity that is sufficient to cause sweating reduced the risk of developing diabetes [7]. In addition, results from a study that followed 87,253 female U.S. nurses over eight years showed that the group that exercised at least once a week at an intensity sufficient to cause sweating had a relative risk of developing diabetes of 0.84 compared with a group that exercised less than once a week [8].

Although WAT was once considered to be merely a site for energy storage, in recent years it has become better understood at the molecular level; for example, how WAT secretes physiologically active substances, collectively known as adipokines, and how obesity-induced dysregulated expression of adipokines in WAT causes insulin resistance, which is the pathogenesis of diabetes [9–11]. Therefore, WAT is considered to be one of the tissues that play a critical role in the onset of lifestyle-related diseases, and the reduction of excess WAT and the improvement of abnormal adipokine secretion are important strategies for the prevention and improvement of lifestyle-related diseases. Exercise training (TR) not only causes a loss of WAT mass, but can also influence the secretory response and expression of adipokines in WAT. This review outlines the impact of TR on the adipokines in WAT.

2. Adipokines and the Inflammatory Response of WAT

The major role of subcutaneous and visceral WAT is to supply and store energy via adipocytes in WAT. Most of the ingested excess energy is stored within adipocytes in the form of triglycerides, which are formed through the binding of glycerol and fatty acids. During exercise, catecholamines (adrenaline and noradrenaline) secreted from the adrenal medulla or the sympathetic nerve terminal break down triglycerides within adipocytes, and the resultant fatty acids are carried to skeletal muscle via the blood [12]. However, following the discovery of leptin by Zhang et al. [13] in 1994, leptin was established as a hormone that is secreted by WAT, and a string of new humoral factors that are secreted by WAT were discovered. Therefore, the old concept of WAT as a mere storage site for energy has been revised to also acknowledge it as an endocrine organ. The humoral factors secreted from WAT are collectively referred to as adipokines (Figure 1).

In recent years, it has become clear that obesity is a chronic and mild systemic inflammatory condition, and there is much evidence that chronic inflammation of WAT contributes to the development of insulin resistance. This systemic inflammation has become closely acknowledged as the molecular basis of diabetes [9–11]. When adipocyte hypertrophy occurs due to excessive energy intake or lack of exercise, infiltration by macrophages, which are one type of immunocompetent cell, is observed in WAT. In

![Figure 1: Adipokines secreted by white adipose tissue. White adipose tissue (WAT) secretes various humoral factors called adipokines. Adipokines have important effects on lipid and glucose metabolism, and so on. TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor-1.](image-url)

WAT infiltrated by macrophages, the production of proinflammatory adipokines, such as tumor necrosis factor-α (TNF-α) and monocyte chemoattractant protein 1 (MCP-1), is increased and the production of anti-inflammatory adiponectin is decreased, thereby causing chronic inflammation of WAT (Figure 2) [14–16]. This increase in proinflammatory adipokines is not limited to WAT, but also promotes insulin resistance in skeletal muscle and liver as a paracrine agent. Thus, the inflammatory response plays an important role in WAT activity.

3. Representative Adipokines and the Effects of TR

3.1. Leptin. Leptin is a hormone that acts on leptin receptors (ob-R) in the hypothalamus to strongly suppress appetite and promote increased energy expenditure [17–19]. There is strong ob-R expression in the arcuate nucleus, ventromedial hypothalamic nucleus, dorsomedial hypothalamic nucleus, and lateral hypothalamic area of the hypothalamus [18]. Although the expression of mRNA for leptin is elevated in the WAT of obese humans and animals and blood levels also increase, since there is impaired leptin action called “leptin resistance”, leptin does not function sufficiently to suppress appetite or promote energy expenditure [18, 20–22]. On the other hand, it is also known that leptin has inflammatory effects, such as increasing the expression of inflammatory cytokines involving TNF-α by acting on monocytes [9].

Evidence shows that seven weeks of spontaneous running TR reduces the expression of mRNA for leptin in the visceral and subcutaneous WAT of obese rats (Table 1) [23]. Additionally, other research indicates that even a short duration (four weeks) of spontaneous activity reduces leptin mRNA expression in rat WAT (Table 1) [24]. For obese humans, however, one study found that even 12 weeks of one-hour aerobic
| Citation               | Experimental animals                           | Exercise program            | Diet restriction | Duration of intervention | WAT used in experiment | Effects of TR on expression of adipokines in WAT | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFm) |
|-----------------------|------------------------------------------------|----------------------------|------------------|--------------------------|------------------------|-----------------------------------------------|----------------------------------------------------------------------------------|
| Zachwieja et al. [23] | Diet-induced obesity sensitive rats           | Voluntary wheel running    | None             | 7 weeks                  | Epididymal and inguinal WAT | Leptin mRNA: decrease (*p* < 0.05)           | Epididymal and inguinal FM: decrease                                             |
|                       | Diet-induced obesity resistant rats           | Voluntary wheel running    | None             | 7 weeks                  | Epididymal and inguinal WAT | Leptin mRNA: decreasing trend                |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | Leptin mRNA: decrease (*p* < 0.05)           |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | Epididymal and inguinal FM: decrease         |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | BM: decrease; Visceral and subcutaneous FM: decrease |                                                                                   |
|                       |                                                 |                            |                  |                          |                        |                                                |                                                                                   |
| Gollisch et al. [24]  | Rats chow diet                                 | Voluntary wheel running    | None             | 4 weeks                  | Visceral and subcutaneous WAT | Leptin mRNA: decrease (*p* < 0.05)           | BM: NS; Visceral and subcutaneous FM: decrease                                      |
|                       | Rats HFD                                      | Voluntary wheel running    | None             | 4 weeks                  | Visceral and subcutaneous WAT | Leptin mRNA: decrease (*p* < 0.05)           | BM: NS; Visceral and subcutaneous FM: decrease                                      |
|                       |                                                 |                            |                  |                          |                        | TNF-α mRNA and protein: NS                   |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | MCP-1 mRNA: NS                               |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | Adiponectin mRNA: NS                          |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | IL-6 mRNA: NS                                |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | Leptin mRNA: increase (*p* < 0.05)            |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | TNF-α mRNA and protein: increase              |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | TNF-α protein: NS                             |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | MCP-1 mRNA: NS                               |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | Adiponectin mRNA: NS                          |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | IL-6 mRNA: NS                                |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | TNF-α mRNA: increase (*p* < 0.05)             |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | MCP-1 mRNA: NS                               |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | Adiponectin mRNA: decrease                   |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | IL-6 mRNA: NS                                |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | TNF-α mRNA: increase (*p* < 0.01)             |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | TNF-α protein: NS                             |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | MCP-1 mRNA: NS                               |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | Adiponectin mRNA: decrease                   |                                                                                   |
|                       |                                                 |                            |                  |                          |                        | IL-6 mRNA: increase (*p* < 0.05)              |                                                                                   |

Table 1: Effects of exercise training on expression of adipokines in white adipose tissue. (a) Animal studies
| Citation          | Experimental animals | Exercise program                          | Diet restriction | Duration of intervention | WAT used in experiment | Effects of TR on expression of adipokines in WAT | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BF M) |
|-------------------|----------------------|-------------------------------------------|------------------|--------------------------|------------------------|-------------------------------------------------|---------------------------------------------------------------------------------|
| Bradley et al. [25] | Mice chow diet       | Voluntary wheel running                   | None             | 10 weeks (exercise: 6 weeks) | Perigonadal and mesenteric WAT | Perigonadal WAT TNF-α mRNA: decrease ($P < 0.05$) MCP-1 mRNA: decrease ($P < 0.05$) | BM and FM: decrease |
|                   | Mice HFD             | Voluntary wheel running                   | None             | 10 weeks (exercise: 6 weeks) | Perigonadal and mesenteric WAT | Mesenteric WAT MCP-1 mRNA: decrease ($P < 0.05$) Perigonadal WAT TNF-α mRNA: decrease ($P < 0.05$) | BM and FM: decrease |
| Vieira et al. [26] | Mice HFD             | Treadmill running for 40 min/day on 5 times/week at 65–70% VO₂ max | None             | 18 weeks (exercise: 6 or 12 weeks) | Epididymal and retroperitoneal WAT | Exercise for 6 weeks Leptin mRNA: decreasing trend TNF-α mRNA: NS MCP-1 mRNA: NS | Exercise for 6 weeks BM and epididymal FM: decrease |
|                   |                      |                                           |                  |                          |                        | Exercise for 12 weeks Leptin mRNA: decreasing trend TNF-α mRNA: decrease ($P < 0.001$) MCP-1 mRNA: decrease ($P < 0.001$) | Exercise for 12 weeks BM and epididymal FM: decrease |
| Sakurai et al. [27] | Rats chow diet       | Treadmill running on 5 times/week. On the first day of training, all rats ran for 30 min at 15 m/min, and then running time and velocity were extended until rats were running for 90 min at 30 m/min. | None             | 9 weeks                  | Epididymal WAT         | TNF-α protein: decrease ($P < 0.05$) | BM and epididymal FM: decrease |
| Sakurai et al. [28] | Rats chow diet       | Treadmill running on 5 times/week. On the first day of training, all rats ran for 30 min at 15 m/min, and then running time and velocity were extended until rats were running for 90 min at 30 m/min. | None             | 9 weeks                  | Epididymal, retroperitoneal, and subcutaneous WAT | Epididymal adipocyte TNF-α mRNA: decrease ($P < 0.05$) MCP-1 mRNA: decrease ($P < 0.05$) Epididymal WAT TNF-α protein: decrease ($P < 0.05$) MCP-1 protein: decrease ($P < 0.05$) Retroperitoneal WAT TNF-α protein: decreasing trend MCP-1 protein: decrease ($P < 0.05$) Subcutaneous WAT TNF-α protein: NS MCP-1 protein: decrease ($P < 0.05$) | BM: decrease epididymal, retroperitoneal, and subcutaneous % BF M: decrease |
| Citation                     | Experimental animals | Exercise program                                                                 | Diet restriction | Duration of intervention | WAT used in experiment | Effects of TR on expression of adipokines in WAT | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|------------------------------|-----------------------|-----------------------------------------------------------------------------------|------------------|--------------------------|------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------|
| (a) Continued.              |                       |                                                                                   |                  |                          |                        |                                                 |                                                                                           |
| Lira et al. [29]            | Rats chow diet        | Treadmill running on 5 times/week at 55–65% VO₂ max. On the first day of training, all rats ran for 30 min. On the subsequent days of training, running time was extended 10 min each day until rats were running 60 min/day. | None             | 9 weeks                  | Retroperitoneal and mesenteric WAT | Retroperitoneal WAT TNF-α protein: NS Mesenteric WAT TNF-α protein: increase ($P < 0.05$) | BM and retroperitoneal FM: decrease Mesenteric FM: NS                                        |
| Nara et al. [30]            | Rats high-sucrose diet | Voluntary wheel running                                                             | None             | 4 and 12 weeks           | Mesenteric and subcutaneous WAT | Mesenteric WAT Exercise for 4 and 12 weeks TNF-α mRNA: increase ($P < 0.05$) TNF-α protein: increase ($P < 0.05$) Subcutaneous WAT Exercise for 4 and 12 weeks TNF-α mRNA: NS TNF-α protein: NS | Exercise for 4 weeks BM: NS Mesenteric and subcutaneous FM: decrease                        |
| Miyazaki et al. [31]        | Rats chow diet        | Treadmill running on 5 times/week. On the first day of training, all rats ran for 30 min at 15 m/min, and then running time and velocity were extended until rats were running for 90 min at 30 m/min. | None             | 9 weeks                  | Epididymal, retroperitoneal, and inguinal WAT | Epididymal adipocyte Leptin mRNA: NS Adiponectin mRNA: increase ($P < 0.05$) Retroperitoneal adipocyte Leptin mRNA: NS Adiponectin NS Inguinal adipocyte Leptin mRNA: NS Adiponectin mRNA: increase ($P < 0.05$) | BM: decrease epididymal, retroperitoneal, and inguinal FM: decrease                       |
| (b) Human studies           |                       |                                                                                   |                  |                          |                        |                                                 |                                                                                           |
| Citation                     | Subjects              | Exercise program                                                                 | Diet restriction | Duration of intervention | WAT used in experiment | Effects of TR on expression of adipokines in WAT | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
| Christiansen et al. [32]    | Obese exercise (9 m, 10 f) | Aerobic exercise for 65–75 min on 3 times/week (energy expenditure of 500–600 kcal/session) | None             | 12 weeks                 | Abdominal subcutaneous WAT | Leptin mRNA: NS TNF-α mRNA: NS MCP-1 mRNA: NS Adiponectin mRNA: increase ($P < 0.01$) IL-6 mRNA: NS | BM and BMI: NS Changes in body weight after intervention were 3.5% |
| Citation       | Subjects                        | Exercise program                                                                 | Diet restriction                                                                 | Duration of intervention | WAT used in experiment | Effects of TR on expression of adipokines in WAT | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|---------------|---------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------|------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Christiansen et al. [32] | Obese exercise + hypocaloric diet (10 m, 11 f) | Same as above                                                                   | Very low energy diet (800 kcal/day) for 8 weeks followed by a weight maintenance diet for 4 weeks | 12 weeks                  | Abdominal subcutaneous WAT                                                      | Leptin mRNA: decrease ($P < 0.01$)  
TNF-α mRNA: NS  
MCP-1 mRNA: NS  
Adiponectin mRNA: increase ($P < 0.01$)  
IL-6 mRNA: NS  
Leptin mRNA: decrease ($P < 0.01$)  
TNF-α mRNA: NS  
MCP-1 mRNA: NS  
Adiponectin mRNA: increase ($P < 0.01$)  
IL-6 mRNA: NS                                                                 | BM and BMI: NS changes in body weight after intervention were 11.1% |
|               | Obese hypocaloric diet (10 m, 9 f) | None                                                                            | Very low energy diet (600 kcal/day) for 8 weeks followed by a weight maintenance diet for 4 weeks | 12 weeks                  | Abdominal subcutaneous WAT                                                      |                                                                                               | BM and BMI: NS changes in body weight after intervention were 10.5% |
| Bruun et al. [33] | Obese (11 m, 12 f)             | Exercise training consisted of at least 2-3 h of moderate intensity physical activity (e.g., walking, swimming, aerobics) on 5 times/week | Hypocaloric diet calculated to reduce the subject’s body weight by ~1%/week       | 15 weeks                  | Abdominal subcutaneous WAT                                                      | TNF-α mRNA: decrease ($P < 0.01$)  
MCP-1 mRNA: NS  
Adiponectin mRNA: increase ($P < 0.001$)  
IL-6 mRNA: decrease ($P < 0.05$)                                                                 | BM, BMI, and FM: decrease                                                                 |

Results are reported as mean ± SD or SE; $P$ value reported for sedentary control group versus exercise trained group or pre- versus postvalues. f: female; HFD: high fat diet; m: male; NS: not significant; $\dot{VO}_2$ max: maximal oxygen uptake; WAT: white adipose tissue.
exercise sessions had no effect on the expression of mRNA for leptin in subcutaneous WAT (Table 1) [32]. On the other hand, there have been many studies on the effects of TR on the human blood levels of leptin (Table 2) [34–50]. Many cases have shown that concentrations of leptin decrease a reduction in WAT mass (Table 2) [34, 36, 41–45, 47, 48]. By contrast, when no significant differences are observed in blood leptin levels after TR, neither is body fat reduced (Table 2) [34, 35, 39]. Therefore, the reduced blood concentration of leptin after TR is due more to the reduction in body fat caused by TR than to the effects of TR itself. Some studies, however, suggest that a longer duration (≥12 weeks) of TR or TR with caloric restriction can contribute to a reduction in blood leptin concentration that is independent of the influence of body fat reduction (Table 2) [34, 37, 40, 46].

Several studies have also concentrated on the effects of resistance training, such as the bench press exercise, on blood leptin levels (Table 2). One study on postmenopausal obese women found that after performing three days a week of resistance training using machines and restricting diet for 16 weeks, blood leptin levels were decreased compared with pretraining levels, but that resistance training alone had no effect on leptin [49]. However, when elderly individuals were divided into low intensity (45–50% 1 repetition maximum [RM]), moderate intensity (60–65% 1 RM), and high intensity (80–85% 1 RM) groups and performed 60-minute exercise sessions three times a week for 6 months, blood leptin levels were lower in all the groups compared with the respective pretraining levels, and the magnitude of this decrease was significantly greater in the high intensity group than in the low and moderate intensity groups [50]. Furthermore, although blood leptin levels were higher at six months after the end of training than immediately after the end of training, the levels remained significantly lower than their pretraining values in the high intensity group [50].

3.2. TNF-α. Since the discovery that gene expression of the major inflammatory cytokine TNF-α is elevated in WAT in animal models of obesity, there have been many studies on its involvement in insulin resistance and its other actions [51, 52]. Expression of TNF-α increases not only in the WAT of obese animals, but also in that of obese humans; that is, TNF-α has a strong positive correlation with body mass index (BMI) and blood insulin levels [53–55]. TNF-α weakens insulin signaling by insulin receptor substrate 1-mediated inhibition of insulin receptor tyrosine kinase activity in areas such as skeletal muscle and causes reduced expression of glucose transporters and adiponectin in adipocytes, which contributes to the development of insulin resistance [56–58].

There is no clear consensus regarding the effects of TR on TNF-α in WAT (Table 1). For example, increased expression of TNF-α in visceral WAT in mice that became obese after six weeks of consuming a high-fat diet can be suppressed by spontaneous running [25, 26]. Additionally, our studies showed that nine weeks of treadmill running decreased the TNF-α protein content of the rat WAT [27, 28], but some results have shown a contrasting increase after TR [24, 29, 30]. Studies regarding obese individuals have also examined the effects of TR on TNF-α expression in WAT. Although one study found that TNF-α expression in the subcutaneous WAT of severely obese male and female adults decreased after 15 weeks of performing TR, such as walking for five days a week and undergoing diet therapy; a conflicting study on obese adults found that there was no change in TNF-α mRNA expression in subcutaneous WAT even when weight or body fat decreased after 12 weeks of aerobic exercise [32, 33].
| Citation          | n, gender | Group                          | Exercise program                                                                 | Diet restriction | Duration of intervention | Preleptin (ng/mL) | Postleptin (ng/mL) | P-value | Changes of body mass (BM), BMI, fat mass index (FFM), fat mass (% BM) |
|-------------------|-----------|--------------------------------|----------------------------------------------------------------------------------|------------------|--------------------------|------------------|-------------------|---------|---------------------------------------------------------------|
| Houmard et al.    | 7 m, 9 f  | Younger lean subjects with max for 60 min | Cycle ergometer at 70–75% $\dot{V}O_2$ max for 60 min                             | None             | 7 days                   | 7.6 ± 1.3         | 7.1 ± 1.3         | NS      | BM: NS                                                        |
|                   | 6 m, 8 f  | Older subjects with relatively more adipose tissue | Same as above                                                                  | None             | 7 days                   | 11.0 ± 1.3        | 11.2 ± 2.7        | NS      | BMI: increase                                                |
| Halle et al.      | 20 m      | Obese with T2DM                 | Cycle ergometer for 30 min on 5 times/week at 70% $\dot{V}O_2$ max for 60 min    | None             | 4 weeks                  | 7.9 ± 4.4         | 5.6 ± 3.5         | P < 0.001 | BMI: decrease                                                |
|                   |           |                                 | Same as above                                                                  | Diet consisted of a 1,000-kcal diabetic diet with a carbohydrate content of ~50%, a fat content of ~25%, and a protein content of ~25% | 6 weeks                  | 7.2 ± 3.6         | 5.5 ± 3.5         | NS      | BM, BMI, and %                                                |
| Ishii et al.      | 9 m, 14 f | T2DM exercise training with diet therapy | Walking and cycle ergometer exercise at 50% of $\dot{V}O_2$ max for 60 min       | T2DM diet therapy | 6 weeks                  | 7.2 ± 3.6         | 4.6 ± 2.5         | NS      | BM, BMI, and %                                                |
|                   |           |                                 | Exercise at 50% of $\dot{V}O_2$ max for 60 min and at least 5 times/week         | Diet (54% carbohydrate, 22% protein, 20% fat) | 6 weeks                  | 7.2 ± 3.6         | 5.6 ± 2.9         | NS      | BM, BMI, and %                                                |
|                   |           |                                 | Same as above                                                                  | Diet consisted of a 25% carbohydrate, 25% protein, and 50% fat content          | 6 weeks                  | 6.9 ± 3.4         | 5.6 ± 2.9         | NS      | BM, BMI, and %                                                |
| Kraemer et al.    | 8 m       | T2DM exercise control          | Endurance exercise (75% $\dot{V}O_2$, peak 45 min) twice a week, intermittent exercise (five 2 min exercises at 85% $\dot{V}O_2$, peak separated by 3 min exercises at 50% $\dot{V}O_2$, peak) once a week on a cycle ergometer | None             | 8 weeks                  | 7.26 ± 3.85       | 740 ± 3.95        | NS      | BM and BMI: NS, Visceral and subcutaneous adipose tissue (cm²): NS |
|                   | 14 f      | T2DM exercise control          | Endurance exercise (75% $\dot{V}O_2$, peak 45 min) twice a week, intermittent exercise (five 2 min exercises at 85% $\dot{V}O_2$, peak separated by 3 min exercises at 50% $\dot{V}O_2$, peak) once a week on a cycle ergometer | None             | 8 weeks                  | 6.05 ± 4.20       | 5.60 ± 4.30       | NS      | BM and BMI: NS, Visceral and subcutaneous adipose tissue (cm²): NS |
|                   | 16 f      | T2DM exercise control          | Endurance exercise (75% $\dot{V}O_2$, peak 45 min) twice a week, intermittent exercise (five 2 min exercises at 85% $\dot{V}O_2$, peak separated by 3 min exercises at 50% $\dot{V}O_2$, peak) once a week on a cycle ergometer | None             | 8 weeks                  | 7.26 ± 3.85       | 740 ± 3.95        | NS      | BM and BMI: NS, Visceral and subcutaneous adipose tissue (cm²): NS |
| Kraemer et al.    | 16 f      | T2DM exercise control          | Endurance exercise (75% $\dot{V}O_2$, peak 45 min) twice a week, intermittent exercise (five 2 min exercises at 85% $\dot{V}O_2$, peak separated by 3 min exercises at 50% $\dot{V}O_2$, peak) once a week on a cycle ergometer | None             | 8 weeks                  | 6.05 ± 4.20       | 5.60 ± 4.30       | NS      | BM and BMI: NS, Visceral and subcutaneous adipose tissue (cm²): NS |
|                   | 16 f      | T2DM exercise control          | Endurance exercise (75% $\dot{V}O_2$, peak 45 min) twice a week, intermittent exercise (five 2 min exercises at 85% $\dot{V}O_2$, peak separated by 3 min exercises at 50% $\dot{V}O_2$, peak) once a week on a cycle ergometer | None             | 8 weeks                  | 7.26 ± 3.85       | 740 ± 3.95        | NS      | BM and BMI: NS, Visceral and subcutaneous adipose tissue (cm²): NS |
Table 2: Continued.

| Citation            | n, gender | Group       | Exercise program                                                                 | Diet restriction | Duration of intervention | Preleptin (ng/mL) | Postleptin (ng/mL) | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BF) |
|---------------------|-----------|-------------|----------------------------------------------------------------------------------|------------------|--------------------------|-------------------|-------------------|---------|------------------------------------------------------------------------------------------|
| Hickey et al. [40]  | 9 m       | Middle aged sedentary | Exercise training consists of overground and/or treadmill walking and/or running for 45 min on 4 times/week at 85% HRM | None             | 12 weeks                 | NS                | 12 weeks          | NS      | BM, FM, and % FM: NS                                                                      |
|                     | 9 f       | Middle aged sedentary | Same as above                                                                    | None             | 12 weeks                 | Decrease of 175%   | P < 0.05          | BM, FM, and % FM: NS |
| Ozcelik et al. [41] | 14 f      | Obese       | Cycle ergometer for approximately 45 min on 3-4 times/week. Training exercise intensity was established using the anaerobic threshold. | None             | 12 weeks                 | 23.62 ± 3.5       | 13.13 ± 3.4       | P = 0.0001 | BM, BMI, and FM: decrease                                                               |
| Polak et al. [42]   | 25 f      | Obese premenopausal | Aerobic exercise (aerobic exercise performed in gymnasium and cycleergometer) for 45 min on 5 times/week at 50% VO₂ max | None             | 12 weeks                 | 24.3 ± 8.7        | 18.1 ± 8.3        | P < 0.001 | BM, BMI, and % BFM: decrease                                                             |
| Okazaki et al. [43] | 15 f      | Obese       | Cycle ergometer or indoor walking for 30 min and low-impact aerobics for 30 min at 50% VO₂ max | Mild hypocalbolic diet | 12 weeks                 | 14.7 ± 5.3        | 8.9 ± 3.6         | P < 0.001 | BM, BMI, and FM: decrease                                                               |
|                     | 26 f      | Nonobese    | Same as above                                                                    | Same as above    | 12 week                  | 7.6 ± 3.9         | 5.6 ± 2.2         | P < 0.01  | BM, BMI, and FM: decrease                                                               |
| Pérusse et al. [44] | 51 m      | Sedentary adult | The subjects worked on cycle ergometer at an intensity corresponding to 55% of VO₂ max for 30 min per session at the beginning, increasing progressively toward an intensity of 75% of VO₂ max for 50 min during the last 6 weeks of the training protocol. | None             | 20 weeks                 | 4.6 ± 4.4         | 3.9 ± 4.2         | P = 0.004 | BMI: NS; FM and % BFM: decrease                                                           |
|                     | 46 f      | Same as above | None                                                                              | 20 weeks         | NS                       | 11.9 ± 8.5        | 12.4 ± 8.1        | NS      | BM, BMI, and % BFM: NS                                                                   |
| Kondo et al. [45]   | 8 f       | Nonobese control | None                                                                             | None             | 7 months                 | 6.7 ± 1.2         | 6.5 ± 2.2         | NS      | BM, BMI: NS; FM and % BFM: decrease                                                      |
|                     | 8 f       | Obese       | Exercise training (fast slope walking, slope jogging, dumbbells, stretching, leg cycling, and jumping rope) for 30–60 min at 60–70% HRR on 4-5 times/week | None             | 7 months                 | 16.4 ± 4.6        | 12.3 ± 5.4        | P < 0.05 | BM, BMI, FM, and % BFM: decrease                                                        |
| Citation | n, gender | Group | Exercise program | Diet restriction | Duration of intervention | Preleptin (ng/mL) | Postleptin (ng/mL) | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|----------|-----------|-------|------------------|-------------------|------------------------|------------------|-------------------|---------|----------------------------------------------------------------------------------|
| Reseland et al. [46] | 37 m | MS control | None | None | 1 year | 12.0 ± 10.1 | 0.5 ± 4.6 (Change) | NS | BMI, FM, and % BFM: NS |
| | 44 m | MS diet | None | Dietary counseling | 1 year | 8.7 ± 4.3 | −0.7 ± 3.0 | P < 0.05 | BMI, FM, and % BFM: decrease |
| | 48 m | MS exercise | Endurance exercise (aerobics, circuit training, and fast walking) and jogging for 60 min on 3 times/week | None | 1 year | 9.8 ± 4.9 | −0.4 ± 2.3 | NS | BMI: NS; FM and % BFM: decrease |
| | 57 m | MS diet + exercise | Same as above | Dietary counseling | 1 year | 9.1 ± 6.2 | −2.2 ± 2.4 | P < 0.001 | BMI, FM, and % BFM: decrease |
| Miyatake et al. [47] | 36 m | Overweight | Aerobic exercise (walking, aerobic dance, and swimming) and resistance training (leg extension and leg flexion) for 90 min at 50–65% HRM | None | 1 year | 6.7 ± 4.0 | 5.1 ± 3.1 | P < 0.01 | BMI, BMI, FM, and % BFM: decrease |
| Hsieh and Wang [48] | 22 m, 30 f | Younger T2DM | Endurance exercise for 20 min at 50–74% HRM | Subjects were prescribed a diet with 500 kcal/day deficit. | 1 year | 17.62 ± 3.18 | 14.00 ± 3.16 | P = 0.03 | BMI, and % BFM: decrease |
| | 20 m, 30 f | Older T2DM | Same as above | Same as above | 1 year | 17.81 ± 2.15 | 12.63 ± 2.09 | P = 0.02 | BMI, and % BFM: decrease |
| Ryan et al. [49] | 8 f | Nonobese postmenopausal women RT | Three exercise sessions/week on pneumatic variable resistance machines | None | 16 weeks | 14.6 ± 3.3 | 14.8 ± 3.0 | NS | BMI, BMI, FM, and % BFM: NS |
| | 7 f | Obese postmenopausal women RT + WL | Same as above | Dietar counseling and energy restriction (hypocaloric diets) | 16 weeks | 22.9 ± 3.9 | 14.6 ± 2.6 | P < 0.01 | BMI, BMI, FM, and % BFM: decrease |
| Fatouros et al. [50] | 10 m | Overweight elderly control | None | None | 24 weeks | 9.5 ± 0.8 | 9.4 ± 0.7 | NS | BM and BMI: NS |
| | 14 m | Overweight elderly low-intensity RT | RT for approximately 60 min on 3 times/week at 45–50% of 1RM | None | 24 weeks | 9.1 ± 0.7 | 8.8 ± 0.7 | P < 0.05 | BM: NS; BMI: decrease |
| | 12 m | Overweight elderly moderate-intensity RT | RT for approximately 60 min on 3 times/week at 60–65% of 1RM | None | 24 weeks | 8.9 ± 0.6 | 8.7 ± 0.4 | P < 0.05 | BM: NS; BMI: decrease |
| | 14 m | Overweight elderly high-intensity RT | RT for approximately 60 min on 3 times/week at 80–85% of 1RM | None | 24 weeks | 9.7 ± 0.6 | 7.8 ± 0.6 | P < 0.05 | BM: NS; BMI: decrease |

Results are reported as mean ± SD or SE; P value reported for pre- versus postvalues. f: female; HRM: heart rate maximum; m: male; NS: not significant; RM: repetition maximum; RT: resistance training; T2DM: type 2 diabetes; VO2 max: maximal oxygen uptake; WL: weight loss.
There are also conflicting results for the blood concentrations of TNF-α (Table 3) [33, 42, 45, 59–63]. A study on diabetic patients showed that although there is no change in blood TNF-α concentration after four weeks of dietary restrictions and walking TR in nonobese diabetic patients, the concentration decreased in obese patients [59]. Furthermore, when obese adult women exercised on a bicycle ergometer for 30 minutes a day, five days a week at 70% VO₂ max for 12 weeks, decreases in blood concentrations of both TNF-α and soluble TNF receptor 2 were observed in both the women with insulin resistance and those without [60]. In another study, however, a 15-week combination of diet therapy and TR did not affect the TNF-α level in obese individuals [33]. In yet another study, 12 weeks of endurance TR actually increased the blood concentration of TNF-α in adult women [61].

3.3. MCP-1. MCP-1, which is identified as a monocyte chemotactic factor, shows increased expression in the WAT of obese mice, and elevated MCP-1 contributes to inflammatory changes by inducing macrophage infiltration into WAT via its receptor, C-C chemokine receptor-2, which is expressed in monocytes and macrophages [70, 71]. In mice that are genetically modified to only express MCP-1 excessively in adipocytes, infiltration into visceral WAT by macrophages is elevated when compared with control mice, and there is increased expression of macrophage markers and TNF-α genes in the tissue, as well as increased insulin resistance [70, 71]. Mice that consume a high-fat diet show increased expression of MCP-1 mRNA in visceral WAT, but this expression is suppressed by six weeks of spontaneous running activity (Table 1) [25]. Additionally, other studies where mice both consumed a high-fat diet and underwent treadmill running, MCP-1 mRNA expression, which had increased due to the mouse’s high-fat diet, was reduced by TR (Table 1) [26]. Moreover, nine weeks of treadmill running has reduced MCP-1 protein levels in rat subcutaneous and visceral WAT (Table 1) [27]. However, there were no changes in expression of mRNA for MCP-1 either in the subcutaneous and visceral WAT of rats that performed four weeks of spontaneous running or in the subcutaneous WAT of obese humans who performed 12 weeks of aerobic exercise (Table 1) [24, 32].

There seems to be consensus that TR diminishes blood levels of MCP-1 (Table 3). The blood concentration of MCP-1 was reduced in rats by nine weeks of treadmill running TR [27]. Studies on human patients with metabolic syndrome [64] and obese individuals [32] have also shown reductions and downward trends in MCP-1 after 12 weeks of TR. A 15-week combination of TR and diet therapy also reduced the blood concentration of MCP-1 in obese individuals [33].

3.4. Adiponectin. Adiponectin increases fatty acid oxidation and glucose uptake in skeletal muscle and inhibits gluconeogenesis in the liver [72, 73]. Adiponectin also inhibits the expression and secretion of TNF-α in macrophages and increases the production of anti-inflammatory cytokines such as interleukin (IL)-10 [74]. Therefore, adiponectin is thought to have anti-inflammatory effects. In accordance with that function, the expression of mRNA for adiponectin is reduced in the WAT of genetically obese mice and obese humans, and both obese individuals and diabetic patients have a lower blood concentration compared with healthy individuals [75, 76]. Insulin resistance and hypertension are improved when KKAy mice (mouse models of obesity and diabetes) are administered physiological concentrations of adiponectin, and insulin resistance is observed in KO mice deficient in adiponectin, suggesting that obesity-induced decreases in adiponectin expression in WAT are closely associated with the development of insulin resistance and the onset of diabetes [72, 73].

A 15-week combination of TR and diet therapy or 12 weeks of aerobic exercise has shown increases in the expression of mRNA for adiponectin in the subcutaneous WAT of obese individuals (Table 1) [32, 33]. In studies on rats, nine weeks of treadmill running has increased the mRNA expression in visceral and subcutaneous adipocytes (Table 1) [31]. In at least one study, short periods of consuming a high-fat diet increased adiponectin expression in the subcutaneous WAT of rats, and TR by spontaneous running activity suppressed this increase. That study found no effect of TR on adiponectin mRNA expression in visceral WAT (Table 1) [24].

As with leptin, there have been many studies on the effects of TR on the blood levels of adiponectin (Table 4) [32, 33, 38, 42, 45, 50, 65–69]. Although most indicate that there is no change, some studies show that it increases, so there is no consensus on this point. Hulver et al. [69] found that the blood concentration of adiponectin did not change after obese adults performed aerobic exercises such as running at 65–85% VO₂ max four times a week over a period of six months. Another study on diabetic men also found no change in the blood concentration of adiponectin after eight weeks of performing aerobic exercise three times a week, even though the amount of visceral fat decreased [38]. Even after elderly obese men and women performed TR for 60 minutes on a treadmill or bicycle ergometer at 80–85% of their maximum heart rate five times a week for 12 weeks, there was no change in the blood concentration of adiponectin despite the decreases in BMI and body fat [67]. Contrary studies have found that 60 minutes of TR, such as running performed four times a week for four weeks, has led to increases in the blood concentration of adiponectin along with decreases in body fat in diabetics and individuals presenting impaired glucose tolerance [65]. In a similar manner, the blood concentration of adiponectin has been increased along with reduced BMI and body fat mass after seven months of TR such as slope jogging and dumbbells performed four to five times a week in obese young women [45].

3.5. IL-6. IL-6 is a cytokine that has a variety of functions such as regulating hematopoiesis, immune response, and inflammatory response. This cytokine also is known to have anti-inflammatory effects, and may have both proinflammatory and anti-inflammatory properties [77, 78]. Diabetic and obese individuals have high blood concentrations of IL-6, and its mRNA expression is elevated in the subcutaneous adipocytes of individuals presenting insulin resistance. Furthermore, IL-6 acts on adipocytes to inhibit insulin signaling [79, 80].
### Table 3: Effects of exercise training on human blood levels of TNF-α and MCP-1.

#### (a) TNF-α

| Citation            | $n$, gender | Group                     | Exercise program                                                                 | Diet restriction                                      | Duration of intervention | Pre-TNF-α (pg/mL) | Post-TNF-α (pg/mL) | $P$ value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|---------------------|-------------|---------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------|--------------------------|-------------------|-------------------|------------|------------------------------------------------------------------------------------------|
| Katsuki et al.      | 11m, 1f     | Nonobese NIDDM            | Walking about 15,000 steps daily                                                | Dietary treatment (1400–1720 kcal/day with a diet consisting of 20 en% protein, 25 en% fat, and 55 en% carbohydrates) | 4 weeks                  | 3.88 ± 0.49       | 3.27 ± 0.54       | NS         | BMI and visceral adipose tissue area (cm²): decrease; subcutaneous adipose tissue (cm²): NS |
| Strz˙kowski et al.  | 8f          | Obese with normal glucose tolerance | Cycle ergometer for 30 min on 5 times/week at 70% HRM                         | None                                                  | 12 weeks                 | 6.59 ± 2.31       | 5.15 ± 1.19       | $P < 0.05$ | BM, BMI, FM, and % BFM: decrease                                                         |
| Kondo et al.        | 8f          | Obese                     | Exercise training (fast slope walking, slope jogging, dumbbells, stretching, leg cycling, and jumping rope) for 30–60 min at 60–70% HRM on 4-5 times/week | None                                                  | 7 months                 | 7.6 ± 2.3         | 4.8 ± 1.2         | $P < 0.01$ | BM, BMI, FM, and % BFM: decrease                                                         |
### Table 1: Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (%BFM)

| Citation       | n, gender | Group                          | Exercise program                                                                 | Diet restriction | Duration of intervention | Pre-TNF-α (pg/mL)          | Post-TNF-α (pg/mL)         | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (%BFM) |
|----------------|-----------|--------------------------------|----------------------------------------------------------------------------------|-----------------|--------------------------|-----------------------------|-----------------------------|---------|------------------------------------------------------------------------------------------|
| Horne et al. [61] | 7 m       | Healthy endurance training   | Cycle ergometers 2 times/week for 30 min and progressed to 42 min (a 4-min increase every 4 weeks) at a power output equivalent to that at ventilation threshold | None            | 12 weeks                 | 5.7 ± 4.4 (6 weeks)         | 6.0 ± 4.0 (12 weeks)         | NS      |                                                                                           |
|                | 4 f       | Same as above                | None                                                                              | 12 weeks        | 5.6 ± 3.7                | 37.8 ± 24.7 (6 weeks)       | 17.6 ± 6.4 (12 weeks)       | ^P < 0.05 | (versus pre and 6 weeks)                                                                 |
| Horne et al. [61] | 7 m       | Healthy resistance training | Resistance training by using machine on 3 times/week                              | None            | 12 weeks                 | 9.5 ± 3.0                   | 10.8 ± 4.6 (6 weeks)         | NS      |                                                                                           |
|                | 4 f       | Same as above                | None                                                                              | 12 weeks        | 2.8 ± 2.0                | 5.8 ± 2.9 (12 weeks)        | 6.6 ± 4.0 (6 weeks)          | NS      |                                                                                           |
|                | 8 m       | Healthy endurance and resistance training | Combination of above endurance and resistance training                        | None            | 12 weeks                 | 2.3 ± 1.9                   | 5.6 ± 2.9 (12 weeks)        | NS      |                                                                                           |
|                | 5 f       | Same as above                | None                                                                              | 12 weeks        | 4.5 ± 2.0                | 4.7 ± 0.5 (6 weeks)         | 5.0 ± 0.5 (12 weeks)        | NS      |                                                                                           |
| Kohut et al. [62] | 40       | Overweight aerobic exercise with or without β-blocker treatment | Aerobic exercise for 45 min on 3 times/week                                      | None            | 10 months                | Decrease                    | Decrease                    | Main effect of time, BMI: NS |
|                | 47       | Overweight flexibility/strength exercise with or without β-blocker treatment | Flexibility/strength exercise for 45 min on 3 times/week                          | None            | 10 months                | Decrease                    | Decrease                    | Main effect of time, BMI: NS |
| Citation               | n, gender | Group                      | Exercise program                                                                 | Diet restriction                           | Duration of intervention | Pre-TNF-α (pg/mL) | Post-TNF-α (pg/mL) | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|-----------------------|-----------|----------------------------|----------------------------------------------------------------------------------|--------------------------------------------|--------------------------|-------------------|--------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------|
| Nicklas et al. [63]   | Baseline: 70, 6 months: 63, 18 months: 60 | Overweight or obese older control | None                                                                             | None                                       | 18 months              | 3.8 ± 7.5        |                    | NS      | BM: NS                                                                                                                             |
|                       | Base line: 67, 6 months: 58, 18 months: 53 | Overweight or obese exercise    | Exercise program consisted of an aerobic phase (15 min), a resistance-training phase (15 min), a second aerobic phase (15 min), and a cool-down phase (15 min) on 3 times/week. | None                                       | 18 months              | 3.4 ± 0.8         |                    | NS      | BM: NS                                                                                                                             |
|                       | Base line: 71, 6 months: 63, 18 months: 53 | Overweight or obese dietary WL | None                                                                             | Counseling to decrease their energy intake by 500 kcal/day | 18 months              | 2.5 ± 1.8         |                    | NS      | BM: decrease                                                                                                                      |
|                       | Base line: 64, 6 months: 58, 18 months: 53 | Overweight or obese exercise + dietary WL | Exercise program consisted of an aerobic phase (15 min), a resistance-training phase (15 min), a second aerobic phase (15 min), and a cool-down phase (15 min) on 3 times/week. | Same as above                             | 18 months              | 3.4 ± 6.4         |                    | NS      | BM: decrease                                                                                                                      |

| Troseid et al. [64]   | MS with or without administration of pravastatin control | None | None                                             | None                                       | 12 weeks               |                    | ~2.0 (the changes from baseline in plasma levels of MCP-1) | NS      | BM: NS                                                                                                                             |
| Citation       | n, gender | Group                        | Exercise program                                                                 | Diet restriction | Duration of intervention | Pre-MCP-1 (pg/mL) | Post-MCP-1 (pg/mL) | P value | Changes of BM, BMI, FM, and % BFM |
|----------------|-----------|------------------------------|----------------------------------------------------------------------------------|------------------|--------------------------|-------------------|-------------------|---------|----------------------------------|
| Christiansen et al. [32] | 10 m, 11 f | Obese exercise + hypocaloric diet | Aerobic exercise for 65–75 min on 3 times/week (energy expenditure of 500–600 kcal/session) | None             | 12 weeks                 | Decreasing trend (Relative changes) | P = 0.06          | BM and BMI: NS                  |
|                |           |                              |                                                                                   |                  |                          |                   |                   |         | Changes in body weight after intervention were 3.5% BM and BMI: NS Changes in body weight after intervention were 11.1% BM and BMI: NS Changes in body weight after intervention were 10.5% |
|                | 10 m, 9 f | Obese hypocaloric diet       | None                                                                             | Hypocaloric diet calculated to reduce the subject's body weight by −1%/week | 12 weeks         | Decrease                      | P < 0.05         | BM and BMI: NS                  |
| Bruun et al. [33] | 11 m, 12 f | Obese                        | Exercise training consisted of at least 2-3 h of moderate intensity physical activity (e.g., walking, swimming, aerobics) on 5 times/week | Hypocaloric diet | 15 weeks                 | 141.2 ± 8.3      | 122.0 ± 6.3       | P < 0.01 | BM, BMI, and FM: decrease        |

Results are reported as mean ± SD or SE; P value reported for pre- versus post values. f: female; HRM: heart rate maximum; m: male; MS: metabolic syndrome; NIDDM: noninsulin dependent diabetes mellitus; NS: not significant; RM: repetition maximum; VO₂ max: maximal oxygen uptake; WL: weight loss.
### Table 4: Effects of exercise training on human blood levels of adiponectin.

| Citation            | n, gender | Group                   | Exercise program                                                                 | Diet restriction | Duration of intervention | Preadiponectin $(\mu g/mL)$ | Postadiponectin $(\mu g/mL)$ | $P$ value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|---------------------|-----------|-------------------------|----------------------------------------------------------------------------------|------------------|--------------------------|-----------------------------|-------------------------------|-----------|------------------------------------------------------------------------------------------|
|                     |           |                         |                                                                                  |                  |                          |                             |                               |                   |                                                                                         |
|                     |           |                         |                                                                                  |                  |                          |                             |                               |                   |                                                                                         |
| Aerobic exercise    |           |                         |                                                                                  |                  |                          |                             |                               |                   |                                                                                         |
|                     |           |                         |                                                                                  |                  |                          |                             |                               |                   |                                                                                         |
| Blüher et al. [65]  | 9 m, 11 f | Normal glucose tolerance| Exercise training consisted of 20 min of warming and cool-down periods, 20 min of running or biking, and 20 min of swimming on 3 times/week | None             | 4 weeks                  | $8.7 \pm 0.6$              | $9.8 \pm 0.6$               | $P < 0.01$ | BM, BMI, and % BFM: decrease                                                              |
|                     | 9 m, 11 f | Impaired glucose tolerance| Same as above                                                                      | None             | 4 weeks                  | $3.4 \pm 0.26$              | $6.7 \pm 0.7$               | $P < 0.001$ | BM, BMI, and % BFM: decrease                                                              |
|                     | 11 m, 9 f | T2DM                    | Same as above                                                                      | None             | 4 weeks                  | $3.5 \pm 0.4$              | $6.5 \pm 0.6$               | $P < 0.001$ | BM, BMI, and % BFM: decrease                                                              |
|                     |           |                         |                                                                                  |                  |                          |                             |                               |                   |                                                                                         |
| Oberbach et al. [66]| 9 m, 11 f | Normal glucose tolerance| Exercise training consisted of 20 min warming and cool-down periods, 20 min of running or biking, and 20 min of powertraining | None             | 4 weeks                  | NS                          |                               |                   |                                                                                         |
|                     | 9 m, 11 f | Impaired glucose tolerance| Same as above                                                                      | None             | 4 weeks                  | Increase                   | $P < 0.001$                  | BM, BMI, and % BFM: decrease                                                              |
|                     | 11 m, 9 f | T2DM                    | Same as above                                                                      | None             | 4 weeks                  | Increase                   | $P < 0.001$                  | BM, BMI, and % BFM: decrease                                                              |
|                     |           |                         |                                                                                  |                  |                          |                             |                               |                   |                                                                                         |
| Boudou et al. [38]  | 8 m       | T2DM control            | None                                                                              | None             | 8 weeks                  | $7.30 \pm 2.55$             | $7.05 \pm 2.10$             | NS                      | BM and BMI: NS; visceral and subcutaneous adipose tissue area (cm$^2$): NS                |
|                     | 8 m       | T2DM exercise           | Endurance exercise (75% VO$_2$ peak, 45 min) twice a week, with intermittent exercise (five 2 min exercises at 85% VO$_2$ peak separated by 3 min exercises at 50% VO$_2$ peak) once a week, on a cycle ergometer | None             | 8 weeks                  | $6.30 \pm 2.75$             | $6.00 \pm 3.50$             | NS                      | BM and BMI: NS; visceral and subcutaneous adipose tissue area (cm$^2$): decrease          |
| Citation        | n, gender | Group                                      | Exercise program                                                                 | Diet restriction                                                                 | Duration of intervention | Preadiponectin (μg/mL) | Postadiponectin (μg/mL) | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|-----------------|-----------|--------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------|------------------------|-------------------------|---------|------------------------------------------------------------------------------------------|
| O’Leary et al.  | 4 m, 7 f  | Older insulin-resistant exercise + hypocaloric diet | Aerobic exercise for 60 min at 80–85% HRM on 5 times/week                       | Diet with total energy content calculated to reduce body weight by 10–15% (~1,300 kcal/day). Weight maintenance diet that consisted of their usual food consumption (~1,800 kcal/day) | 12 weeks                | 7.6 ± 0.9              | 6.6 ± 1.0               | NS      | BM, BMI, and FM: decrease                                                                |
| Polak et al.    | 3 m, 7 f  | Older insulin-resistant exercise + eucaloric diet | Same as above                                                                    |                                                                                  | 12 weeks                | 7.7 ± 1.2              | 6.8 ± 1.6               | NS      | BM, BMI, and FM: decrease                                                                |
| Nassis et al.   | 25 f      | Obese premenopausal                        | Aerobic exercise (aerobic exercise performed in gymnasium and cycleergometer) for 45 min on 5 times/week at 50% VO₂ max | None                                                                                | 12 weeks                | 10.9 ± 6.1             | 10.0 ± 4.4              | NS      | BM, BMI, and % BFM: decrease                                                              |
| Christiansen et al. [32] | 21 f      | Overweight/obese girls                     | Aerobic training for 40 min (10 min of warm up, 25 min of physical training games, and 5 minutes of cool down) on 3 times/week | None                                                                                | 12 weeks                | 9.57 ± 3.0l            | 9.08 ± 2.32             | NS      | BM, BMI, and % BFM: NS                                                                    |
| Christiansen et al. [32] | 9 m, 10 f | Obese exercise                             | Aerobic exercise for 65–75 min on 3 times/week (energy expenditure of 500–600 kcal/session) | None                                                                                | 12 weeks                | NS                     |                         |         | Changes in body mass (BM) Changes in body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
| 10 m, 11 f      | Obese exercise + hypocaloric diet           | Same as above                                                                    | Very low energy diet (800 kcal/day) for 8 weeks followed by a weight maintenance diet for 4 weeks Very low energy diet (600 kcal/day) for 8 weeks followed by a weight maintenance diet for 4 weeks | 12 weeks                | Increase               | P < 0.05                |         | BM and BMI: NS Changes in body weight after intervention were 3.5%BM and BMI: NS Changes in body weight after intervention were 11.1%BM and BMI: NS Changes in body weight after intervention were 10.5% |
| 10 m, 9 f       | Obese hypocaloric diet                       | None                                                                            |                                                                                  | 12 weeks                | Increase               | P < 0.05                |         | BM and BMI: NS Changes in body weight after intervention were 3.5%BM and BMI: NS Changes in body weight after intervention were 11.1%BM and BMI: NS Changes in body weight after intervention were 10.5% |
| Citation          | n, gender | Group       | Exercise program                                                                 | Diet restriction                                                                 | Duration of intervention | Preadiponectin (µg/mL) | Postadiponectin (µg/mL) | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BF M) |
|-------------------|-----------|-------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------|-------------------------|-------------------------|---------|------------------------------------------------------------------------------------------|
| Bruun et al. [33] | 11 m, 12 f| Obese       | Exercise training consisted of at least 2-3 h of moderate intensity physical activity (e.g., walking, swimming, aerobics) on 5 times/week | Hypocaloric diet calculated to reduce the subjects body weight by ~1%/week       | 15 weeks                | 5.2 ± 0.6               | 6.9 ± 0.5               | P < 0.001 | BM, BMI, and FM: decrease                                                                  |
| Hulver et al. [69]| 8 m, 3 f  | Nonobese    | Treadmill walking/running, stair climbing, and cycling for 45 min at 65–80% VO₂ max on 4 times/week | None                                                                               | 6 months                | 6.3 ± 1.5               | 6.6 ± 1.8               | NS       | BM, BMI, and FM: NS                                                                        |
|                   | 3 m, 11 f | Obese weight loss | None                                                                                         | Gastric bypass surgery                                                            | 6 months                | 4.4 ± 0.8               | 13.6 ± 2.2              | P < 0.05 | BM and BMI: decrease                                                                      |
| Kondo et al. [45] | 8 f       | Nonobese control | Exercise training (fast slope walking, slope jogging, dumbbells, stretching, leg cycling, jumping rope) for 30–60 min at 60–70% HRM on 4-5 times/week | None                                                                               | 7 months                | 8.3 ± 1.5               | 8.2 ± 2.3               | NS       | BM, BMI: NS; FM and % BF M: decrease                                                        |
| Hsieh and Wang  [48]| 22 m, 30 f| Younger T2DM | Endurance exercise for 20 min at 50–74% HRM                                               | Subjects were prescribed a diet with 500 kcal/day deficit.                        | 1 year                  | 4.13 ± 0.88             | 5.47 ± 0.59             | P = 0.04 | BMI, and % BF M: decrease                                                                  |
|                   | 20 m, 30 f| Older T2DM   | Same as above                                                                                 | Same as above                                                                      | 1 year                  | 4.26 ± 0.97             | 6.56 ± 0.86             | P = 0.03 | BMI, and % BF M: decrease                                                                  |
| Fatouros et al. [50] |          | Resistance exercise | None                                                                                         | Resistance training for approximately 60 min on 3 times/week at 45–50% of 1RM     | 24 weeks                | 7.22 ± 2.7              | 7.84 ± 3.5              | NS       | BM and BMI: NS                                                                            |
|                   | 10 m      | Overweight elderly control | None                                                                                         | Resistance training for approximately 60 min on 3 times/week at 45–50% of 1RM     | 24 weeks                | 7.45 ± 2.3              | 8.48 ± 2.2              | NS       | BM: NS; BMI: decrease                                                                    |
|                   | 14 m      | Overweight elderly low-intensity RT | None                                                                                         | Resistance training for approximately 60 min on 3 times/week at 60–65% of 1RM     | 24 weeks                | 7.79 ± 1.4              | 9.48 ± 1.1              | P < 0.05 | BM: NS; BMI: decrease                                                                    |
|                   | 12 m      | Overweight elderly moderate-intensity RT | None                                                                                         | Resistance training for approximately 60 min on 3 times/week at 80–85% of 1RM     | 24 weeks                | 7.04 ± 1.6              | 11.36 ± 1.6             | P < 0.05 | BM: NS; BMI: decrease                                                                    |
|                   | 14 m      | Overweight elderly high-intensity RT | None                                                                                         | Resistance training for approximately 60 min on 3 times/week at 80–85% of 1RM     | 24 weeks                | 7.04 ± 1.6              | 11.36 ± 1.6             | P < 0.05 | BM: NS; BMI: decrease                                                                    |

Results are reported as mean ± SD or SE; P value reported for pre- versus post values. F: female; HRM: heart rate maximum; m: male; NS: not significant; RM: repetition maximum; RT: resistance training T2DM; type 2 diabetes; VO₂ max: maximal oxygen uptake.
Many studies show that IL-6 levels increase in response to acute exercise; for instance, a single bout of exercise has increased the blood concentration of IL-6 more than 100 times. However, this increase in blood concentration was not due to increased production by WAT, but rather by increased production in skeletal muscle, an organ that produces IL-6 [78, 81]. A 15-week combination of TR and diet therapy reduces the expression of mRNA for IL-6 in the subcutaneous WAT of obese individuals (Table 1) [33]. However, although some studies show that the blood concentration of IL-6 decreases after TR, other studies have shown no change, so yet again there is no consensus (Table 5) [33, 42, 62, 63, 66, 68, 78].

4. The Relationship between TR-Induced Changes in Adipokine Expression and WAT Mass

The size of WAT (adipocytes) greatly affects the expression of adipokines. As for leptin, mRNA expression and secretion are positively correlated with the size of adipocytes isolated from rodents and humans [31, 75, 76, 83]. Similarly, in isolated adipocytes of humans, secretion of TNF-α, MCP-1, and IL-6 is positively correlated with cell size, and after correction for the cell surface, there is still a significant difference between very large and small adipocytes for MCP-1 and IL-6 [83]. Nevertheless, mRNA levels for TNF-α show no significant correlation with mouse adipocyte volume [84]. On the other hand, although the expression of adiponectin is reduced in the WAT of genetically obese mice and obese humans, the mRNA expression and secretion of adiponectin is positively correlated with isolated adipocyte size in rats and humans [31, 75, 76, 83]. One of the reasons for this discrepancy is speculated that reduced adiponectin expression in vivo may be the result of inflammatory adipokines, such as TNF-α, rather than increases in the size of adipocytes [58]. It is well known that TR reduces WAT mass, and, therefore, the reduction of WAT is thought to be a major factor in the effects of TR on adipokine expression in WAT (Figure 3). However, further research is needed regarding other effects of TR. Recently, an interesting study has examined the relationship between TR-induced changes in adipokine expression and WAT mass. Christiansen et al. [32] divided obese subjects into a group that underwent 12 weeks of combined aerobic exercise and diet therapy and a group that underwent diet therapy only, and after adjusting weight loss to approximate amounts, found no difference in changes in either the expression of inflammatory-related adipokines in subcutaneous WAT or in the circulating markers of inflammation; that is, TR seemed to have had no weight-independent effects in that study. On the other hand, when the authors observed a reduced level of leptin mRNA and an elevated mRNA level of adiponectin in rat visceral adipocytes after nine weeks of treadmill running, it suggested that the decrease in leptin mRNA expression depended on a reduction in adipocyte size, and that the increase in adiponectin mRNA was mediated by factor(s) other than adipocyte size [31]. In addition, Oberbach et al. [66] found that actual increases in blood adiponectin after TR were of a higher magnitude than increases in blood adiponectin levels that were predicted according to a regression line drawn from the negative correlation between body fat and the blood concentration of adiponectin.

During exercise, the secretion of catecholamines from the adrenal medulla and sympathetic nerve peripheries breaks down triglycerides within the adipocytes [12]. Several reports have indicated that β-adrenoceptor agonists affect the expression of some adipokines, such as TNF-α and adiponectin in WAT. Administration of β-adrenoceptor agonists in lean mice results in upregulation of TNF-α and downregulation of adiponectin in epididymal WAT [85, 86]. These findings seem to conflict with the beneficial effects of exercise on the disturbance of adipokines. Nevertheless, during exercise, since energy consumption is enhanced, the blockage of lipogenesis by the impaired insulin signaling in WAT might play reasonable roles in the proper execution of exercise. In contrast to lean mice, β-adrenoceptor agonists recovered the declined mRNA expression of adiponectin and suppressed the overexpressed mRNA level of TNF-α in WAT of KKAY mice [87]. Therefore, in obese and type 2 diabetic patients, it is likely that the secretion of catecholamines during exercise is one of the reasons for the attenuation of dysregulated adipokine expression in WAT (Figure 3).

Various possible mechanisms besides decreased WAT mass and secretion of catecholamines have been proposed, including decreased oxidative stress and improvement of hypoxia in WAT (Figure 3). Adipocytes have produced reactive oxygen, and obesity-induced increases in oxidative stress in WAT may be a cause of the dysregulated expression of inflammatory-related adipokines [88]. Studies have shown significantly lower levels of lipid peroxidation in WAT around the epididymis and retroperitoneum of rats that had undergone TR compared with a control group, and elevated protein levels of the antioxidant enzyme manganese superoxide dismutase (Mn-SOD) in the epididymal WAT of TR group rats [27, 28]. In that study, not only were protein levels of TNF-α and MCP-1 significantly lower in the epididymal WAT of the TR group, compared with those of the control group, the phosphorylation of extracellular signal-regulated kinase, which is activated by reactive oxygen and is important for the expression of MCP-1, also was reduced by TR in WAT around the epididymis and retroperitoneum [27, 89]. TR reduced WAT mass, which likely contributed to decreased oxidative stress in WAT. Nevertheless, because acute exercise elevates oxidative stress in the body [90], the adaptation of WAT against exposure to oxidative stress from exercise, in other words, the expansion of antioxidant systems via increases in Mn-SOD, could be one reason for decreased levels of proinflammatory adipokines.

Recent evidence that tissue hypoxia is involved in obesity-induced inflammatory changes in WAT has attracted the attention of researchers. In fact, oxygen partial pressure is lower in the WAT of obese animals and humans compared with controls, and results show that this may be related to the inflammatory response in WAT [91, 92]. Although some studies have focused on the impact of TR on blood flow in WAT, results from those studies appear to indicate that when WAT mass decreases due to TR, blood flow in the
| Citation          | n, gender | Group           | Exercise program                                                                 | Diet restriction | Duration of intervention | Pre-IL-6 (pg/mL) | Post-IL-6 (pg/mL) | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (% BFM) |
|-------------------|-----------|-----------------|----------------------------------------------------------------------------------|------------------|-------------------------|------------------|------------------|---------|----------------------------------------------------------------------------------------|
| Oberbach et al. [66] | 9 m, 11 f | Normal glucose tolerance | Exercise training consisted of 20 min warming and cool-down periods, 20 min of running or biking, and 20 min of power training | None             | 4 weeks                 | NS               | BM, BMI, and % BFM: decrease |
|                  | 9 m, 11 f | Impaired glucose tolerance   | Same as above                                                                   | None             | 4 weeks                 | NS               | BM, BMI, and % BFM: decrease |
|                  | 11 m, 9 f | T2DM                          | Same as above                                                                   | None             | 4 weeks                 | NS               | BM, BMI, and % BFM: decrease |
| Polak et al. [42] | 25 f      | Obese premenopausal          | Aerobic exercise (aerobic exercise performed in gymnasium and cycleergometer) for 45 min on 5 times/week at 50% \( \dot{V}O_2 \) max | None             | 12 weeks                | 3.1 ± 3.7        | 1.4 ± 1.5         | NS      | BM, BMI, and % BFM: decrease                                                              |
| Nassis et al. [68] | 21 f      | Overweight/obese girls        | Aerobic training for 40 min (10 min of warm up, 25 min of physical training games, and 5 minutes of cool down) on 3 times/week | None             | 12 weeks                | 1.67 ± 1.29      | 1.65 ± 1.25       | NS      | BM, BMI, and % BFM: NS                                                                    |
| Bruun et al. [33] | 11 m, 12 f | Obese                          | Exercise training consisted of at least 2-3 h of moderate intensity physical activity (e.g., walking, swimming, aerobics) on 5 times/week | Hypocaloric diet calculated to reduce the subject’s body weight by ∼1% per week | 15 weeks         | 4.6 ± 0.6         | 3.4 ± 0.6         | P < 0.01 | BM, BMI, and FM: decrease                                                                  |
| Kohut et al. [62] | 40        | Overweight aerobic exercise with or without \( \beta \)-blocker treatment | None | 10 months | Decrease | Significant treatment × time interaction. \( P < 0.05 \) | BMI: NS |
|                  | 47        | Overweight flexibility/strength exercise with or without \( \beta \)-blocker treatment | None | 10 months | NS | BMI: NS |
Table 5: Continued.

| Citation | n, gender | Group | Exercise program | Diet restriction | Duration of intervention | Pre-IL-6 (pg/mL) | Post-IL-6 (pg/mL) | P value | Changes of body mass (BM), body mass index (BMI), fat mass (FM), and % body fat mass (%BFM) |
|----------|-----------|-------|------------------|------------------|-------------------------|-----------------|------------------|---------|-----------------------------------------------------------------------------------|
| Nicklas et al. [63] | | | | | | | | | |
| Base line: 71 | 6 months: 63; 18 months: 53 | Overweight or obese | None | Counseling to decrease their energy intake by 500 kcal/day | 18 months | 4.7 ± 3.4 | Changes −0.51 ± 2.1 (6 months) −0.71 ± 2.4 (18 months) | Main effect of WL, P = 0.009 | BM: decrease |
| Base line: 64 | 6 months: 58; 18 months: 53 | Overweight or obese exercise + dietary WL | Same as above | | 18 months | 4.9 ± 3.0 | Changes −0.35 ± 2.15 (6 months) −0.35 ± 1.8 (18 months) | Main effect of WL, P = 0.009 | BM: decrease |

Results are reported as mean ± SD or SE; P value reported for pre- versus post values. f: female; HRM: heart rate maximum; m: male; NS: not significant; WL: weight loss.
tissue increases [93]. We found that expression of mRNA for vascular endothelial growth factor and its receptor was elevated in the WAT stromal vascular fraction cells of rats that had engaged in TR, and that the vascular endothelial cell count per unit area had increased [94]. Thus, the increased blood flow to WAT produced by TR eliminated the obesity-induced hypoxia in WAT and could possibly have led to a weakening of the inflammatory changes in WAT.

5. Can TR That Does Not Alter Body and WAT Mass Alleviate Dysregulated Expression of Adipokines?

In many of the previous studies that examined the effects of TR on adipokine expression in WAT and on the blood levels of adipokines in human subjects, body mass, BMI, or WAT mass reduction is observed (Tables 1–5). For this reason, it remains unknown whether or not low-intensity TR that does not entail such reduction alters adipokine expression in WAT or blood adipokine levels. As described in the previous chapter, adipokine expression is affected by the size of the WAT (adipocyte). Among adipokines, expression of leptin seems to be especially largely affected by adipocyte size [82–84]. In studies that examined the effect of TR on the blood leptin level in human subjects, results indicated that, in many cases, blood leptin levels do not change without a reduction in body fat; that is, decreased blood leptin levels are thought to be caused by exercise-induced WAT mass reduction (Table 2) [34, 36, 41–45, 47]. In contrast, some studies have reported that the reduced blood leptin level shows beneficial effects of TR without WAT mass reduction.
For example, studies on adult males and females have shown that only the female subjects exhibit reduced blood leptin levels without body fat loss after undergoing 12 weeks of TR [40]. Similarly, Ishii et al. [37] have demonstrated that TR in type 2 diabetic subjects reduces serum leptin levels independent of changes in body fat mass. On the other hand, increased blood adiponectin level through TR is also accompanied by reductions in body mass, BMI, or WAT mass (Table 4) [33, 45, 48, 65, 66]. Although Hsieh and Wang [48] observed that the adiponectin level was significantly elevated in type 2 diabetes patients who performed low-intensity TR (20 min/day, 50–74% maximum heart rate) and adequate calorie restriction for one year, this particular study showed that body mass reduction seemed to be beneficial for increases in adiponectin. However, other reports indicate that blood adiponectin levels do not change if body mass is decreased [38, 42, 67]. Thus, it is difficult to conclude at this stage whether loss of body and/or WAT mass is indispensable for adiponectin elevation. Moreover, the effects on TR-induced body and WAT mass reduction may differ depending on the type of adipokine. Taken together, these results show that although further examination is necessary, it is conceivable that changes in adipokine expression in WAT and blood adipokine level require TR that is sufficiently intense to reduce body mass or more specifically WAT mass.

6. Changes in Skeletal Muscle through TR and Its Impact on Expression of Adipokines in WAT

Skeletal muscle is responsible for physical exercise, and it is the largest tissue in the body. Undernutrition, aging, and sickness cause a decline in skeletal muscle mass (a condition known as muscular atrophy), deteriorating one’s exercise capacity [95, 96]. Moreover, skeletal muscle has a substantial impact on the overall metabolism of the body. For instance, skeletal muscles in patients with obesity and type 2 diabetes have reduced glucose metabolic capacity due to insulin resistance [97], and these observations are considered to be associated with the patients’ clinical conditions. Many studies have shown that TR can increase mitochondrial proliferation and boost the expression of a glucose transporter 4 (GLUT4), and can in turn enhance lipid and glucose metabolic capacities [98–100]. Among the molecules involved in exercise-induced enhancement of glucose/lipid metabolic capacity in skeletal muscle, AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) have been gaining a great deal of attention.

AMPK is an enzyme that is activated when ATP is converted to AMP and is a sensor of energy status that maintains cellular energy homeostasis [101, 102]. Skeletal muscle AMPK is activated by muscle contraction [103], treadmill running [104], and stimulation by its agonist aminoimidazole carboxamide ribonucleotide (AICAR) [105]. Upon activation, AMPK induces the phosphorylation of downstream effectors to elevate glucose uptake. Glucose uptake elevation has been associated with the induction of GLUT4 translocation to the cell membrane [106–108]. AMPK activity has also been reported to be involved in fatty acid uptake through the fatty acid translocase FAT/CD36 and fatty acid oxidation mediated by reduced acetyl-CoA carboxylase enzymatic activity [103, 109]. TR has been shown to enhance both expression and activation of AMPK in skeletal muscle, and chronic AMPK activation in skeletal muscle can increase the number of mitochondria even in the absence of TR, suggesting that TR-induced AMPK activation is strongly involved in the increase in the mitochondria of skeletal muscle [110, 111]. However, a conclusion is yet to be drawn because AMPK KO mice that underwent TR also showed increases in skeletal muscle mitochondria [112].

Transcription coactivator PGC-1α forms a complex with nuclear receptors and transcription factors to regulate gene transcriptions, or more specifically, expression of genes involved in mitochondrial biosynthesis [113–115]. In fact, mice with PGC-1α overexpression showed (1) increased number of mitochondria, (2) enhanced expressions of oxidizing enzymes such as cytochrome oxidase in skeletal muscle, and (3) transition to type I muscle fibers [114, 115]. Physical exercise increases PGC-1α transcription and potentially PGC-1α activity through posttranslational modifications, and concomitant PGC-1α-mediated gene regulation is suggested to be an underlying mechanism for adaptations in skeletal muscle, when exercise is repeated [115].

Muscle consumes the most energy out of all tissues in the body. Therefore, increases in mitochondria and increased insulin sensitivity in skeletal muscle by endurance TR are thought to dramatically impact the energy consumption of the whole body. Moreover, enhanced glucose/lipid metabolism in skeletal muscle is considered to be indirectly involved in WAT reduction, which results in altered adipokine expression (Figure 3). Additionally, because resting metabolic rate (RMR), which is the largest component of the daily energy budget in most human societies, is reportedly elevated owing to both aerobic and resistance training in human subjects, although some studies have failed to find such an effect [116], enhanced RMR is likely to cause alteration of adipokine expression following WAT mass reduction due to increased energy expenditure in the resting state (Figure 3). Nevertheless, the detailed mechanisms and whether mediators, such as myokines, from skeletal muscle act on the existence of WAT remain unknown. On the other hand, it is interesting that evidence is mounting on the new effects of adipokine on skeletal muscle metabolic capacity. Recent observation of KO mice showed that a lack of adiponectin receptor in their skeletal muscle showed a reduced mitochondrial content, reduced type I muscle fibers, and decreased capacity for exercise, suggesting that adiponectin is involved in mitochondrial biogenesis in skeletal muscles [117]. Furthermore, there is a significant positive correlation between blood adiponectin level and AMPK activity in the lateral great muscles in men [118]. In the future, it is crucial to examine the effect of TR on adipokine expression not only in WAT alone but also in terms of cross-talk between WAT and other tissues involving skeletal muscle. Further investigations are warranted.
7. Conclusions

Although reports on the effects of exercise on adipokine levels in WAT and blood may not always agree due to differences in experimental subjects, exercise intensity, or exercise duration, it is reasonable to believe that there is at least a positive effect. Although TR-induced WAT reduction is one of the key reasons for attenuation of deregulated expression of adipokines, detailed studies about not only WAT-reducing effects of TR but also other effects, such as antioxidative effects and angiogenic effects, will be necessary to show the usefulness and distinctiveness of TR. Furthermore, it may be significantly beneficial to examine the cross-talk between WAT and other tissues involving skeletal muscle and to what degree WAT contributes to TR-induced changes in blood adipokine levels. Because the importance of exercise as a tool for preventing and improving obesity and lifestyle-related diseases can be expected to grow in the future, further research is desirable.

Conflict of Interests

The authors have no conflict of interests.

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