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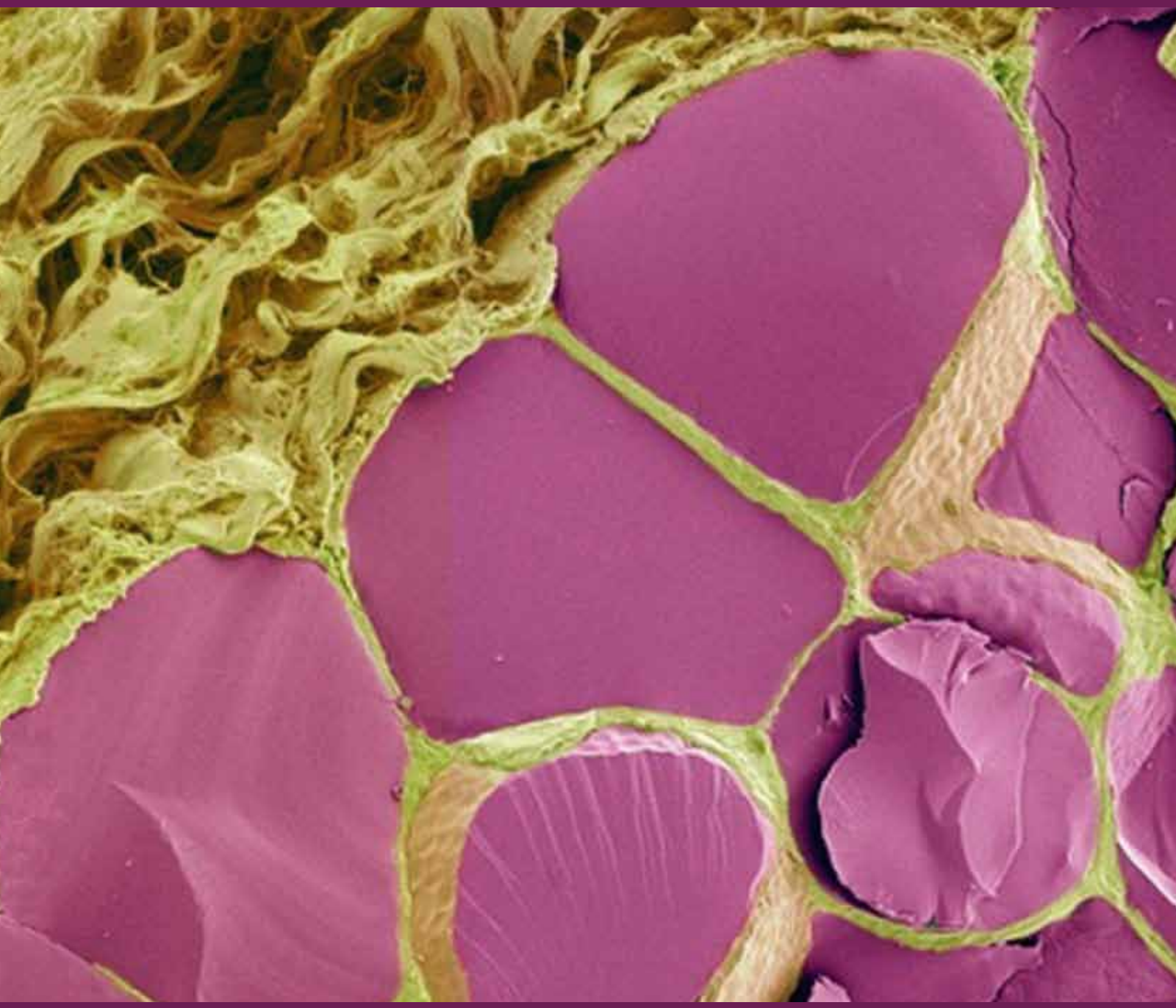
Adipocytokines, Metabolic Syndrome, and Exercise

Guest Editors: Philip D. Chilibeck, Faustino R. Pérez-López, Peter F. Bodary, Eun Seok Kang, and Justin Y. Jeon



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Editorial Board

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Editorial

Adipocytokines, Metabolic Syndrome, and Exercise

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Cardiovascular disease is responsible for about one-third of deaths in developed countries and contributes to substantial health care costs [1]. Even in developing nations, cardiovascular disease is on the rise, especially in urban areas [2]. Increased central adiposity is associated with a clustering of risk factors for cardiovascular disease, including elevation in fasting triglycerides and glucose, increased resting blood pressure, and decreased levels of fasting high density lipoproteins. This clustering of risk factors is termed the "metabolic syndrome" [3]. Increased visceral adipose tissue is integral to development of metabolic syndrome and increases risk of type 2 diabetes, cardiovascular disease complications, cancer, sleep disorders, sexual dysfunction, and mortality [4–7]. Exercise training can have a profound effect on reducing visceral adiposity and therefore reduces metabolic syndrome risk [8, 9].

As outlined in the review by T. Sakurai et al., adipose tissue does not only serve as a storage site for energy but is now recognized as having substantial endocrine function, releasing a number of "adipokines" and "cytokines." Adipokines include leptin and adiponectin and cytokines include inflammatory (i.e., TNF-alpha, IL-6) and anti-inflammatory (i.e., IL-10) cytokines. Adiponectin is considered to be anti-inflammatory and associated with improved insulin sensitivity, whereas leptin affects the hypothalamus to suppress appetite. Increased fat cell size is associated with dysregulation of adipokines and cytokines so that adiponectin release is decreased and inflammatory cytokine release is increased [10, 11]. This increased inflammatory state is association with increased insulin resistance. Exercise training or increased physical activity, especially that which is associated with reduced fat mass, corrects the dysfunction in adipokine and cytokine expression so that expression of adiponectin is increased in adipose tissue and production of inflammatory cytokines is reduced [12, 13].

A number of articles in this issue investigate the effects of exercise programs on metabolic syndrome, insulin resistance, and adipokine and cytokine dysfunction in understudied populations, including children, breast cancer survivors, and those who have had adipose tissue removed through liposuction. Y. Kim and H. Park review the effects of exercise training programs for alleviating insulin resistance in children. This is an important population to investigate as the proportion of adolescents with metabolic syndrome is estimated at between 6.5 and 7.8% [14] and metabolic syndrome risk in adolescence tracks into adulthood in longitudinal studies [15]. As outlined by Y. Kim and H. Park, there is good evidence that exercise training independent of weight loss is effective for reducing insulin resistance in adults but limited evidence that aerobic or resistance training is effective in children and adolescents. Therefore, there is a need for larger randomized controlled trials to determine optimal doses and modalities of exercise

for prevention of metabolic syndrome and insulin resistance in children.

G. A. Thomas et al. investigated the effects of a randomized controlled trial comparing aerobic exercise training to usual care in postmenopausal breast cancer survivors. Breast cancer survivors tend to be sedentary and overweight and susceptible to development of metabolic syndrome; however, 9–14.9 metabolic equivalent task (MET) hours per week of physical activity (equivalent to walking at an average pace approximately 3–5 hours per week) is associated with 50% reduction in the risk of mortality compared to those with lower physical activity levels (i.e., <3 MET hours per week) [16]. Metabolic syndrome may not only increase risk of cardiovascular disease in this population but is also associated with increased risk of breast cancer recurrence. Overall the 6-month aerobic training intervention resulted in a significant reduction in fasting glucose levels. In addition, those compliant with the exercise intervention (defined as 120 minutes per week of aerobic exercise) reduced metabolic syndrome (as a sum of z-scores calculated from each metabolic syndrome risk factor) compared to those who were not compliant with the exercise program. This study has two important implications: (1) only a minimal amount of aerobic exercise can reduce metabolic syndrome risk in breast cancer survivors (i.e., less than 20 minutes per day); and (2) it is important to focus on strategies that can increase adherence to exercise programs in this population to derive best results.

M. Y. Solis et al. assessed the effects of exercise training in a normal-weight group of women who had undergone abdominal liposuction surgery. There were some negative effects on adiponectin and cytokine levels six months after the surgery, including increased TNF-alpha and IL-6 mRNA levels in subcutaneous adipose tissue biopsies and decreased adipose tissue mRNA and serum levels of adiponectin. Exercise improved insulin sensitivity but had no effect on correcting the deleterious effect of the surgery on adiponectin and cytokines. Overall the negative effect of the surgery on adiponectin and cytokines was not associated with insulin resistance. Future studies will have to determine whether a longer follow-up after liposuction surgery is associated with development of metabolic dysregulation associated with the negative effects on adipokines and cytokines.

A challenge with many studies evaluating the effect of exercise training or fitness levels on central adipose tissue is separating the subcutaneous adipose tissue from the more metabolically active visceral adipose tissue depots. S. Kim et al. utilized computed tomography scans to provide a careful quantitation of these adipose depots in a cross-section of overweight and obese individuals. They demonstrated that cardiovascular fitness (determined by recovery heart rate) was inversely associated with visceral but not subcutaneous adipose tissue. This association suggests that there may be a link between fitness and adipose tissue deposition. In addition, it intimates that improvement in cardiovascular fitness may target the adipose tissue depot that is most associated with development of dysfunction of adipokines and cytokines and metabolic syndrome.

Adipokine and cytokine dysfunction is one of the leading mechanisms linking obesity with insulin resistance, type 2 diabetes, cardiovascular disease, and cancer. Moreover, visceral adipose tissue is associated with a distinct adipokine and cytokine profile that is more detrimental than subcutaneous adipose tissue. For example, visceral adipose tissue secretes high levels of plasminogen activator inhibitor 1, an anti-fibrinolytic protein with prothrombotic effects, and accumulation of visceral adipose tissue is associated with hyposecretion of adiponectin [17]. Liposuction removes mainly subcutaneous adipose tissue, leaving visceral adipose tissue intact; this could explain the minimal beneficial effect of liposuction on insulin resistance [18]. M. Y. Solis et al. reported a detrimental impact of abdominal liposuction on adiponectin and cytokines. Weight reduction through exercise and proper diet, therefore, still remains as the best way to reduce adiposity and improve metabolic profiles. The study by S. Kim et al. draws some attention to this point in that CT-measured visceral adipose tissue mass and not subcutaneous adipose tissue mass was inversely associated with cardiopulmonary fitness. The group of manuscripts in this issue highlights the importance of exercise for attenuating adipokine and cytokine dysfunction and ameliorating metabolic disease in a variety of populations.

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Research Article

Distribution of Abdominal Obesity and Fitness Level in Overweight and Obese Korean Adults

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Background. Abdominal obesity and its relative distribution are known to differ in association with metabolic characteristics and cardiorespiratory fitness. This study aimed to determine an association between fitness level and abdominal adiposity in overweight and obese adults. *Methods.* 228 overweight and obese individuals were classified as either cardiorespiratory unfit or fit based on their recovery heart rate. Visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), the visceral-to-subcutaneous adipose tissue ratio (VAT/SAT ratio), and cardiometabolic characteristics were analyzed to examine the relationship between recovery heart rate and abdominal adiposity components. *Results.* After adjustments for age and sex, significant relationships of recovery heart rate and VAT, SAT, and VAT/SAT ratio were found; however, SAT was not significantly associated after further adjustment for body mass index (BMI) ($r = 0.045$, $P = 0.499$), whereas VAT ($r = 0.232$, $P < 0.001$) and VAT/SAT ratio ($r = 0.214$, $P = 0.001$) remained associated. Through stepwise multiple regression analyses after adjustment for age, sex, BMI, lifestyle factors, mean blood pressure, fasting glucose, HOMA-IR, lipid profiles, and hsCRP, recovery heart rate was identified as an independent variable associated with VAT ($\beta = 0.204$, $P < 0.001$) and VAT/SAT ratio ($\beta = 0.163$, $P = 0.008$) but not with SAT ($\beta = 0.097$, $P = 0.111$). *Conclusions.* Cardiorespiratory fitness level is independently associated with VAT and the VAT/SAT ratio but not with SAT in overweight and obese adults.

1. Introduction

Abdominal obesity is a major risk factor for metabolic dysregulation, leading to diabetes, hypertension, and cardiovascular diseases in overweight and obese individuals, beyond overall amount of body fat [1, 2]. Accordingly, to assess abdominal adiposity, waist circumference and the waist-to-hip ratio are commonly used over body mass index (BMI) [3]. However, these anthropometric measures contain little information regarding the anatomical location of stored excess fat, which contributes to abdominal obesity and metabolic consequences. The key components of abdominal obesity are visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), which are known to differ in their structural composition, function, and metabolic activity [4].

Visceral fat accumulation undergoes more unfavorable adverse metabolism than subcutaneous fat [5]. Previous studies have indicated that VAT demonstrates a stronger association with metabolic disturbances and cardiovascular risks than SAT [6, 7]. On the other hand, subcutaneous fat is thought to have protective properties as an adipose tissue depot [8]. Moreover, the visceral-to-subcutaneous adipose tissue ratio (VAT/SAT ratio), a measure to quantify abdominal fat distribution with regard to the propensity to store excess fat viscerally rather than subcutaneously, was found to be a correlate of cardiometabolic risk [9, 10].

Cardiorespiratory or aerobic fitness refers to the ability of the circulatory and respiratory systems to supply oxygen to muscles and organs during continuous physical

activity without tiring and can be measured by recovery heart rate after exercise [11, 12]. The association of low level of cardiorespiratory fitness and high VAT, as well as high prevalence of metabolic abnormalities, was shown in several previous studies [13, 14]. Furthermore, a recent meta-analysis demonstrated that a decrease in visceral adipose tissue can be obtained by exercise in overweight adults [15]. However, few studies have examined correlations between fitness level and abdominal adipose tissue distribution in overweight and obese individuals at present.

The purpose of this study was to assess the association between cardiorespiratory fitness level expressed as recovery heart rate and VAT, SAT, and the VAT/SAT ratio measured by computed tomography (CT) scan in healthy overweight and obese adults.

2. Materials and Methods

2.1. Study Participants. Two hundred twenty-two men and women were enrolled in this subsection of the Korean Physical activity and Obesity Program (K-POP) study, which is an ongoing study designed to evaluate cardiorespiratory fitness and metabolism in overweight and obese adults in Seoul, Korea. The participants were recruited from visitors to the Obesity Clinic in the Department of Family Medicine at Severance Hospital from January 2011 to March 2013. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital.

Overweight was defined as having a BMI greater than or equal to 23 kg/m^2, and obesity was defined as having a BMI greater than or equal to 25 kg/m^2, following Asian-Pacific population-specific BMI criteria after consultation with a World Health Organization expert [16]. Among the overweight and obese participants, subjects aged 18 to 70 years, without history of diabetes, hypertension, dyslipidemia, or chronic liver disease, were included in the study. Also, those taking medications that affect cardiometabolic activity, such as antiobesity drugs, hypoglycemic agents, or drugs lowering blood pressure, were also excluded from the study.

Individuals who were unable to complete the cardiorespiratory fitness evaluation due to their physical or psychological conditions were excluded as well.

2.2. Clinical and Anthropometric Evaluation. BMI was calculated with dividing weight by square of height (kg/m^2). Body weight was measured to the nearest 0.1 kg with an electronic scale, and height was measured to the nearest 0.1 cm with a stadiometer. Waist circumference was measured midway between the lowest rib and the iliac crest; hip circumference was measured at the widest part of the hip region in the standing position, and the waist-to-hip ratio was calculated based on these measurements. Blood pressure was measured twice by mercury sphygmomanometer after a 10 min seated rest, and mean blood pressure was calculated as [1/3 (systolic BP) + 2/3 (diastolic BP)] based on the average of the two measurements [17]. Data on past and current medical conditions and medications were collected from participants' medical records. Lifestyle factors including smoking status, alcohol consumption, and basal physical activity status were provided by participants through questionnaires. Smoking status was considered yes if the participants reported themselves to be a current smoker. Alcohol consumption was defined as a positive factor if the subjects' alcohol consumption was 72 g or more per week. Physical activity status was analyzed from a participant's overall energy expenditure calculated in metabolic equivalents- (METs-) hour per week (MET-h/week) from information collected by the Korean version of the International Physical Activity Questionnaire (IPAQ) [18].

Abdominal adipose tissue area was measured by CT scan (Tomoscan 350; Philips, Mahwah, NJ, USA). Specifically, a 10 mm CT slice scan was acquired at the L4-L5 level with subjects in the supine position to measure total abdominal tissue (TAT) and VAT areas. VAT was quantified by defining the intra-abdominal cavity at the internal aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The SAT area was calculated by subtracting the VAT area from the TAT area. The VAT/SAT ratio was calculated using these measured areas. The coefficients of variation for inter- and intraobserver reproducibility were 1.4% and 0.5%, respectively.

2.3. Biochemical Analyses. Biochemical analyses were performed on blood samples collected after an overnight fast (>12 hrs). Serum levels of glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), and highly sensitive C-reactive protein (hsCRP) were measured with Hitachi 7600 Automatic analyzer (High-Technologies Corporation, Hitachi, Tokyo, Japan). Fasting insulin was measured by an electrochemiluminescence immunoassay using an Elecsys 2010 instrument (Roche, Indianapolis, IN, USA), and insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index [(Insulin (μIU/mL) × fasting glucose (mg/dL)/18)/22.5] [19].

2.4. Cardiorespiratory Fitness. Cardiorespiratory fitness was measured by Tecumseh step test, a standardized 3-minute step test. Participants performed 24 steps per minute for 3 minutes based on the protocol for the Tecumseh step test, maintaining a same stepping rate on a 20.3 cm high step [14]. The participants were aided by an assistant's demonstration and a metronome cadence for proper stepping technique and constant step maintenance. Heart rates were measured by a heart rate monitor (Polar-FS3C, USA) attached to the anterior chest wall of the participant. Heart rates were recorded in a seated position 1 minute prior to exercise after a minimum 5-minute rest and 1-minute rest after the completion of the 3-minute step exercise; 1-minute recovery heart rate was measured and recorded. The expectation of this test was that participants with greater cardiorespiratory fitness would have lower 1-minute postexercise recovery heart rate than those with worse cardiorespiratory fitness [20].

Table 1: Clinical characteristics of the study participants according to fitness level (recovery heart rate).

	Unfit (RHR ≥ 93) (n = 114)	Fit (RHR < 93) (n = 114)	P value[a]
Age (years)	32.46 ± 9.40	34.43 ± 9.97	0.118
Male, n (%)	54 (44.6)	46 (40.4)	0.507
BMI (kg/m^2)	30.09 ± 4.70	28.25 ± 3.63	0.001
Waist (cm)	99.08 ± 12.54	94.61 ± 9.17	0.001
Waist-to-hip ratio	0.91 ± 0.055	0.90 ± 0.052	0.106
Mean BP (mmHg)	98.04 ± 12.92	92.58 ± 11.93	0.001
Alcohol, n (%)	35 (29.2)	34 (29.9)	0.787
Smoking, n (%)	23 (25.2)	26 (23.3)	0.638
Physical activity (MET-h/week)	29.61 ± 24.46	29.82 ± 24.55	0.949
Fasting glucose (mg/dL)	100.82 ± 85.89	88.76 ± 9.58	0.130
Fasting insulin (μU/mL)	15.95 ± 18.75	9.78 ± 7.51	0.001
HOMA-IR	3.68 ± 4.68	2.18 ± 1.76	0.001
Cholesterol (mg/dL)	198.95 ± 37.97	195.60 ± 35.23	0.483
Triglyceride (mg/dL)	142.39 ± 135.98	105.72 ± 50.78	0.006
LDL (mg/dL)	122.68 ± 35.29	121.96 ± 34.04	0.979
HDL (mg/dL)	49.53 ± 11.37	51.50 ± 11.31	0.135
hsCRP (mg/L)	2.15 ± 2.42	1.73 ± 5.27	0.442
VAT area (cm^2)	142.35 ± 89.47	110.75 ± 62.29	<0.001
SAT area (cm^2)	317.51 ± 118.44	276.20 ± 99.17	0.004
VAT/SAT ratio	0.47 ± 0.25	0.39 ± 0.18	0.011
Recovery heart rate	105.96 ± 12.02	81.26 ± 7.18	0.001

RHR: recovery heart rate; BMI: body mass index; BP: blood pressure; MET-h/week: metabolic equivalents-hour per week; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low-density lipoprotein; HDL: high-density lipoprotein; hsCRP: highly sensitive C-reactive protein; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; VAT/SAT ratio: visceral-to-subcutaneous adipose tissue ratio.
Values are expressed as means ± SD for continuous variables or % for categorical variables.
[a]P values are calculated by an independent sample t-test for continuous variables or the Chi-square test for categorical variables.

Table 2: Correlation coefficients between fitness level (recovery heart rate) and cardiometabolic characteristics and abdominal adiposity (VAT, SAT, and the VAT/SAT ratio).

	VAT	SAT	VAT/SAT ratio
Waist (cm)	0.273**	0.640**	0.008
Waist-to-hip ratio	0.230**	0.159*	0.110
Mean BP (mmHg)	−0.054	−0.006	0.005
Physical activity (MET-h/week)	−0.027	0.013	0.015
Fasting glucose (mg/dL)	0.009	0.005	−0.031
Fasting insulin (μU/mL)	0.115**	0.018	0.128
HOMA-IR	0.102**	0.003	0.109
Cholesterol (mg/dL)	0.083	0.111	0.019
Triglyceride (mg/dL)	0.104*	0.034	0.145*
LDL (mg/dL)	0.054	0.067	0.017
HDL (mg/dL)	−0.040	−0.202	−0.197**
hsCRP (mg/L)	−0.074	0.007	−0.076
Recovery heart rate	0.232**	0.045	0.214**

VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; VAT/SAT ratio: visceral-to-subcutaneous adipose tissue ratio; BMI: body mass index; BP: blood pressure; MET-h/week: metabolic equivalents-hour per week; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low-density lipoprotein; HDL: high-density lipoprotein; hsCRP: highly sensitive C-reactive protein.
*$P < 0.05$, **$P < 0.01$, calculated by Pearson's partial correlation adjusted for age, sex, and BMI.

2.5. Statistical Analyses. To compare abdominal adiposity and other metabolic variables according to cardiorespiratory fitness level, participants were grouped as unfit (low fitness level) or fit (high fitness level) individuals. Fitness level was divided into high or low according to the level of recovery heart rate either lower or higher than the median value (50th percentile) of the distribution, respectively.

Data are expressed as means ± standard deviation (SD) or percentages. Normality of the variables was tested using the Kolmogorov-Smirnov test. Data between groups were compared with an independent sample t-test for continuous data or the Chi-square test for categorical data.

To assess the association between fitness level expressed as recovery heart rate and the distribution of abdominal adiposity, Pearson's partial correlation analyses were performed for correlations between recovery heart rate and VAT, SAT, and the VAT/SAT ratio, after adjusting for age, sex, and BMI to assess attenuation of the associations by overall amount of body fat. The analyses were also performed for men and women separately to evaluate any differences according to sex.

Additionally, stepwise method multiple linear regression analyses were used to estimate the magnitude of the independent associations of recovery heart rate and VAT, SAT, and the VAT/SAT ratio, after adjusting for age, sex, BMI, lifestyle factors (smoking, alcohol, and physical activity status), mean blood pressure, fasting glucose, HOMA-IR, lipid profiles (LDL-cholesterol, HDL-cholesterol, and triglyceride), and hsCRP. To determine independent associations of regional adiposity distribution, SAT was included in the recovery heart rate and VAT regression model, and VAT was included in the recovery heart rate and SAT regression model, but neither VAT nor SAT was included in the recovery heart rate and VAT/SAT ratio regression model, due to the collinearity of VAT and SAT with VAT/SAT ratio. In addition, enter-method multiple linear regression analyses were performed to determine the associations with inclusion of the same variables selected in the stepwise method.

Statistical significance for all analyses was set at P less than 0.05. Statistical analyses were performed with SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA).

3. Results

The clinical and biochemical characteristics of the study participants, who were divided into unfit or fit groups, are given in Table 1. Unfit individuals whose recovery heart rate after step exercise was the same or above 93 beats per minute (bpm) showed significantly higher BMI and waist circumference, but no difference was found in the waist-to-hip ratio between the two groups. In addition, mean blood pressure, fasting insulin, HOMA-IR, and triglyceride level were significantly higher in the unfit group. Finally, VAT, SAT, and the VAT/SAT ratio were all also significantly higher in unfit participants compared with fit participants.

In correlation analyses, the significantly positive relationships between insulin resistance markers (fasting insulin and HOMA-IR), lipid profiles (triglyceride and HDL), and recovery heart rate were found after adjusting for age and sex (data not shown). In addition, these cardiometabolic variables were shown to be significantly correlated with abdominal adiposity (VAT, SAT, and the VAT/SAT ratio) after adjusting for age, sex, and BMI (Table 2). Although significant correlations with recovery heart rate and VAT, SAT, VAT/SAT ratio were found after adjustment for age and sex, the association between SAT and recovery heart rate was no longer significant after adjustments were made for age, for sex, and further for BMI ($r = 0.045$; $P = 0.499$), whereas significant correlations were maintained between recovery heart rate and VAT ($r = 0.232$; $P < 0.001$) and the VAT/SAT ratio ($r = 0.214$; $P = 0.001$) (Figure 1).

In addition, significant associations between recovery heart rate and VAT and VAT/SAT ratio but not SAT were also seen when analyzed separately in men: VAT ($r = 0.340$; $P = 0.001$), SAT ($r = 0.102$; $P = 0.325$), and VAT/SAT ratio ($r = 0.288$; $P = 0.005$), respectively (see Supplementary Table 1 in Supplementary Material available online at http://dx.doi.org/10.1155/2014/854392). However, in women, the results were not significant, but only with similar trend found in the relationships: VAT ($r = 0.162$; $P = 0.066$), SAT ($r = 0.022$; $P = 0.804$), and VAT/SAT ratio ($r = 0.170$; $P = 0.050$), respectively (see Supplementary Table 2).

Independent associations of recovery heart rate with regional abdominal adiposity variables were assessed in multivariable adjusted models by stepwise multiple regression analyses. Recovery heart rate was identified as a significant independent variable associated with VAT ($\beta = 0.204$; $P < 0.001$) and the VAT/SAT ratio ($\beta = 0.163$; $P = 0.008$), but not with SAT ($\beta = 0.097$; $P = 0.111$). Furthermore, significant associations of recovery heart rate with VAT ($\beta = 0.203$; $P < 0.001$) and the VAT/SAT ratio ($\beta = 0.163$; $P = 0.008$), but not with SAT ($\beta = 0.038$; $P = 0.337$), were maintained in enter-method multiple regression analyses after adjusting for the same covariates selected in the stepwise analyses (Table 3).

4. Discussion

In this cross-sectional study, we demonstrate that VAT and SAT, comprising abdominal adiposity, differently associate with fitness level expressed as recovery heart rate after adjusting for possible confounding factors including BMI [21]. Additionally, the VAT/SAT ratio, a measure of abdominal fat distribution between visceral and subcutaneous compartments, was also associated with recovery heart rate as was VAT in healthy overweight and obese Korean adults. Comparing the association between cardiorespiratory fitness level and abdominal obesity distribution measures, our study findings suggest that VAT is a better correlate with cardiorespiratory fitness than is SAT and that the VAT/SAT ratio is also a significant correlate with fitness.

In many previous studies, excess accumulation of VAT was indicated as a strong correlate for deteriorated metabolic

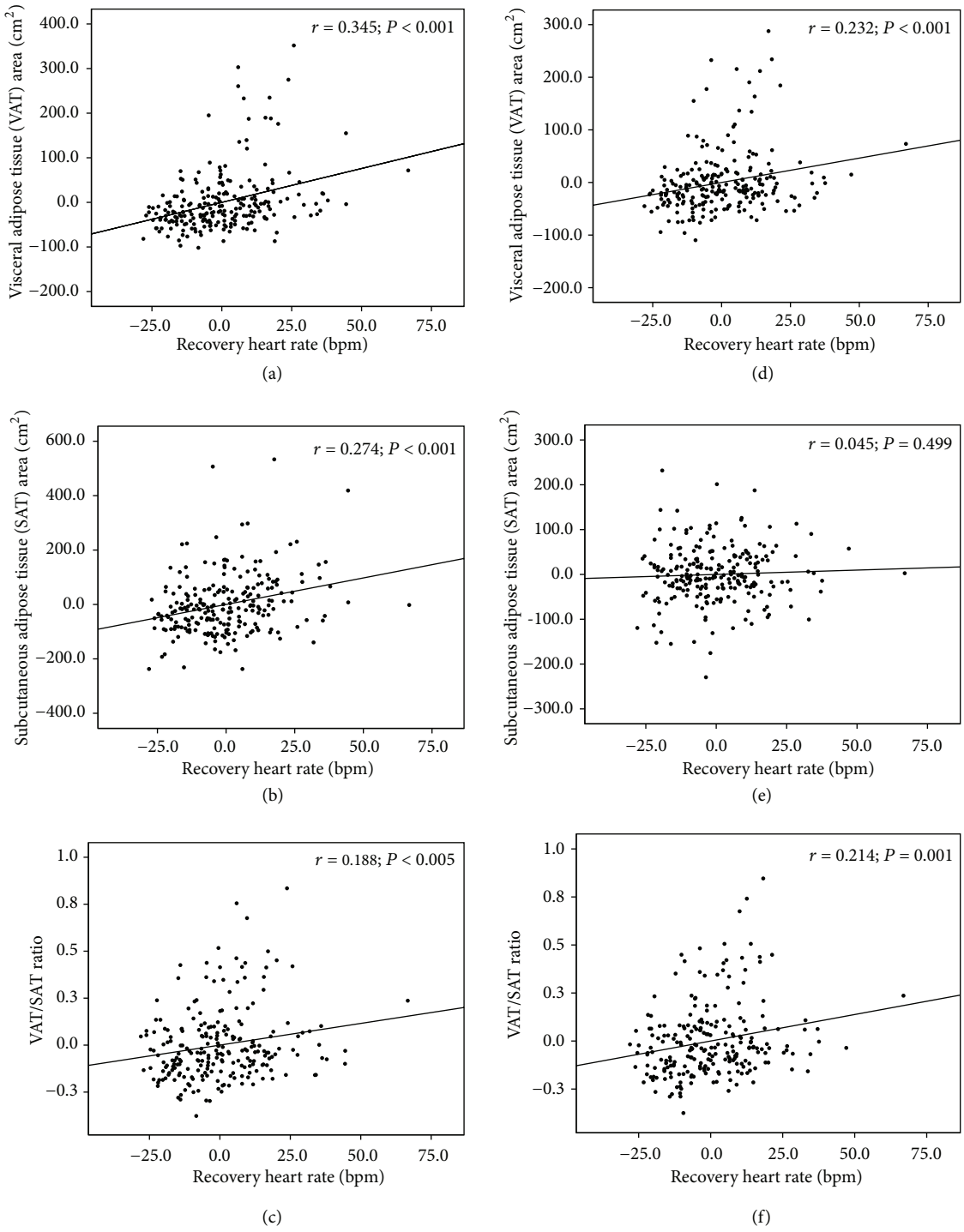

Figure 1: Relationship between fitness level (recovery heart rate) and abdominal adiposity (VAT, SAT, and the VAT/SAT ratio). VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VAT/SAT ratio, visceral-to-subcutaneous adipose tissue ratio; r: Pearson's partial correlation coefficient ($r = 0$: no linear relationship, $r = 1$ or -1: perfect linear relationship). x-axes are based on calculated residuals from regressing fitness level (recovery heart rate) on age and sex (a, b, and c) and for age, sex, and BMI (d, e, and f). y-axes are based on calculated residuals from regressing abdominal adiposity (VAT, SAT, and the VAT/SAT ratio) on age and sex (a, b, and c) and for age, sex, and BMI (d, e, and f).

Table 3: Stepwise method and enter-method multiple linear regression analyses of fitness (recovery heart rate) and other cardiometabolic characteristics and abdominal adiposity (VAT, SAT, and the VAT/SAT ratio).

	VAT		SAT		VAT/SAT ratio		VAT		SAT		VAT/SAT ratio	
	B (SE)	*P* value[a]	*B* (SE)	*P* value[b]	*B* (SE)	*P* value[c]	*B* (SE)	*P* value[d]	*B* (SE)	*P* value[d]	*B* (SE)	*P* value[d]
RHR	0.204 (0.264)	<0.001	0.097 (1.601)	0.111	0.163 (0.001)	0.008	0.203 (0.262)	<0.001	0.038 (0.282)	0.337	0.163 (0.001)	0.008
Age	0.396 (0.414)	<0.001			0.484 (0.001)	<0.001	0.405 (0.407)	<0.001	−0.056 (0.437)	0.142	0.488 (0.001)	<0.001
Sex			0.179 (9.243)	<0.001			−0.023 (8.444)	0.691	0.190 (9.078)	<0.001	−0.154 (0.027)	0.011
BMI (kg/m^2)	0.429 (0.974)	<0.001	0.883 (1.093)	<0.001			0.429 (0.974)	<0.001	0.870 (1.113)	<0.001	−0.146 (0.003)	0.024
HDL (mg/dL)			0.125 (0.423)	0.004	−0.177 (0.001)	0.003	−0.030 (0.511)	0.610	0.121 (0.417)	0.004	−0.177 (0.001)	0.003
hsCRP (mg/L)					−0.136 (0.003)	0.024	−0.078 (0.960)	0.151	0.013 (1.032)	0.735	−0.136 (0.003)	0.024

VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; VAT/SAT ratio: visceral-to-subcutaneous adipose tissue ratio; RHR: recovery heart rate; BMI: body mass index; HDL: high-density lipoprotein; hsCRP: highly sensitive C-reactive protein.

[a,b,c]*P* values are calculated by stepwise method multiple linear regression analyses.

[a]Model variables included age, sex, BMI, smoking, alcohol, physical activity status, mean BP, fasting glucose, HOMA-IR, lipid profiles (LDL, HDL, and triglyceride), hsCRP, and SAT.

[b]Model variables included age, sex, BMI, smoking, alcohol, physical activity status, mean BP, fasting glucose, HOMA-IR, lipid profiles (LDL, HDL, and triglyceride), hsCRP, and VAT.

[c]Model variables included age, sex, BMI, smoking, alcohol, physical activity status, mean BP, fasting glucose, HOMA-IR, lipid profiles (LDL, HDL, and triglyceride), and hsCRP.

[d]*P* values are calculated by enter-method multiple linear regression analyses; variables included age, sex, BMI, HDL, and hsCRP.

health and unfavorable cardiorespiratory fitness level [22–24]. Moreover, visceral fat was shown to be a critical determinant in associations of fitness and metabolic risk modification [15]. On the other hand, even though high SAT accumulation is seen in the obese population, SAT is known to have no or a less-strong independent association with cardiometabolic factors and physical activity level than has VAT [25–27]. Furthermore, the ability to retain fat in the subcutaneous compartment, especially in the superficial layer, is suggested to be beneficial for the obese population [28]. In conditions of chronic energy balance and thus obesity, SAT has been proposed to act as an energy sink for superfluent energy, protecting ectopic fat accumulation in organs such as abdominal visceral compartments and the liver [29]. Dysfunction of SAT and excess VAT energy stores (unfavorable fat partitioning) results in an unfavorable metabolic profile [29, 30]. As a result, the VAT/SAT ratio is suggested to be a reflection of the relative distribution of abdominal fat and predict metabolic health [9, 10, 31].

Regular physical activity is known to be a favorable modifier of metabolic disease risk factors by attenuating positive energy balance and leading to reductions in weight loss and abdominal adiposity [32]. Several previous studies reported that cardiorespiratory fitness is associated with a reduced prevalence of metabolic diseases [33, 34]. In fact, by examining abdominal adipose tissue composition, fitness is more related to visceral fat reduction, even in the absence of weight loss [32, 35]. The distinctive beta-adrenergic responsiveness of VAT is a suggested mechanism to explain the selective and greater mobilization of adipose tissue from the visceral compartment than the subcutaneous region, which is driven by the sympathetic drive associated with exercise [21, 36, 37]. In addition, with reduced visceral adiposity, cardiorespiratory fitness is known to lessen the deleterious actions of unfavorable cytokines and adipokines released from visceral fat and improves responses to advantageous cytokines and adipokines, such as adiponectin and leptin [38, 39]. Moreover, the increase in fat-free lean mass and decrease in VAT through physical exercise are other factors affecting metabolic improvements [21, 39].

Only a few studies have explored the relationship between fitness and VAT compared with SAT and the VAT/SAT ratio. Larsen et al. [27] demonstrated that greater physical activity was associated with less visceral and subcutaneous fat, but after adjusting for BMI, the association only remained for VAT, which is consistent with the results of our study. Furthermore, Borel et al. [40] reported that beneficial effects from physical activity were specifically associated with VAT reduction compared to reductions in SAT. As our study focused on overweight and obese adults, it is particularly important to assess relationships between SAT and fitness and other biomarkers in overweight and obese populations, as SAT function is reported to be modified by increasing weight gain [25, 41]. Additionally, BMI and VAT adjustments are critical for examining independent associations between SAT and fitness, which can lead to different associations, as seen in our study as well as in a previous report [21, 27].

When the population was analyzed in subgroups divided by sex, the significant associations between recovery heart rate and VAT and VAT/SAT ratio, but not SAT, were only found in men, whereas only similar trend of the relationship was seen in women. These findings may indicate that the associations differ sex specifically, but with similar trend demonstrated in women and with cross-sectional analyses with rather small sample in our study. Thus, it is difficult to make concrete conclusions. Further prospective studies with larger samples are necessary to define the sex-specific characteristics.

There are some limitations to this study. First of all, the 3-minute step test was used to estimate cardiorespiratory fitness level and this could be a limitation since the level of adiposity would influence the heart rate; more obese participants would have increased their heart rate more due to having to repetitively lift more weight up and down on a standard-height bench. Regardless of this limitation, the 3-minute step test has been validated previously and it has been used in clinical setting and several prior epidemiologic studies [42–45]. Another limitation of the study is that the directionality and causality of the results cannot be determined with certainty in this cross-sectional design. Finally, as participants were recruited from the obesity clinic with a greater interest in health than the general population, it may be difficult to generalize the results to the public.

5. Conclusions

In conclusion, cardiorespiratory fitness was independently associated with VAT and the VAT/SAT ratio, but not with SAT, in overweight and obese Korean adults. Our findings collectively suggest that fitness may be a modifier of abdominal adiposity distribution, leading to favorable metabolic health. Further studies are required to clarify the clinical associations of these findings and to explore their pathophysiological significance.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

The Liposuction-Induced Effects on Adiponectin and Selected Cytokines Are Not Affected by Exercise Training in Women

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It has been suggested that the abrupt liposuction-induced decrease in adipose tissue could affect adipokine secretion pattern. We hypothesized that exercise training could positively impact adipokine metabolism following liposuction. The aim of this study was to investigate the effects of liposuction on inflammation-related adipokines in women who were either exercise-trained or remained sedentary after surgery. Thirty-six healthy normal-weight women underwent an abdominal liposuction and two months after surgery were randomly allocated into two groups: trained (TR, $n = 18$, four-month exercise program) and nontrained (NT, $n = 18$). Inflammation-related adipokine serum levels (TNF-α, IL-6, IL-10, and adiponectin) and abdominal and thigh subcutaneous adipose tissue (scAT) mRNA levels were assessed before (PRE) and six months after surgery (POST6). TNF-α, IL-6, and IL-10 serum levels were unchanged in both groups. In contrast, TNF-α, IL-6, and IL-10 mRNA levels in scAT were increased, whereas adiponectin scAT mRNA and serum levels were decreased at POST6 ($P < 0.05$, main effect for time). No changes were observed in mRNA levels of MCP-1, CD14, and CD68 in any of the groups. In conclusion, liposuction downregulates adiponectin scAT gene expression and serum levels and upregulates scAT gene expression of inflammation-related genes six months after surgery in normal-weight women, irrespective of exercise training.

1. Introduction

The adipose tissue is a complex and metabolically active tissue which secretes a variety of adipokines (e.g., adiponectin, TNF-α, IL-6, and IL-10) that play pivotal roles in metabolic regulation [1]. Thus, it has been suggested that the abrupt decrease in adipose tissue brought about by liposuction could affect adipokine secretion and, hence, the metabolic profile [2].

Previous studies on liposuction have shown somewhat conflicting results, with most reports showing no changes [2–6] while others demonstrate modest improvements [7–9] in one or more cardiometabolic risk factors, namely, insulin sensitivity, lipid profile, and proinflammatory cytokine levels. However, the lack of control for the subjects' physical activity level in these studies may be an important shortcoming as exercise may largely affect these parameters [10, 11]. For instance, we recently demonstrated [12] that a four-month exercise program was capable of improving insulin sensitivity in sedentary normal-weight women submitted to liposuction surgery whereas no change was observed in the nonexercised group. Additionally, most of these studies have evaluated obese subjects, even though liposuction is recommended as a cosmetic procedure for nonobese individuals [13].

Thus, the purpose of this study was to explore the effects of a small-volume abdominal liposuction on serum levels and adipose tissue gene expression of selected inflammation-related adipokines in normal-weight women who were

either exercise-trained or not after surgery. We hypothesized that an exercise-training program could adjuvantly impact adipokine adipose tissue gene expression and blood levels following surgery.

2. Material and Methods

2.1. Experimental Design and Participants. A six-month randomized controlled trial was conducted (clinicaltrial.gov NCT01174485). This study was part of a clinical trial that aimed to comprehensively explore the effects of a small-volume abdominal liposuction associated with an exercise training program on body composition, energy expenditure, and cardiometabolic risk factors in women. The details of the study (e.g., sample's characteristics, surgery and biopsy procedures, exercise training program, and physical fitness and nutritional assessment) as well as its main findings (e.g., body fat distribution, energy expenditure, insulin sensitivity, lipid profile, and physical capacity) have been reported elsewhere [12].

Briefly, thirty-six normal-weight physically inactive women (20 to 35 years old; BMI = 23.1 ± 1.6 Kg/m^2) were recruited. As previously reported [12], exclusion criteria included BMI over 30 Kg/m^2; smoking; metabolic disorders such as glucose intolerance, diabetes, hypertension, thyroid dysfunction, and dyslipidemia; unstable body weight in the last six months prior to the commencement of the study; current use of medications including antidepressants, appetite suppressants, thyroid hormone medication, orlistat, topiramate, diuretics, anti-inflammatory, or antibiotics; any cardiovascular or musculoskeletal conditions that excluded exercise participation; and previous liposuction surgery. All of the subjects used oral contraceptives throughout the study. This study was approved by the local ethics committee. Before entering the study, all subjects provided written informed consent.

All participants underwent a small-volume abdominal liposuction surgery (mean of 1240.3 ± 363.6 mL harvested fat). Two months after surgery, subjects were randomly allocated into either a trained (TR, $n = 18$, four-month exercise training program) or a nontrained group (NT, $n = 18$). The exercise training program was performed three times per week and consisted of eight strength exercises for the major muscle groups (3 sets of 8–12 RM for each exercise) followed by 30–40 min of aerobic exercise on a treadmill at approximately 75% of the $VO_{2\,max}$. As previously reported, adherence to the exercise program was 74.0 ± 13.2% and only the TR group showed a 12% increase in $VO_{2\,max}$ (PRE versus POST6, $P = 0.001$) and a 38% increase in muscle strength as assessed by 1 RM leg press (TR versus NT, $P = 0.001$) after the intervention. Additionally, no changes in food intake were observed within or between groups throughout the study [12].

Prior to the intervention (PRE), before the beginning of the exercise program (i.e., two months after surgery(POST2)) and at the end of the study (POST6), subjects were assessed for serum levels of adiponectin, IL-6, TNF-α, and IL-10 using enzyme-linked immunosorbent assay kits (Quantikine HS; R&D Systems Ltd., Abingdon, UK) (Millipore, MA, USA).

Additionally, abdominal and thigh subcutaneous adipose tissue (scAT) samples were obtained by biopsies (as comprehensively described elsewhere) [12] and the gene expression of selected cytokines (adiponectin, IL-6, TNF-α, and IL-10) and macrophage-markers (CD14, CD68 and MCP-1) were assessed in a subsample ($n = 6$ per group). Reverse-transcription quantitative polymerase chain reaction (RT-qPCR) was performed as previously described [14] using the following primer sets: adiponectin, 5′-AGGCCGTGATGGCAGAGATG-3′, 5′-CTTCTCCAGGTTCTCCTTTCCTGC-3′; IL-6, 5′-AAAGAGGCACTGGCAGAAAA-3′, 5′-CATGCTACATTTGCCGAAGA-3′; IL-10, 5′-CAGCTGTTCTCCCCAGGAAA-3′, 5′-AGGGAGGCCTCTTCATTCAT-3′; TNF-α, 5′-CTGCCCCAATCCCTTTATT-3′, 5′-CCCAATTCTCTTTTTGAGCC-3′; MCP-1, 5′-CGACATCCTGGAACTGCCCTACC-3′, 5′-CACTGTGCCGCTCTCGTTCAC-3′; CD14, 5′-TAAAGGACTGCCAGCCAAGC-3′, 5′-AGCCAAGGCAGTTTGAGTCC-3′; CD68, 5′-GCTACATGGCGGTGGAGTACAA-3′, 5′-ATGATGAGAGGCAGCAAGATGG-3′; IPO8 (reference gene), 5′-CGAGAACGAGCTCAACCAGTCCT-3′, 5′-AGCTGCCTGTCGTACTGGGA-3′. Quantification cycle (Cq) and ΔCq values were calculated in every sample for each gene of interest as follows: $Cq^{\text{gene of interest}} - Cq^{\text{reference gene}}$, with IPO8 as the reference control gene. Relative changes in the expression level of the specific genes (Δ − ΔCq) were calculated by subtraction of the ΔCq at PRE (used as a calibrator) to the corresponding ΔCq at POST6. Finally, fold change was determined as $2^{-\Delta-\Delta Cq}$. mRNA was purified from the adipose tissue biopsies using a commercially available kit following manufacture's recommendations (RNeasy Lipid Tissue Mini Kit, Qiagen). mRNA quantification and quality assessment were performed spectrophotometrically (NanoDrop 2000, Thermo Scientific) and integrity was verified through electrophoresis on a denaturing agarose gel. cDNA was synthesized from 1 μg of mRNA using oligo-dT primers (Promega catalog number C1101) and M-MLV reverse transcriptase enzyme (Promega catalog number M170B). cDNA amplification and detection were conducted in a real-time thermal cycler (Rotor Gene Q, Qiagen) using the SYBR Green dye (Applied Biosystems, catalog number 4367659).

Finally, all of the POST6 assessments in the trained subjects were performed 60–72 hours after the last exercise training session.

2.2. Statistical Analysis. The dependent variables were compared using a mixed model for repeated measures assuming exercise training (TR and NT), time (PRE, POST2, and POST6), and adipose tissue depot (for the mRNA analyses only) as fixed factors and subjects as random factors (SAS 8.2, SAS Institute Inc., Cary, NC, USA). The significance level was set at $P < 0.05$. Data are presented as means ± SD.

3. Results

No between-group differences were observed at baseline for any of the parameters analyzed including age (TR: 26.6 ± 3.4

years; NT: 27.5 ± 4.8 years; $P = 0.52$, between-group difference).

TNF-α serum levels were undetectable in 18 subjects, IL-6 serum levels were undetectable in 1 subject, and IL-10 serum levels were undetectable in 2 subjects. Thus, sample sizes for TNF-α, IL-10, and IL-6 serum levels were TR: 7, 18, and 18; NT: 11, 17, and 16, respectively, for all times.

TNF-α, IL-6, and IL-10 serum levels were unchanged throughout the study in both groups. Adiponectin serum levels were unchanged at POST2 ($P > 0.05$) and markedly reduced at POST6 ($P < 0.0001$, 95% CI = 4.43 to 9.87, main effect for time) (Table 1).

Abdominal scAT gene expression of TNF-α, IL-6, and IL-10 were significantly increased from PRE to POST6 ($P = 0.003$, 95% CI = −5.3 to −1.4; $P = 0.0006$, 95% CI = −10.7 to −3.9; and $P = 0.03$, 95% CI = −14.0 to −0.6, resp., main effect for time). A similar increase in TNF-α, IL-6, and IL-10 gene expression was observed in thigh scAT ($P = 0.009$, 95% CI = −3.9 to −0.7; $P = 0.02$, 95% CI = −3.4 to −0.4; $P = 0.04$, 95% CI = −9.0 to −0.2, resp.; main effect for time). In contrast, adiponectin gene expression was modestly but significantly decreased both in abdominal scAT ($P = 0.05$, 95% CI = −0.01 to 0.67; main effect for time) and in thigh scAT ($P = 0.04$, 95% CI = 0.01 to 0.78; main effect for time) (Figure 1). No changes were observed in mRNA levels of MCP-1, CD14, and CD68 in any of the groups. Additionally, there we no differences between abdominal and thigh scAT mRNA levels for any of the genes in either group throughout the study.

Finally, for a comprehensive overview of the results of the present study, Table 2 shows the previously published data [12] regarding the biochemical and anthropometric parameters, which were assessed at PRE, POST2, and POST6 in both groups.

4. Discussion

The main and novel findings of this study were twofold: (a) a liposuction surgery downregulates adiponectin scAT gene expression and blood levels and upregulates pro- and anti-inflammatory cytokine scAT gene expression; and (b) a structured exercise training program does not affect these responses.

Because of its remarkable secretory capacity, it has been suggested that scAT removal through liposuction could impact inflammation-related adipokine secretion and metabolic profile [2]. To the best of our knowledge, this is the first study to demonstrate a significant decrease in serum adiponectin levels, which was paralleled by a decreased adiponectin gene expression in scAT in normal-weight women after liposuction.

Decreased adiponectin levels have been consistently associated with impaired insulin signaling and insulin resistance and increased cardiovascular risk [15]. Interestingly, despite the significant decrease in adiponectin levels, our previously published data demonstrated no detrimental effects of liposuction on insulin sensitivity in the nontrained group. Furthermore, the exercise-trained group showed an improvement in this parameter further supporting a lack of association between the liposuction-induced responses in adiponectin and insulin sensitivity [12]. In fact, several studies have shown an uncoupling between changes in adiponectin levels and insulin sensitivity [16], indicating that factors other than adiponectin may regulate insulin action. Additionally, the fact that the subjects were not insulin resistant at baseline may partially explain these findings. Notwithstanding these observations, we cannot rule out the potential longer-term deleterious effects of liposuction on metabolism, especially when considering the pleiotropic beneficial effects of adiponectin [1].

The underlying mechanisms by which liposuction may downregulate adiponectin scAT gene expression and serum levels remain undisclosed. Nevertheless, the increase in scAT mRNA levels of TNF-α and IL-6 may have resulted in suppressed adiponectin expression in an autocrine manner, despite the concomitant increase in the anti-inflammatory cytokine IL-10 mRNA levels, [17, 18]. It is noteworthy that this increased scAT inflammatory milieu may not be accounted for an increase in macrophage infiltration as evidenced by the unchanged scAT mRNA levels of the macrophage-specific markers, but rather to an increase in adipocyte cytokine gene expression *per se*. Moreover, in our previously published paper [12], we showed data demonstrating that both adipocyte size and abdominal and thigh scAT mRNA expression of lipid metabolism-related genes (i.e., HSL, C/EBP-α, SREBP-c, LPL, and PPARγ) remained unchanged throughout the study in both groups, with the exception of a decrease in thigh scAT gene expression of LPL and PPARγ in the trained group only. Thus, it is unlikely that changes in adipocyte size or lipid metabolism could explain the current findings. Collectively our data points towards an inflammatory mechanism rather than a metabolic or an adipocyte function-related one. Importantly, previous studies have demonstrated a positive effect of dietary interventions on cytokines gene expression without any changes in adiponectin levels [19]. These data are hard to reconcile with those from the present study as they substantially differ in regard of their intervention protocols (i.e., dietary intervention versus liposuction surgery).

Importantly, although the exercise training program was effective in improving physical capacity and cardiometabolic risk factors in our sample as previously reported [12], exercise did not prevent the liposuction-induced impact on scAT cytokine expression profile. Previous studies have demonstrated improved circulating cytokine levels despite a lack of changes in scAT cytokine mRNA levels in response to an exercise program in overweight/obese subjects, suggesting a dissociation between serum levels and adipocyte gene expression of cytokines [20, 21]. This dissociation could be explained by posttranscriptional mechanisms and, most importantly, by the fact that immune cells, namely, monocytes, macrophages, dendritic cells, and T cells, may be the main accountable source for these cytokines' systemic levels [1].

This study was not without limitations. The follow-up period is rather short, thus warranting further long-term studies on the effects of decreased adiponectin levels on metabolism. Additionally, an exercise-only group would allow further insights on the effects of exercise *per se* on

Table 1: Effects of liposuction and exercise training on adipokine levels in normal-weight women.

Variable	PRE	POST2	POST6	Difference (CI 95%)	P
Adiponectin (μg/dL)					
Trained (n = 18)	19.3 (7.3)[a]	17.5 (6.8)[a]	12.5 (4.1)[b]	7.6 (2.8 to 12.4)	0.0003
Nontrained (n = 18)	19.4 (8.0)[a]	18.1 (8.4)[a]	12.8 (3.9)[b]	6.7 (2.0 to 11.3)	0.001
TNF-α (pg/mL)					
Trained (n = 11)	0.64 (0.72)[a]	0.86 (0.99)[a]	0.52 (0.40)[a]	0.19 (−0.73 to 1.11)	0.99
Nontrained (n = 7)	0.83 (0.42)[a]	0.90 (0.58)[a]	1.22 (1.10)[a]	−0.36 (−1.50 to 0.78)	0.92
IL-6 (pg/mL)					
Trained (n = 18)	1.15 (0.90)[a]	1.38 (1.33)[a]	0.80 (0.34)[a]	0.30 (−0.56 to 1.14)	0.90
Nontrained (n = 17)	0.85 (0.55)[a]	1.29 (0.87)[a]	1.23 (0.88)[a]	−0.38 (−1.20 to 0.46)	0.77
IL-10 (pg/mL)					
Trained (n = 18)	1.78 (0.76)[a]	1.79 (0.73)[a]	1.69 (0.94)[a]	0.11 (−0.54 to 0.76)	0.99
Nontrained (n = 16)	1.55 (0.76)[a]	1.64 (0.47)[a]	1.42 (0.60)[a]	0.14 (−0.53 to 0.81)	0.98

Data are expressed as mean (SD), estimated mean of differences (confidence interval of 95%), and level of significance (P) between PRE versus POST6 (within-group comparisons; mixed model for repeated measures). Equal superscripted letters represent equal means and different superscripted letters represent statistically different means ($P < 0.05$, between- or within-group comparisons).

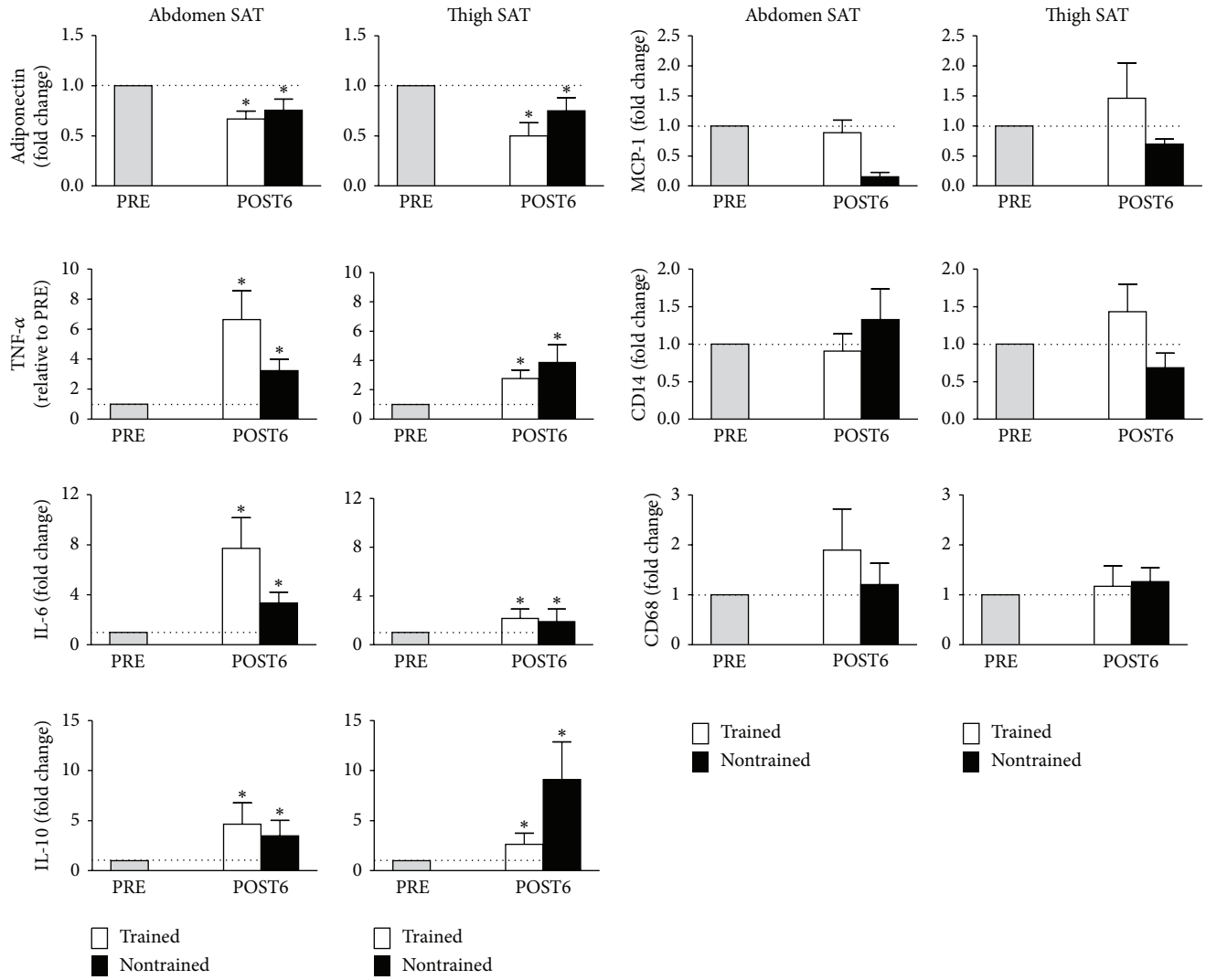

Figure 1: Subcutaneous abdominal and thigh gene expression of adiponectin, IL-6, IL-10, TNF-α, MCP-1, CD68, and e CD64. Data are expressed as means and standard deviation of fold change at POST6 with levels at PRE for both groups arbitrarily set to 1. * indicates main effects for time (PRE versus POST6).

Table 2: Effects of liposuction combined with exercise training on body composition and blood parameters in adult women.

Variable	PRE	POST2	POST6	Diff (CI 95%)	P
Body weight (Kg)					
Trained (n = 18)	61.7 (5.4)^{a}	60.8 (5.2)^{b}	61.4 (5.7)^{ab}	0.3 (−0.9 to 1.5)	0.98
Nontrained (n = 18)	59.7 (5.8)^{a}	58.5 (6.1)^{b}	58.9 (6.4)^{ab}	0.9 (−0.4 to 2.1)	0.32
Fat mass (Kg)					
Trained (n = 18)	17.9 (3.0)^{a}	16.7 (2.7)^{b}	16.3 (2.8)^{b}	1.6 (0.5 to 2.7)	0.001
Nontrained (n = 18)	17.6 (3.2)^{a}	16.1 (3.1)^{b}	16.6 (3.5)^{ab}	0.9 (−0.2 to 1.9)	0.14
Lean mass (Kg)					
Trained (n = 18)	43.9 (3.7)^{a}	44.2 (3.7)^{a}	45.1 (3.8)^{b}	−1.3 (−2.3 to −0.2)	0.008
Nontrained (n = 18)	42.3 (3.9)^{a}	42.4 (4.1)^{a}	42.2 (4.1)^{a}	−0.1 (−1.1 to 1.0)	1.0
Abdominal scAT area (cm^2)					
Trained (n = 18)	246 (42)^{a}	166 (36)^{b}	159 (30)^{b}	87.2 (64.4 to 110.0)	0.0001
Nontrained (n = 18)	244 (52)^{a}	170 (42)^{b}	170 (49)^{b}	73.2 (51.1 to 95.4)	0.0001
Abdominal VAT area (cm^2)					
Trained (n = 18)	42.9 (10.2)^{a}	41.2 (11.0)^{a}	38.1 (9.1)^{a}	4.5 (−0.4 to 9.4)	0.10
Nontrained (n = 18)	43.1 (14.9)^{a}	42.5 (14.7)^{a}	47.2 (14.2)^{b}	−4.1 (−7.3 to −0.8)	0.01
Plasma leptin (ng/mL)					
Trained (n = 18)	27.2 (7.8)^{a}	23.2 (7.5)^{a}	21.6 (8.1)^{a*}	5.9 (−0.5 to 12.4)	0.08
Nontrained (n = 18)	27.2 (11.4)^{a}	21.9 (10.1)^{a}	28.4 (12.4)^{a}	−1.2 (−7.2 to 4.9)	0.99
Plasma glucose (mg/dL)					
Trained (n = 18)	88.4 (8.8)^{a}	86.5 (5.8)^{a}	88.1 (7.4)^{a}	0.3 (−5.4 to 6.0)	1.0
Nontrained (n = 18)	86.7 (8.9)^{a}	87.0 (5.0)^{a}	88.1 (6.6)^{a}	−1.5 (−7.2 to 4.2)	0.99
Plasma insulin (mg/dL)					
Trained (n = 18)	7.7 (3.7)^{a}	8.2 (6.6)^{a}	7.1 (3.4)^{a}	0.6 (−2.6 to 3.7)	0.99
Nontrained (n = 18)	8.7 (3.8)^{a}	8.5 (3.3)^{a}	8.2 (3.2)^{a}	0.5 (−2.8 to 3.7)	0.99
AUC—glucose (mg/dL/min)					
Trained (n = 18)	13496 (2081)^{a}	13507 (2390)^{a}	12340 (2457)^{a}	1156 (−677 to 2989)	0.40
Nontrained (n = 18)	12932 (1952)^{a}	13698 (3191)^{a}	13230 (3210)^{a}	−298 (−2131 to 1534)	0.99
AUC—insulin (μU/mL/min)					
Trained (n = 18)	6262 (2634)^{a}	5213 (1655)^{a}	4251 (1151)^{b}	1738 (104 to 3371)	0.03
Nontrained (n = 18)	6725 (1966)^{a}	6640 (2505)^{a}	6496 (3013)^{a}	482 (−1235 to 2199)	0.96

scAT: subcutaneous adipose tissue. VAT: visceral adipose tissue. AUC: area under the curve. Data are expressed as mean (SD), estimated mean of differences (confidence interval of 95%), and level of significance (P) between PRE versus POST6 (within-group comparisons; mixed model for repeated measures). Equal superscripted letters represent equal means and different superscripted letters represent statistically different means ($P < 0.05$, between- or within-group comparisons). *indicates $P < 0.05$ for single degree of freedom contrast analysis (between-group comparisons at POST6).

adipokines. The subjects in the present study were otherwise healthy at baseline, precluding the generalization of this data to other populations and the sample size for the gene expression analysis was relatively low. Finally, the gene expression analysis may not reflect adipose tissue actual synthesis and secretion of adipokines, that is, protein levels.

In conclusion, the results of this study indicate that a small-volume liposuction markedly downregulates the scAT expression and serum levels of adiponectin whereas it upregulates scAT expression of pro- and anti-inflammatory genes in normal-weight women, irrespective of an exercise training program. These findings suggest that a liposuction surgery may not be free of long-term metabolic effects in this population. Notably, although exercise training was incapable of counteracting these potential associated risks, it improved several cardiometabolic risk factors (data previously published) [12] and should be recommended following this procedure.

Conflict of Interests

The authors also declare that they have no conflict of interests.

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Review Article

Does Regular Exercise without Weight Loss Reduce Insulin Resistance in Children and Adolescents?

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Despite considerable efforts to tackle childhood obesity, it is recognized as one of the biggest health problems globally. Childhood obesity is a leading cause of many comorbid conditions such as metabolic syndrome and insulin resistance as well as type 2 diabetes. A strong body of evidence suggests that regular exercise without calorie restriction or weight loss is associated with reduced insulin resistance as well as improved insulin sensitivity in overweight and obese adults. However, despite the well-known benefits associated with regular exercise alone, the independent role of exercise training without calorie restriction on insulin resistance is still uncertain in youth. Some studies observed that both the aerobic and resistance type of exercise training without calorie restriction resulted in meaningful changes in insulin sensitivity, suggesting that exercise alone is an effective therapeutic strategy for reducing insulin resistance in overweight and obese youth. However, only few studies are available on the optimal dose of exercise training without calorie restriction or preferred exercise modality for reducing insulin resistance, which warrants further investigations in the pediatric population.

1. Introduction

The prevalence of childhood obesity has been increasing throughout the world during the past few decades [1]. According to the recent report by the National Health and Nutrition Examination Survey (NHANES), more than one-third of children and adolescents aged 6–19 years are considered at risk for overweight (BMI ≥ 85th percentile) or overweight (BMI ≥ 95th percentile) in the USA [2]. Childhood obesity is recognized as a major public health concern since the simultaneous increase in obesity is paralleled by an increased prevalence of impaired glucose tolerance [3], metabolic syndrome (MetS) [4], and type 2 diabetes [5, 6] in youth. The overall prevalence of MetS, determined by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) definition, was approximately 4.2% in the US children and adolescents [4], which was present in 28.7% in overweight youth (BMI ≥ 95th percentile) but only 0.1% in those with BMI ≤ 85th percentile [7]. Furthermore, it is well established that obese youth are more insulin resistant than their leaner counterparts [8, 9] and more likely to develop diabetes than those with normal weight [10].

Independent of ethnicity, age, and sex, obesity represents the most important risk factor for insulin resistance as well as increased circulating levels of insulin, leading to decreased insulin sensitivity and impaired β-cell function, thereby developing type 2 diabetes in youth [11]. In addition, earlier onset of insulin resistance may be afflicted with the increase in cardiovascular morbidity and mortality risks in adult life [12]. Therefore, it is important to develop effective strategies to prevent or treat obesity as well as insulin resistance in the pediatric population.

In adults, a number of well-controlled studies have reported that insulin resistance is improved with regular exercise training even without calorie restriction or weight loss [13–16]. Although the mechanisms for the beneficial effects of regular exercise training alone have not been fully understood, improved insulin sensitivity and glucose uptake induced by muscle contraction after exercise training seem to play an important role in alleviating insulin resistance [17, 18]. Although some intervention studies in youth [19–22] have also reported significant improvements in insulin resistance after exercise training alone (without calorie restriction or

weight loss), the independent role of exercise training alone as a therapeutic strategy to reduce insulin resistance has not been firmly established yet. Furthermore, very little attention has been directed toward the impact of resistance exercise training alone on insulin resistance in children and adolescents.

Thus, in this review, we present the available evidence regarding the role of exercise training without calorie restriction for reducing insulin resistance in children and adolescents. In addition, we distinguish the exercise modality for enhancing insulin sensitivity, which should be recommended for the treatment of insulin resistance in this age group.

2. Physical Activity, Fitness, and Insulin Resistance

In adults, it is well established that physical activity and cardiorespiratory fitness are significantly associated with the constellation of diabetes-associated risk factors [23] as well as cardiovascular disease risks [24]. Thus, increased physical activity has a beneficial effect on reduction in the diabetes-associated risks by enhancing insulin sensitivity [25, 26]. Consistent with the observations in adults, cross-sectional studies in youth [27–29] have also shown that increased physical activity is associated with higher insulin sensitivity. Schmitz et al. [27] examined the association of questionnaire-determined physical activity and insulin sensitivity, assessed by the hyperinsulinemic euglycemic clamp technique known as the criterion measure of *in vivo* insulin sensitivity, in non-diabetic children aged 10–16 years ($n = 357$). They observed significant relationships between physical activity and lower fasting insulin ($r = -0.12$) and insulin sensitivity ($r = 0.18$) even after accounting for BMI, percent body fat, and/or waist circumference. In a recent report by Thomas et al. [28], accelerometer-determined physical activity, less prone to error than questionnaire, was also positively associated with intravenous glucose tolerance independent of fat free mass and race in black and white adolescents aged 12–18 year old.

With regard to the relationship between cardiorespiratory fitness and insulin sensitivity, previous cross-sectional studies in youth have reported conflicting results. Some studies [30–32] have suggested that cardiorespiratory fitness is not an independent predictor of insulin sensitivity when total or abdominal adiposity was taken into account, suggesting that fatness is of greater importance as a determinant of insulin sensitivity than cardiorespiratory fitness in youth. Conversely, other studies [29, 33–36] have demonstrated that cardiorespiratory fitness is inversely associated with insulin sensitivity even after accounting for body adiposity, suggesting that the negative effects of body fatness on insulin sensitivity may be mediated by the degree of cardiorespiratory fitness in youth. Although these conflicting results may be partially explained by the different subject characteristics or assessment techniques for insulin sensitivity and cardiorespiratory fitness, it is still inconclusive which component is a better contributor to insulin sensitivity in children and adolescents, which warrants further investigations.

It is well known that a single bout of aerobic exercise with sufficient duration and intensity can increase insulin-stimulated glucose uptake in contracting skeletal muscles and insulin sensitivity via increased translocation of glucose transporter (e.g., GLUT4) to the cell surface [17, 18]. However, studies have also reported that the positive effects of acute exercise on insulin sensitivity only persisted for about 48–72 hours [17]. In addition, detraining or inactivity can reduce the exercise-induced enhancement of insulin sensitivity in skeletal muscles in adults [37]. In youth, improved insulin sensitivity was also observed after a single bout of moderate-intensity (75% peak heart rate) exercise, which lasts at least 17 hours [38]. These observations suggest that exercise should be performed on a regular basis for the long-term improvement in insulin sensitivity.

A single bout of resistance exercise is also known to enhance insulin sensitivity at least 24 hours after the last exercise session in healthy individuals [39]. However, only limited evidence is available on this issue in the pediatrics, and the mechanisms by which the acute resistance exercise improves glucose regulation, as observed after the acute aerobic exercise, are not clearly understood, thereby requiring further investigations.

Combined together, the above observations clearly suggest that people should add regular exercise in their daily routine to increase or at least to maintain insulin sensitivity, which may further reduce the increased incidence of insulin resistance or associated risk factors in children and adolescents.

3. Aerobic Exercise and Insulin Resistance

Although many interventional studies have focused on the beneficial impact of exercise and calorie restriction-induced weight loss on insulin resistance and body composition, growing evidence also suggests that exercise training without substantial weight loss can induce meaningful improvements in insulin resistance in adults [13–16]. Duncan et al. [16] previously showed that a 6-month period of aerobic exercise training (3–7 days/week, 30 min/session, ~75% of heart rate reserve) without weight loss significantly increased insulin sensitivity, accessed by the frequently sampled intravenous glucose tolerance test (FSIVGTT) in sedentary adults. The change in insulin sensitivity was also inversely correlated with BMI ($r = -0.48$) in this study [16]. Although it is still questionable if the enhanced insulin sensitivity after aerobic exercise training depends on concomitant changes in total or abdominal adiposity or on the residual effects of the last exercise session, it is plausible that regular exercise alone significantly alters total or abdominal adiposity, particularly visceral adipose tissue, thereby influencing positive changes in insulin sensitivity.

Despite extensive observations and experiments in adults demonstrating the beneficial effects of aerobic exercise alone on insulin resistance, only limited evidence is available on this issue in children and adolescents (Table 1). Nassis et al. [40] examined the effect of a 12-week aerobic exercise training (3 days/week, 40 min/session, HR $\geq$ 150 bpm) without weight

Table 1: Aerobic exercise and insulin resistance (nonrandomized controlled trials).

References	Gender	Age	Treatment	BW (kg)	BMI (kg/m^2)	IS	Study Duration	Protocol	ΔBW (kg)	ΔBMI (kg/m^2)	ΔIS (%)	IS Measure
Nassis et al. [40]	19 girls	9–15	Exercise	67.9	26.8	4.34	12 wk	3 days/wk, 40 min/day running, steps, stair climbing, and so forth HR > 150 bpm	0.4	−0.1	1.1	HOMA-IR
Caranti et al. [48]	37 boys 46 girls	15–19	Exercise	102.8 92.5	36.2 35.7	4.8 3.6	1 yr	Exercise combined with nutrition, psychological, clinical therapy 3 days/wk, 60 min/day (walking, cycling, etc.)	−10.5* −4.9*	−4.1* −2.1*	−33.3* −13.6	HOMA-IR
Monzavi et al. [49]	60 boys 49 girls	8–16	Exercise	78.2	33.7	5.52	12 wk	Lifestyle intervention program 90 min/session (weekly) 45 min of exercise (dodge ball, jump rope, etc.) + 45 min of nutrition education	0.1	−0.5*	−32.6	HOMA-IR
Kelishadi et al. [50]	19 boys 16 girls	12–18	Exercise	57.1	25.3	5.4	6 wk	3 days/wk, 60 min/day (30 min fitness + 30 min of games)	−2.4*	−1.2*	−22.2*	HOMA-IR
Van der Heijden et al. [41]	17 boys 12 girls	15.1	Obese exercise Lean exercise	91.7 57.2	33.7 20.6	4.9 1.7	12 wk	2 days/wk, 30 min/day ≥70% of VO_2 peak treadmill, elliptical, cycle	−0.5† 0.8*	−0.4† 0.1	−16.3*† 11.8	HOMA-IR

BMI: body mass index; BW: body weight; HOMA-IR: homeostasis model assessment of insulin resistance; IS: insulin sensitivity; Δ: Change score.
*Significantly different from baseline within each group ($P < 0.05$).
†Significantly different from controls or other groups ($P < 0.05$).

loss on insulin sensitivity in overweight and obese girls aged 9–15 years. After the exercise training, the authors observed a significant reduction in the insulin area under the curve (insulin AUC) following an oral glucose tolerance test (OGTT) by 23.3% without changes in body weight or total adiposity. Similarly, a recent study by Van Der Heijden et al. [41] also demonstrated that a 12-week period of moderate aerobic exercise training (2 days/week, 30 min/session, ≥70% of VO_2 peak) resulted in decreased insulin resistance in postpubertal obese adolescents. Indeed, the decreased fasting insulin was significantly correlated ($r^2 = 0.40$) with the decreased visceral adiposity in this study.

To the best of our knowledge, there are 6 randomized controlled trials wherein the effects of aerobic exercise on insulin sensitivity were examined in children and adolescent (Table 2). Meyer et al. [42] reported that a 6-month period of aerobic exercise training (3 times/week, 60~30 min/session) without calorie restriction resulted in a significant decrease in fasting insulin (21%) in obese adolescents aged 11–16 years. Recently, Davis et al. [21] compared dose-response effects of the short-term (13 weeks) aerobic exercise training (5 times/week, low dose: 20 min/session versus high dose: 40 min/session) on insulin resistance in overweight and obese youth aged 7–11 years with the exercise intensity held constant at a moderate-to-vigorous level (HR ≥ 150 bpm). After the exercise training, the decrease in insulin AUC was significantly greater in both exercise groups than the controls although the magnitude of the decrease in insulin action and adiposity was somewhat greater in the high-dose exercise training group versus low-dose exercise training group. These observations suggest that low- and high-dose of moderate-to-vigorous physical activity in most days are similarly effective in improving insulin resistance in overweight and obese youth.

Savoye et al. [19] examined the influence of 1-year behavioral modification program combined with nutrition education and aerobic exercise (1–6 month: 2 times/week, 50 min/session, 7–12 month: 2 times/month, 100 min/session, 65–80% of maximal HR) on body composition and insulin resistance in overweight youth aged 8–16 years. The authors reported significant decreases in fasting insulin levels (−28.3%) and homeostasis model assessment of insulin resistance (HOMA-IR, −29.8%) in the exercise training group as compared to the controls after the intervention. Furthermore, these improvements were sustained at 12 months of the intervention in the exercise training group.

Taken together, these observations provide some evidence that engaging in regular aerobic types of exercise in the absence of weight loss or calorie restriction is beneficial to improve insulin resistance in overweight and obese youth.

4. Resistance (or Combined) Exercise and Insulin Resistance

Although majority of studies have implemented aerobic exercise training as an efficient exercise modality for reducing insulin resistance, considerable evidence also suggests a beneficial effect of carefully supervised resistance (or combined) exercise training without calorie restriction on insulin resistance in adults [43–45]. Davidson et al. [45] reported that resistance or combined exercise training without weight loss or calorie restriction is associated with a significant improvement in insulin sensitivity in overweight or obese adults, which may be also attributed to increased fat free mass (muscle mass) or decreased total or abdominal fat mass after resistance training. However, relatively little evidence is available on the impact of resistance exercise training alone on insulin resistance in overweight youth. Indeed, it is still unclear if resistance type of exercise training is more effective than aerobic type of exercise training to improve insulin resistance particularly in overweight or obese children and adolescents.

Previously, Treuth et al. [46] have demonstrated that although modest changes were observed, a 5-month resistance training (3 times/week, 20 min/session, >50% of 1-repetition maximum) did not significantly alter fasting insulin (−4.1%) or fasting glucose levels (−4.0%) in obese girls aged 7–10 years (Table 3). Conversely, using the clamp technique, Bell et al. [47] reported that an 8-week period of combined exercise training (3 times/week, 60 min/session) without weight loss was associated with a significant improvement in insulin sensitivity (22.2%), determined within 48 hours after the last training session in obese youth. The improvement in insulin sensitivity was correlated with the improved cardiorespiratory fitness levels but not with body composition changes, suggesting that fitness level is of importance to reduce or prevent insulin resistance in obese children and adolescents. However, given the combined exercise training format applied in this study [47], it is limited to distinguish if the improvements may be solely due to resistance exercise training in this population.

To the best of our knowledge, there are 6 randomized controlled studies wherein the effects of resistance (or combined) exercise training without calorie restriction on insulin sensitivity were examined in children and adolescent (Table 4). Shaibi et al. [22] examined whether resistance training alone is effective for improvements in insulin sensitivity in overweight Latino male adolescents ($n = 22$). The subjects were randomly assigned to either resistance training group (2 times/week, 60 min/session) or control group. After the intervention, insulin sensitivity, determined by FSIVGTT, significantly increased (45.1%) in the exercise group, as compared to the controls. In this study, the increased insulin sensitivity was induced independent of cardiorespiratory fitness or body composition changes. Recently, Lee et al. [20] conducted a randomized controlled trial examining the effects of aerobic exercise versus resistance exercise without calorie restriction on insulin sensitivity in black and white obese male adolescents aged 12–18 years. They demonstrated a significant improvement in insulin sensitivity (27.6%), assessed by the euglycemic clamp technique, after a 3-month resistance exercise training (3 times/week, 60 min/session) without calorie restriction but not after the aerobic exercise training. Unlike the observations by Shaibi et al. [22], the improvements in insulin sensitivity was associated with exercise-induced increases in skeletal muscle mass as well as cardiorespiratory fitness levels in the resistance exercise

Table 2: Aerobic exercise and insulin resistance (randomized controlled trials).

References	Gender	Age	Treatment	BW (kg)	BMI (kg/m^2)	IS	Study Duration	Protocol	ΔBW (kg)	ΔBMI (kg/m^2)	ΔIS (%)	IS Measure
Kelly et al. [51]	9 boys 11 girls	11.0	Control exercise	73.5 75.4	30.5 32.1	6.0 6.2	8 wk	4 times/wk, 30–50 min/session 50–80% of VO_2 peak	0.8 1.1	−0.1 0.0	−2.8 5.2	2 h Glucose (OGTT) (mmol/L)
Meyer et al. [42]	47 boys 49 girls	12–16	Control exercise	NA	31.0 29.8	4.4 3.9	6 mo	3 days/wk, 60–90 min/day swimming, games, and so forth	NA	0.3 −2.6*	11.0 −20.8*	HOMA-IR
Kim et al. [52]	26 boys (Korean)	17.0	Control exercise	90.4 89.7	29.4 29.6	2.9 2.5	6 wk	5 days/wk, 40 min/day Jump rope (60–90 jumps/min)	0.0 −2.2*	−0.3 −1.0*	−18.2 −33.6*	HOMA-IR
Savoye et al. [19]	68 boys 106 girls	8–16	Control exercise	91.2 87.0	36.2 35.8	5.2 5.1	1 yr	Exercise & behavior modification. >100 min/wk for the first 6 mo >200 min/mo for the last 6 mo 65–80% of maximal HR	6 mo/1 yr 5.0/7.7 −2.6†/0.3†	6 mo/1 yr 1.1/1.6 −2.1†/−1.7†	6 mo/1 yr 6.1/16.8 −27.7†/−27.8†	HOMA-IR
Lee et al. [20]	45 boys	12–18	Control exercise	100.0 106.5	33.9 36.6	2.7 2.2	3 mo	3 days/wk, 60 min/session 50~75% of VO_2 peak	2.6* −0.04	0.3 −0.3	−3.7 18.2*†	Euglycemic clamp (mL/kg/min per μU/min)
Davis et al. [21]	94 boys 128 girls	7–11	Control Low-dose exercise High-dose exercise	NA	26.3 25.9 25.6	2.5 2.2 2.4	10–15 wk	5 days/wk, HR > 150 bpm Low-dose: 20 min/day High-dose: 40 min/day	NA	NA	Adjusted mean diff. 0.11 (high versus low) 0.56 (low versus con.) 0.67 (high versus con.)	Matsuda index of insulin sensitivity

BMI: body mass index; BW: body weight; HOMA-IR: homeostasis model assessment of insulin resistance; IS: insulin sensitivity; OGTT: oral glucose tolerance test; Δ: Change score.

*Significantly different from baseline within each group ($P < 0.05$).

†Significantly different from controls or other groups ($P < 0.05$).

Table 3: Resistance or combined exercise and insulin resistance (nonrandomized controlled trials).

References	Gender	Age	Treatment	BW (kg)	BMI (kg/m^2)	IS	Study Duration	Protocol	ΔBW (kg)	ΔBMI (kg/m^2)	ΔIS (%)	IS Measure
Treuth et al. [46]	22 girls	7–10	Control (lean) exercise	29.1 46.6	NA	NA 315.9	5 mo	3 days/wk, 50% of 1RM 2 sets, 12–15 reps, 7 exercises	2.9* 4.0*	NA	NA −8.2	Insulin AUC (OGTT) (pmol/L)
Bell et al. [47]	8 boys 6 girls	12.7	Exercise	80.6	31.6	8.2	8 wk	3 days/wk, 60 min/session Strength exercise (2 sets, 10 exercises, 55–65% of 1RM) + Aerobic exercise (cycling)	0.6	−0.4	22.2*	Euglycemic clamp $M_{(lbm)}$ (mg/kg/min)
Van der Heijden et al. [53]	6 boys 6 girls	15.5	Exercise	97.0	35.3	3.0	12 wk	2 times/wk, 60 min/session 2-3 sets, 8–20 reps	2.6*	0.8*	24.0*	Hepatic insulin sensitivity index

BMI: body mass index; BW: body weight; HOMA-IR: homeostasis model assessment of insulin resistance; IS: insulin sensitivity; OGTT: oral glucose tolerance test; RM: repetition maximum; Δ: Change score.
*Significantly different from baseline within each group ($P < 0.05$).
†Significantly different from controls or other groups ($P < 0.05$).

Table 4: Resistance or combined exercise and insulin resistance (randomized controlled trials).

References	Gender	Age	Treatment	BW (kg)	BMI (kg/m^2)	IS	Study Duration	Protocol	ΔBW (kg)	ΔBMI (kg/m^2)	ΔIS (%)	IS Measure
Shaibi et al. [22]	22 boys	15.6 15.1	Control exercise	98.3† 90.0	34.6 32.5	1.7 2.3	16 wk	2 days/wk, <1 h/session 2 sets, ~15 reps, 10 exercises ~97% of 1RM	2.1 1.9	0.4 0.4	5.9 39.1*†	FSIVGTT ($\times 10^{-4}$/min/μU/mL)
Chang et al. [54]	36 boys 13 girls (Chinese)	12–14	Control exercise	71.3 75.8	27.1 27.5	7.5 6.8	1 yr	2–5 times/wk, 60–90 min/session Aerobic + strength exercise 0–9-months: supervised exercise 10–12-months: no intervention	9 mo/1 yr ≈4.5/7.5 ≈1.2/6.2	9 mo/1 yr ≈0.5/0.7 ≈−0.6/0.6	9 mo/1 yr NA/44.0* −48.5*/44.1	HOMA-IR
Benson et al. [55]	46 boys 32 girls	10–15	Control exercise	51.7 59.2	22.1 24.0	1.1 1.3	8 wk	2 days/wk, 2 sets, 8 reps 11 exercises, 80% of 1RM	2.0 1.5	0.4 0.0	0.2 (log) 0.1 (log)	HOMA-IR
Davis et al. [56]	28 boys 26 girls	14–18	Control nutrition EDU (NU) NU + exercise	93.0 87.9 95.3	33.7 32.3 34.9	1.8 1.6 1.5	16 wk	2 days/wk, <1 h/session 2 sets, ~15 reps, 10 exercise ~97% of 1RM + 1 time/wk of nutrition EDU, 90 min/session	0.6 0.1 −0.3	0.2 −0.1 0.0	5.6 12.5 0.0	FSIVGTT ($\times 10^{-4}$/min/μU/mL)
Davis et al. [57]	44 youth	14–18	Control exercise Motivation + exercise	94.4 80.2 88.5	36.4 32.4 34.6	4.9 2.0 1.6	16 wk	2 days/week, 60–90 min/session 30–45 min of aerobic exercise (70–85% of maximal HR) + 30–45 min of strength exercise 8 motivation interview sessions	NA	NA	−4.0 −21.0 NA	HOMA-IR
Lee et al. [20]	45 boys	12–18	Control exercise	100.0 97.7	33.9 34.5	2.7 2.9	3 mo	3 days/wk, 60 min/session 1-2 sets, 8–12 reps, 10 exercises >60% of baseline 1RM	2.6* −0.6	0.3 −0.6*	−3.7 27.6*†	Euglycemic clamp (mL/kg/min per μU/min)

BMI: body mass index; BW: body weight; EDU: education; FSIVGTT: frequently sampled intravenous glucose tolerance test; HOMA-IR: homeostasis model assessment of insulin resistance; IS: insulin sensitivity; OGTT: oral glucose tolerance test; RM: repetition maximum; Δ: change score.

*Significantly different from baseline within each group ($P < 0.05$).

†Significantly different from controls or other groups ($P < 0.05$).

training group in this study [20]. Furthermore, when both exercise groups were combined, the improvements in insulin sensitivity was significantly correlated with decreased total adiposity ($r = -0.43$) and visceral adipose tissue ($r = -0.42$), suggesting that improvements in body composition may play an important role to enhance insulin sensitivity in obese adolescents. In addition, the authors also noted that as compared with aerobic exercise, resistance exercise may be a better exercise modality to enhance body composition and insulin sensitivity particularly in obese male adolescents.

Taken together, despite the lack of conclusive evidence in the pediatrics, the observations demonstrating that resistance exercise training is associated with improvement in insulin resistance are clearly encouraging children and adolescents to participate in resistance type of exercise on daily basis. However, future studies are also required to explore the long-term effects of resistance exercise training on insulin resistance as well as determining the optimal exercise modality, as the effective therapeutic strategy to reduce insulin resistance in this population.

5. Summary

The dramatic increase in childhood obesity in recent years is paralleled by decreased physical activity as well as cardiorespiratory fitness levels, which is also attributed to increase insulin resistance and diabetes-associated risk factors in children and adolescents. As observed in adults, an increasing body of evidence suggests that acute physical activity and chronic exercise have a beneficial effect on reductions in insulin resistance through multiple adaptations such as improved insulin sensitivity and glucose uptake of skeletal muscles and body composition changes in overweight children and adolescents. Studies also demonstrated that both aerobic and resistance type of exercise alone (without weight loss or calorie restriction) resulted in significant improvement in insulin sensitivity, suggesting that exercise alone is an effective therapeutic strategy for reducing insulin resistance in overweight and obese children and adolescents. However, future studies are required to explore the optimal dose of exercise and efficacious modality to elicit meaningful reductions in insulin resistance in youth.

Conflict of Interests

No potential conflict of interests relevant to this paper was reported.

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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, catchecolamines (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 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.

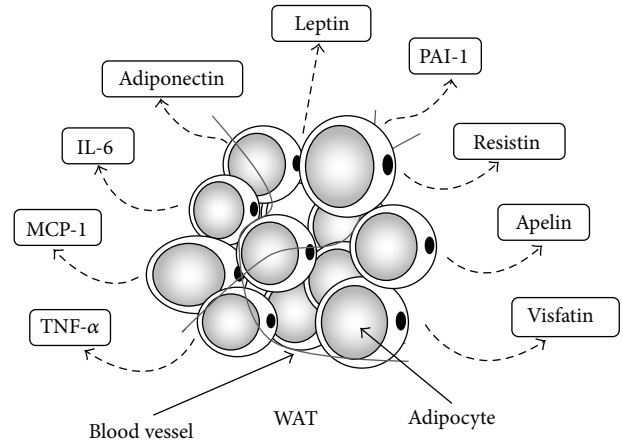

Figure 1: Adipokines secreted by white adipose tissue. White adipose tissue (WAT) secretes various humoral factors called adipokines. Adipokines have important effects on lipid and glucose metabolism, and so on. TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin-6;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

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

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 (% BFM)
Zachwieja et al. [23]	Diet-induced obesity sensitive rats	Voluntary wheel running	None	7 weeks	Epididymal and inguinal WAT	**Epididymal WAT** Leptin mRNA: decrease ($P < 0.05$) **Inguinal WAT** Leptin mRNA: decreasing trend	Epididymal and inguinal FM: decrease
	Diet-induced obesity resistant rats	Voluntary wheel running	None	7 weeks	Epididymal and inguinal WAT	**Epididymal WAT** Leptin mRNA: decrease ($P < 0.05$) **Inguinal WAT** Leptin mRNA: decreasing trend	Epididymal and inguinal FM: decrease
Gollisch et al. [24]	Rats chow diet	Voluntary wheel running	None	4 weeks	Visceral and subcutaneous WAT	**Visceral WAT** Leptin mRNA: decrease ($P < 0.05$) TNF-α mRNA and protein: NS MCP-1 mRNA: NS Adiponectin mRNA: NS IL-6 mRNA: NS **Subcutaneous WAT** Leptin mRNA: NS TNF-α mRNA and protein: increase ($P < 0.05$) MCP-1 mRNA: NS Adiponectin mRNA: NS IL-6 mRNA: increase ($P < 0.05$)	BM: NS; Visceral and subcutaneous FM: decrease
	Rats HFD	Voluntary wheel running	None	4 weeks	Visceral and subcutaneous WAT	**Visceral WAT** Leptin mRNA: decrease ($P < 0.05$) TNF-α mRNA and protein: NS MCP-1 mRNA: NS Adiponectin mRNA: NS IL-6 mRNA: NS **Subcutaneous WAT** Leptin mRNA: decrease ($P < 0.05$) TNF-α mRNA: increase ($P < 0.05$) TNF-α protein: NS MCP-1 mRNA: NS Adiponectin mRNA: decrease ($P < 0.01$) IL-6 mRNA: increase ($P < 0.05$)	BM: decrease; Visceral and subcutaneous FM: decrease

(a) Continued.

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)
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 ($P < 0.05$) **Mesenteric WAT** 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	**Perigonadal WAT** TNF-α mRNA: decrease ($P < 0.05$) MCP-1 mRNA: decrease ($P < 0.05$) **Mesenteric WAT** MCP-1 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% $\dot{V}O_2$ 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 12 weeks** Leptin mRNA: decreasing trend TNF-α mRNA: decrease ($P < 0.001$) MCP-1 mRNA: decrease ($P < 0.001$)	**Exercise for 6 weeks** BM and epididymal FM: decrease **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 % BFM: decrease

(a) Continued.

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)
Lira et al. [29]	Rats chow diet	Treadmill running on 5 times/week at 55–65% $\dot{V}O_2$ 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: NS **Exercise for 12 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%

(b) Continued.

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	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	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 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; $\dot{V}O_2$ max: maximal oxygen uptake; WAT: white adipose tissue.

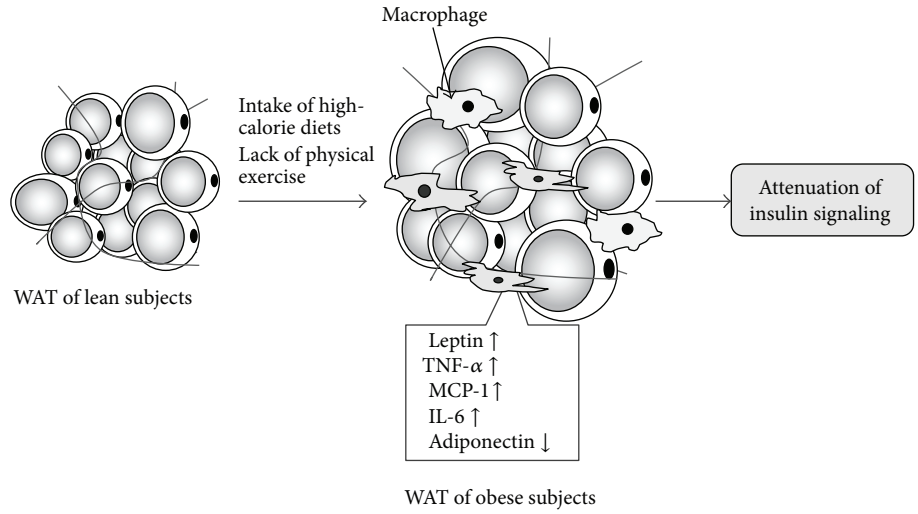

Figure 2: Model of the development of chronic inflammation in WAT. Adipocytes begin to grow as a result of factors such as excess energy intake and lack of exercise, and MCP-1 is secreted from these enlarged adipocytes. Macrophages infiltrate into WAT by the action of MCP-1, and as a result, increased expression of inflammatory adipokines (TNF-α, MCP-1, and IL-6) and decreased expression of anti-inflammatory adipokines (adiponectin) occur in WAT. Dysregulated expression of adipokines-induced inflammation of WAT contributes to the development of insulin resistance.

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 six 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].

Table 2: Effects of exercise training on human blood levels of leptin.

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)
				Aerobic exercise					
Houmard et al. [35]	7 m, 9 f	Younger lean	Cycle ergometer at 70–75% $\dot{V}O_2$ max for 60 min	None	7 days	7.1 ± 1.3	7.6 ± 1.3	NS	BM: NS
	6 m, 8 f	Older subjects with relatively more adipose tissue	Same as above	None	7 days	14.2 ± 2.7	11.0 ± 1.3	NS	BM: NS
Halle et al. [36]	20 m	Obese with T2DM	Cycle ergometer for 30 min on 5 times/week at 70% HRM (1,100 kcal/wk)	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%	4 weeks	7.9 ± 4.4	5.6 ± 3.5	$P < 0.001$	BMI: decrease
Ishii et al. [37]	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 on at least 5 times/week	25- to 27-kcal/kg/day diet (54% to 58% carbohydrate, 22% to 24% protein, 18% to 20% fat)	6 weeks	7.2 ± 3.6	4.6 ± 2.5	$P < 0.05$	BM, BMI, and % BFM: NS
	11 m, 16 f	T2DM diet therapy alone	None	Same as above	6 weeks	6.9 ± 3.4	5.6 ± 2.9	NS	BM, BMI, and % BFM: NS
Boudou et al. [38]	8 m	T2DM control	None	None	8 weeks	7.26 ± 3.85	7.40 ± 3.95	NS	BM and BMI: NS; Visceral and subcutaneous adipose tissue (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	6.05 ± 4.60	5.60 ± 4.30	NS	BM and BMI: NS; Visceral and subcutaneous adipose tissue (cm^2): decrease
Kraemer et al. [39]	14 f	Overweight control	None	None	9 weeks	33.24 ± 3.78	34.69 ± 3.14	NS	BM, BMI, and % BFM: NS
	16 f	Overweight exercise	Three-four times/week of four 20–30 min/session. Two of the exercise days consisted of step aerobics and 1-2 of the exercise days consisted of treadmill or stationary cycle exercise	None	9 weeks	28.0 ± 2.13	31.04 ± 2.71	NS	BM, BMI, and % BFM: 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 (% BFM)
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	BM, FM, and % FM: NS
	9 f	Middle aged sedentary	Same as above	None	12 weeks		Decrease of 17.5%	$P < 0.05$	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% $\dot{V}O_2$ 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% $\dot{V}O_2$ 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 $\dot{V}O_2$ max for 30 min per session at the beginning, increasing progressively toward an intensity of 75% of $\dot{V}O_2$ 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	11.9 ± 8.5	12.4 ± 8.1	NS	BMI, FM, and % BMF: 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

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 (% 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	$P < 0.01$	BM, 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
				Resistance exercise					
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	BM, BMI, FM, and % BFM: NS
	7 f	Obese postmenopausal women RT + WL	Same as above	Dietary counseling and energy restriction (hypocaloric diets)	16 weeks	22.9 ± 3.9	14.6 ± 2.6	$P < 0.01$	BM, 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; $\dot{V}O_2$ 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% $\dot{V}O_2$ 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 mice'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% $\dot{V}O_2$ 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 deceases 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. [59]	11 m, 1 f	Nonobese NIDDM	Walking about 15,000 steps daily	Dietary treatment (1400–1720 kcal/day with a diet consisting of 20 energy percent (en%) protein, 25 en% fat, and 55 en% carbohydrates	4 weeks			NS	BMI and visceral adipose tissue area (cm^2): decrease; subcutaneous adipose tissue (cm^2): NS
	11 m, 1 f	Obese-NIDDM	Same as above	Same as above	4 weeks		Decrease	$P < 0.01$	BMI, visceral and subcutaneous adipose tissue area (cm^2): decrease;
Strçzkowski et al. [60]	8 f	Obese with normal glucose tolerance	Cycle ergometer for 30 min on 5 times/week at 70% HRM	None	12 weeks	3.88 ± 0.49	3.27 ± 0.54	$P < 0.05$	BM, BMI, FM, and % BFM: decrease
	8 f	Obese with impaired glucose tolerance	Same as above	None	12 weeks	6.59 ± 2.31	5.15 ± 1.19	$P < 0.05$	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 week	6.1 ± 7.6	4.8 ± 4.5	$P = 0.08$	BM, BMI, and % BFM: decrease
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%/week	15 weeks	1.0 ± 0.08	1.0 ± 0.2	NS	BM, BMI, and FM: decrease
Kondo et al. [45]	8 f	Nonobese control	None	None	7 months	2.3 ± 0.9	2.1 ± 1.4	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% 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

(a) Continued.

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	6.0 ± 4.0 (6 weeks) 5.9 ± 2.7 (12 weeks)	NS	
	4 f		Same as above	None	12 weeks	5.6 ± 3.7	37.8 ± 24.7[a] (6 weeks) 17.6 ± 6.4[b] (12 weeks)	[a]$P < 0.05$ (versus pre) [b]$P < 0.05$ (versus pre and 6 weeks)	
	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 week) 5.8 ± 2.9 (12 week)	NS	
	4 f		Same as above	None	12 weeks	2.8 ± 2.0	6.6 ± 4.08 (6 weeks) 0.3 ± 0.5 (12 weeks)	NS	
	8 m	Healthy endurance and resistance training	Combination of above endurance and resistance training	None	12 weeks	2.3 ± 1.9	4.7 ± 0.5 (6 weeks) 5.6 ± 2.9 (12 weeks)	NS	
	5 f		Same as above	None	12 weeks	4.5 ± 2.0	8.0 ± 4.0 (6 weeks) 4.5 ± 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	Main effect of time, $P = 0.001$	BMI: NS
	47	Over weight flexibility/strength exercise with or without β-blocker treatment	Flexibility/strength exercise for 45 min on 3 times/week	None	10 months		Decrease	Main effect of time, $P = 0.001$	BMI: NS

(a) Continued.

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]	Base line: 70 6 months: 63: 18 months: 60	Overweight or obese older control	None	None	18 months	3.8 ± 7.5	Changes −0.74 ± 3.7 (6 months) −0.77 ± 3.7 (18 months)	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	Changes −0.69 ± 5.8 (6 months) 0.28 ± 6.3 (18 months)	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	Changes −0.23 ± 1.8 (6 months) 0.64 ± 5.9 (18 months)	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	Changes −0.46 ± 3.7 (6 months) −0.72 ± 4.6 (18 months)	NS	BM: decrease

(b) MCP-1

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
Trøseid et al. [64]	14	MS with or without administration of pravastatin control	None	None	12 weeks		−2.0 (the changes from baseline in plasma levels of MCP-1)	NS	BMI: NS

(b) Continued.

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
	18	MS with or without administration of pravastatin exercise	The duration of each workout was 45–60 min. Approximately 40% of the scheduled workout was walking/jogging/cycling and 60% was strength training. The strength training was performed in cycles with 15–20 repetitions per cycle, and large muscle groups such as thighs, back, and abdomen were trained.	None	12 weeks		−50	$P < 0.01$	BMI: decrease
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		Decreasing trend (Relative changes)	$P = 0.06$	BM and BMI: NS Changes in body weight after intervention were 3.5%
	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	12 weeks		Decrease	$P < 0.05$	BM and BMI: NS Changes in body weight after intervention were 11.1%
	10 m, 9 f	Obese hypocaloric diet	None	Very low energy diet (600 kcal/day) for 8 weeks followed by a weight maintenance diet for 4 weeks	12 weeks		Decrease	$P < 0.05$	BM and BMI: NS Changes in body weight after intervention were 10.5%
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%/week	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; $\dot{V}O_2$ 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 (μg/mL)	Postadiponectin (μg/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 ± 0.6	9.8 ± 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 ± 0.26	6.7 ± 0.7	$P < 0.001$	BM, BMI, and % BFM: decrease
	11 m, 9 f	T2DM	Same as above	None	4 weeks	3.5 ± 0.4	6.5 ± 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	BM, BMI, and % BFM: decrease
	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 ± 2.55	7.05 ± 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 ± 2.75	6.00 ± 3.50	NS	BM and BMI: NS; visceral and subcutaneous adipose tissue area (cm^2): decrease

Table 4: Continued.

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. [67]	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).	12 weeks	7.6 ± 0.9	6.6 ± 1.0	NS	BM, BMI, and FM: decrease
	3 m, 7 f	Older insulin-resistant exercise + eucaloric diet	Same as above	Weight maintenance diet that consisted of their usual food consumption (~1,800 kcal/day)		7.7 ± 1.2	6.8 ± 1.6	NS	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% $\dot{V}O_2$ max	None	12 weeks	10.9 ± 6.1	10.0 ± 4.4	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	9.57 ± 3.01	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	BM and BMI: NS Changes in body weight after intervention were 3.5%
	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	12 weeks		Increase	$P < 0.05$	BM and BMI: NS Changes in body weight after intervention were 11.1%
	10 m, 9 f	Obese hypocaloric diet	None	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 10.5%

Table 4: Continued.

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)
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%/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 exercise	Treadmill walking/running, stair climbing, and cycling for 45 min at 65–80% $\dot{V}O_2$ 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	None	None	7 months	8.3 ± 1.5	8.2 ± 2.3	NS	BM, BMI: NS; FM and % BFM: decrease
	8 f	Obese	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	2.4 ± 1.3	4.2 ± 1.2	$P < 0.01$	BM, 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	4.13 ± 0.88	5.47 ± 0.59	$P = 0.04$	BMI, and % BFM: 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 % BFM: decrease
Resistance exercise									
Fatouros et al. [50]	10 m	Overweight elderly control	None	None	24 weeks	7.22 ± 2.7	7.84 ± 3.5	NS	BM and BMI: NS
	14 m	Overweight elderly low-intensity RT	Resistance training for approximately 60 min on 3 times/week at 45–50% of 1RM	None	24 weeks	7.45 ± 2.3	8.48 ± 2.2	NS	BM: NS; BMI: decrease
	12 m	Overweight elderly moderate-intensity RT	Resistance training for approximately 60 min on 3 times/week at 60–65% of 1RM	None	24 weeks	7.79 ± 1.4	9.48 ± 1.1	$P < 0.05$	BM: NS; BMI: decrease
	14 m	Overweight elderly high-intensity RT	Resistance training for approximately 60 min on 3 times/week at 80–85% of 1RM	None	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; $\dot{V}O_2$ 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, 82–84]. 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

Table 5: Effects of exercise training on human blood levels of IL-6.

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 powertraining	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%/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 β-blocker treatment	Aerobic exercise for 45 min on 3 times/week	None	10 months		Decrease	Significant treatment × time interaction. $P < 0.05$	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			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: 70 6 months: 63: 18 months: 60	Overweight or obese older control	None	None	18 months	4.7 ± 3.2	Changes 0.19 ± 2.8 (6 months) 0.27 ± 2.8 (18 months)	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	4.4 ± 3.1	Changes 0.15 ± 1.8 (6 months) 0.02 ± 2.4 (18 months)	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	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	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	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.

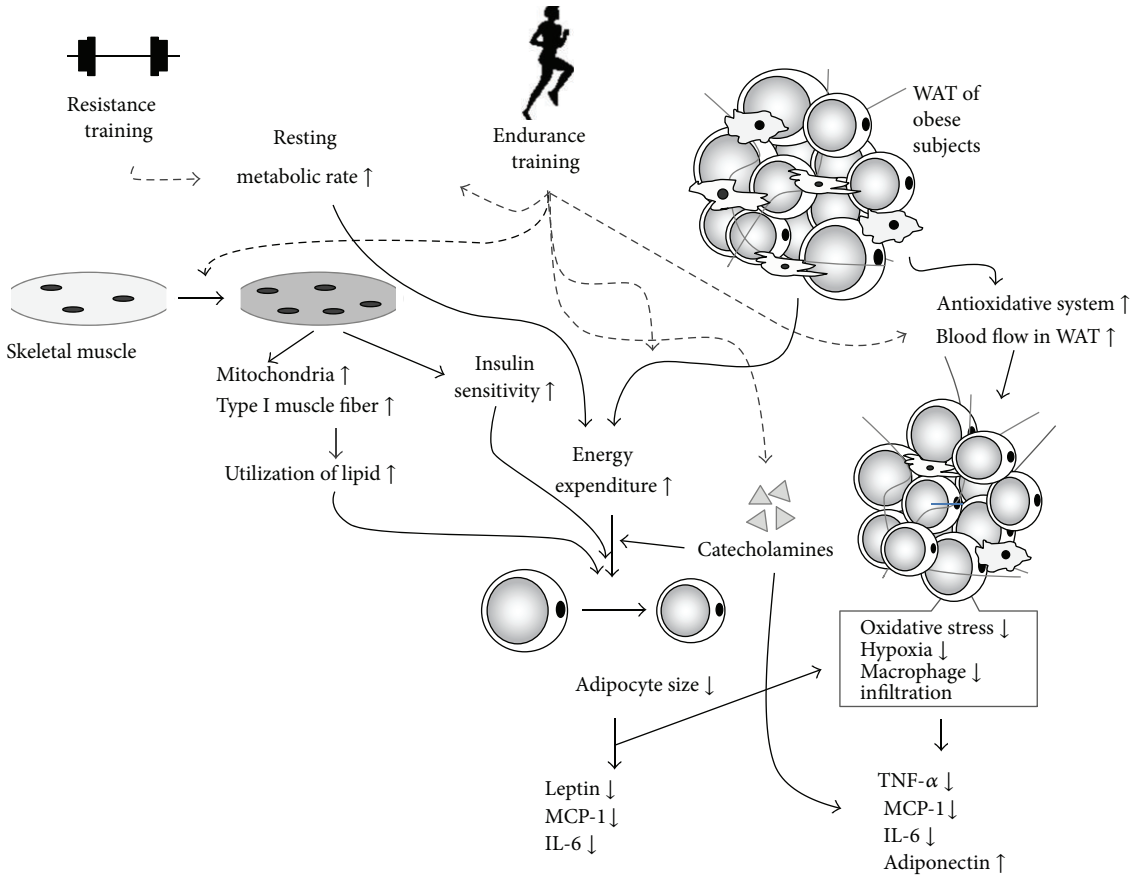

Figure 3: Schematic model for the effects of exercise training on expression of adipokines in WAT. During endurance training, type I muscle fibers in skeletal muscle are selectively used for the execution of exercises, and therefore, energy expenditure using lipid increases. Triglycerides within the adipocytes are broken down due to the secretion of catecholamines, and the resultant fatty acids are transported to tissues such as skeletal muscle. When exercise is repeated, adipocyte size is lessened. Decreases in adipocyte size are considered to result in the attenuation of dysregulated expression of adipocyte size-sensitive adipokines, such as leptin and oxidative stress in WAT. Moreover, catecholamine itself seems to correct disarray of adiponectin and TNF-α in WAT of obese subjects. In addition, endurance training might suppress oxidative stress and a hypoxic state of WAT due to an enhanced antioxidative system and increases in blood flow, respectively, which lead to the attenuation of the dysregulated expression of inflammatory-related adipokines involving TNF-α and MCP-1. In skeletal muscle, endurance training produces transition to type I muscle fiber following the increase in mitochondria biogenesis and enhances insulin sensitivity. Consequently, enhanced glucose/lipid metabolism in skeletal muscle decreases adipocyte size. On the other hand, resistance and endurance training enhance resting metabolic rate, which is likely to cause the alteration of adipokine expression following WAT mass reduction due to increased energy expenditure in the resting state.

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 blood 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 adiponetin. 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 dysregulated 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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Clinical Study

Effect of Exercise on Metabolic Syndrome Variables in Breast Cancer Survivors

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Objective. Breast cancer survivors are highly sedentary, overweight, or obese, which puts them at increased risk for comorbid chronic disease. We examined the prevalence of, and changes in, metabolic syndrome following 6 months of an aerobic exercise versus usual care intervention in a sample of sedentary postmenopausal breast cancer survivors. *Design and Methods*. 65 participants were randomized to an aerobic exercise intervention (EX) ($n = 35$) mean BMI 30.8 (±5.9) kg/m^2 or usual care (UC) ($n = 30$) mean BMI 29.4 (±7.4) kg/m^2. Metabolic syndrome prevalence was determined, as well as change in criteria and overall metabolic syndrome. *Results*. At baseline, 55.4% of total women met the criteria for metabolic syndrome. There was no statistically significant change in metabolic syndrome when comparing EX and UC. However, adhering to the exercise intervention (at least 120 mins/week of exercise) resulted in a significant ($P = .009$) decrease in metabolic syndrome z-score from baseline to 6 months (-0.76 ± 0.36) when compared to those who did not adhere (0.80 ± 0.42). *Conclusions*. Due to a higher prevalence of metabolic syndrome in breast cancer survivors, lifestyle interventions are needed to prevent chronic diseases associated with obesity. Increasing exercise adherence is a necessary target for further research in obese breast cancer survivors.

1. Introduction

Obesity and sedentary lifestyle are associated with a higher risk of breast cancer recurrence and onset of comorbid conditions in women diagnosed with breast cancer [1–4]. Metabolic syndrome is a clustering of symptoms that includes abdominal adiposity, hypertension, dyslipidemia, and glucose dysregulation which can markedly increase the risk of insulin resistance, diabetes, stroke, and cardiovascular disease. Prior research has demonstrated that between 50% and 64% of the 2.5 million breast cancer survivors are either overweight (BMI 25–30 kg/m^2) or obese (BMI > 30 kg/m^2) [5–7]. Additionally, breast cancer survivors are more likely to spend greater than 8 hours a day in a sedentary state when compared to noncancer participants [8]. Breast cancer has been associated in several studies with metabolic syndrome [2, 5] and insulin resistance [2, 4, 6–9]. Given that metabolic dysregulation may affect risk for recurrence of breast cancer and onset of additional chronic disease [10], investigation into effective interventions for reducing metabolic syndrome in breast cancer survivors is a much needed area of research. Physical activity may be an effective intervention for preventing and/or improving metabolic syndrome variables, thereby reducing risk for additional associated chronic diseases.

Recent research has shown that metabolic syndrome variables can be improved by lifestyle modification in the general population. Prior investigations have either prescribed a dietary intervention that reduced dietary fat intake and promoted weight loss [11], prescribed exercise alone with no control condition [12], or prescribed a combined weight loss and exercise intervention [13]. In a study in healthy postmenopausal obese women, investigators found that a walking

program, three days a week for 16 weeks, reduced individual criteria, but not overall prevalence of metabolic syndrome in individuals who had two or more criteria of metabolic syndrome [14]. Additionally, aerobic exercise protocols that resulted in a concomitant reduction in weight over an 18-month period have shown reductions in metabolic syndrome criteria [15]. One prior study examined exercise, diet, and a combination of the two compared to control as an intervention for metabolic syndrome in men and postmenopausal women with dyslipidemia [16]. They found that associations between exercise and diet with metabolic syndrome variables were accounted for by body fat loss. Given the observed benefits of physical activity interventions on metabolic syndrome variables in other clinical populations, it is important to understand whether these effects generalize to breast cancer survivors, a population where having the metabolic syndrome may increase their risk for recurrence [10]. It is also important to examine whether change in body weight or body fat accounts for any observed improvements in metabolic syndrome as this may provide insight into the mechanisms linking exercise to the metabolic syndrome. However, there are few, if any, randomized control trials that have been published examining the effects of exercise on changes in the metabolic syndrome in women diagnosed with breast cancer.

Given the limited prior literature, the purpose of this study was to investigate the prevalence of the metabolic syndrome at baseline and to examine the effect of aerobic exercise versus usual care over 6 months on improving metabolic syndrome criteria and overall metabolic syndrome score in sedentary postmenopausal breast cancer survivors.

2. Methods and Procedures

2.1. Participants. Participants were 65 postmenopausal breast cancer survivors who were enrolled in the Yale Exercise and Survivorship (YES) study that has been described in detail elsewhere [17]. Participants were within 1–10 years of diagnosis of stages 0–111A breast cancer and had completed chemotherapy and/or radiation at least 6 months before enrollment. Inclusion criteria required participating in less than 90 minutes of physical activity per week prior to enrollment; participants were nonsmokers and were free of other serious health problems. Only those women who were sedentary or reported less than 90 minutes of moderate to vigorous physical activity per week and were not currently participating in a weight loss diet program were eligible. Exclusion criteria for the study included women younger than 40 years of age due to potential differences in disease etiology and women over 75 years of age due to likelihood of significant comorbidities and safety concerns for elderly exercise participants.

2.2. Recruitment. We used the Yale-New Haven Hospital Tumor Registry to obtain the names of Connecticut women diagnosed with breast cancer by any Yale-affiliated physician from March 2004 to January 2006. Staff contacted each patient's physician to request permission to contact the participant. An invitation letter was mailed to the participant, followed by a telephone screening questionnaire. From 788 screening calls made, 75 (9.5%) women were eligible, interested, and randomized. Fasting blood was available for 65 of the women.

2.3. Anthropometric, Blood Pressure, and Dual Energy X-Ray Absorptiometry (DXA) Measurement. At baseline and six months, measurements of weight, height, waist circumference, and blood pressure were taken twice in succession by the same technician and averaged for analysis. Weight was measured on an electronic scale and recorded to the nearest 0.1 kg and height was measured with a standard stadiometer, rounding up to the nearest 0.5 cm. One blood pressure measurement was taken at rest with the participant sitting. Dual-energy X-ray absorptiometry (DXA) (Hologic 4500 with a "Discovery" upgrade, Hologic Inc., Waltham, MA, USA) scans were performed to assess total body fat and lean mass.

2.4. Physical Activity Measurement. At baseline and 6 months, participants completed an interview-administered physical activity questionnaire, which was used to assess the past 6 months of recreational activity [17] and a seven-day physical activity log [18]. Women recorded the type and duration of any physical activity done on each day for the physical activity log. Additionally, hours per week of moderate to vigorous intensity aerobic activity were determined using Ainsworth Compendium of Physical Activities [19].

2.5. Medical History and Medications. An interviewer-administered questionnaire was also administered at baseline to collect relevant medical history as well as current medication usage, health habits, and comorbidities. The questionnaire was designed to collect information about history and/or treatment of medical conditions, such as heart disease, high blood pressure, arthritis, diabetes, and cancer, as well as medical symptoms over the past 30 days, and prior and concomitant medications. Additional information on disease stage, hormone-receptor status, histological grade, therapy and evidence of completion, and surgery was provided by participants at baseline and 6 months. The information from these questionnaires was later confirmed by the participant's physician and the review of medical records.

2.6. Food Frequency Questionnaire. All participants completed a 120-item food frequency questionnaire at baseline and 6 months [20]. Participants were told to maintain dietary intake as unchanged throughout the trial.

2.7. Exercise Intervention. The participants in the exercise intervention were instructed to complete 150 minutes of moderate intensity aerobic activity which consisted of three weekly certified exercise trainer supervised exercise sessions at a local health club and two weekly unsupervised exercise sessions. Exercise sessions consisted primarily of walking, which is a preferred activity for breast cancer survivors. However, participants could meet the exercise goal through other forms of aerobic activity such as stationary biking and elliptical training. Resistance exercise and yoga were excluded

activities and did not count towards the exercise goal for each week as they did not involve sustained aerobic effort. Participants completed three 15-minute sessions during Week 1 and gradually built up to five 30-minute moderate intensity sessions by Week 5 which is consistent with the American College of Sports Medicine (ACSM) exercise guidelines for adults. Exercise started at 50% of predicted maximal heart rate (220-age) and was gradually increased in accordance with approximately 60–80% of predicted maximal heart rate. Participants wore heart rate monitors for each exercise session to enable self-monitoring of exercise intensity (Polar Electro, Woodbury, NY). Following each exercise session, participants recorded the type, duration, perceived intensity of activity, and average heart rate during exercise in physical activity logs, which were repeated on a weekly basis. The physical activity logs ensured weekly compliance and were used to determine exercise intensity for the following week.

2.8. Usual Care Group. Women in the usual care group were instructed to continue with their usual activities. If a participant wanted to exercise, she was told she could, but the exercise program and training materials would not be offered to her until the end of the study. At the end of the trial, women in the usual care condition were offered three supervised training sessions, a pedometer, exercise handouts, and the results of their clinical tests. Additionally, all study participants received quarterly newsletters that highlighted issues relevant to breast cancer survivorship.

2.9. Blood Draw and Metabolic Variable Assays. Fasting blood draws were collected at the baseline and 6-month visit and plasma samples were stored at −80°C until assayed. Plasma total cholesterol (TC), high-density lipoprotein (HDL), triglycerides, and glucose were enzymatically measured on an Alfa Wassermann ACE Alera Chemistry Analyzer (Alfa Wassermann, West Caldwell, NJ, USA) with reagents supplied by the company. Intra assay coefficients of variation were as follows: TC 1.1% HDL 2.0%, triglycerides 1.2%, and glucose 0.9%. Interassay coefficents of variation were as follows: TC 1.6%, HDL 4.3%, triglycerides 1.8%, and glucose 1.7%.

2.10. Metabolic Syndrome Criteria. Based on the US National Cholesterol Education Program Adult Treatment Panel III (ATPIII) definition [21], metabolic syndrome was defined as the presence of ≥3 of the following risk factors: waist circumference (WC) ≥ 88 cm, triglycerides (TG) ≥ 150 mg/dL, or taking medication to lower cholesterol; HDL cholesterol < 50; systolic blood pressure (SysBP) ≥ 130 mm Hg or ≥85 mm Hg diastolic blood pressure (DiasBP) or taking blood pressure medication; and fasting glucose ≥ 100 mg/dL or taking diabetes medication.

2.11. Metabolic Syndrome z-Score. Consistent with prior publications examining a dimensional score for metabolic syndrome [22–24], we created a modified z-score for each metabolic syndrome variable and summed for a total score ((50-HDL)/14.5) + ((TG-15)/52.4) + ((Glucose–100)/11.75) + ((WC–88)/13.75) + ((SysBP-130)/15.7) + ((DiasBP-85)/7.9).

2.12. Statistical Analyses. Metabolic syndrome onsets and offsets were coded and tested for significant differences using a likelihood ratio chi-square statistic. A general linear model (GLM) controlling for baseline scores and age was implemented in SAS to examine effects over time between the intervention and usual care groups on the metabolic syndrome. Statistical significance was assumed for $P \leq 0.05$. Exercisers were further classified as adherers if they participated in greater than or equal to 80% of the recommended amount (which is commonly defined as adherent) of 150 min/wk (i.e., 120 minutes of exercise week ($n = 20$)) or nonadherers if they participated in less than 120 minutes per week ($n = 15$). Changes in metabolic syndrome variables and overall score were examined between adherers and nonadherers, controlling for baseline values and age.

3. Results

Demographic and clinical characteristics at baseline in women randomized to exercise versus usual care are shown in Table 1. There were no significant differences between groups at baseline. The percentage of participants at baseline who had metabolic syndrome was 55.4% (see Table 2). At baseline, 24 of the 35 (69%) women randomized to exercise and 12 of 30 (40%) women randomized to usual care met criteria for metabolic syndrome. At 6-month followup, 20 of 35 women in the exercise group (57%) had metabolic syndrome, whereas 13 of 30 women (43%) in the usual care group had metabolic syndrome. At baseline, the average number of physical activity minutes per week was 13.0 minutes per week for the exercise group and 12.0 minutes per week for the usual care group. The frequency distribution of number of metabolic syndrome criteria is also displayed in Table 2. Results from the Chi-square test indicate a significant difference in metabolic syndrome onsets between groups with more onsets in the usual care group at 6 months ($\chi^2 = 6.49$, $P = 0.01$).

At 6 months, the exercise group had a significant increase in moderate to vigorous intensity recreational activity compared to the usual care group (129 minutes/week versus 45 minutes/week, $P < 0.001$). The exercise goal was 150 min/wk of moderate intensity aerobic exercise; 33% of women achieved this amount. 57% of women achieved 80% of the exercise goal or 120 min/wk, and 75% of women achieved 90 min/wk.

Table 3 shows the mean baseline and six-month metabolic syndrome change scores by intervention group for metabolic syndrome criteria. There was no statistically significant difference in the baseline to 6-month metabolic syndrome z-score between exercisers and controls; however, fasting blood glucose significantly decreased in the exercise group compared with a slight increase among women in the usual care group (−1.3 ± 1.2 versus 0.6 ± 1.3, $P < 0.029$).

Adjusting or stratifying by baseline to 6-month change in body weight or body fat did not change the overall main

Table 1: Baseline characteristics of participants.

Characteristic mean (SD) or %	Exercise ($n = 35$)	Usual care ($n = 30$)	Nonadherers ($n = 15$)	Adherers ($n = 20$)
Age (yr)	56.5 (9.8)	55.1 (7.6)	57.5 (12.8)	55.7 (6.9)
Weight (kg)	82.1 (16.5)	77.2 (20.4)	86.6 (17.0)	78.7 (15.6)
Height (cm)	161.8 (6.2)	163.2 (6.5)	161.3 (5.6)	164.6 (6.7)
BMI (kg/m^2)	30.8 (5.9)	29.4 (7.4)	33.1 (4.8)	29.1 (6.1)
Ethnicity (%)				
White	83%	90%	90%	85%
African-American	17%	7%	20%	15%
Asian/Pacific Islander	0%	3%	0%	0%
Education (%)				
High school graduate	43%	50%	30%	60%
College graduate	57%	50%	70%	40%
Time since diagnosis (y)	3.6 (2.2)	3.3 (2.6)	3.5 (2.3)	3.5 (2.1)
Disease stage (%)				
In Situ	11%	10%	13%	10%
Stage I	54%	27%	67%	45%
Stage II	26%	47%	13%	35%
Stage IIIA	9%	17%	7%	10%
Treatment (%)				
None	6%	13%	13%	0%
Radiation only	43%	23%	47%	40%
Any chemotherapy	51%	63%	40%	60%
Hormone therapy (%)				
None	43%	30%	33%	50%
Tamoxifen	29%	23%	33%	25%
Aromatase inhibitors	29%	47%	33%	25%
Physical activity questionnaire (min per week of moderate to vigorous intensity recreational activity)	13.0 (24.0)	12.0 (20.0)	5.7 (10.2)	19.4 (29.6)

Note. No statistically significant differences between exercise, usual care groups, and exercise adherers versus nonadherers at baseline were observed.

Table 2: Percent and number of participants defined as having the metabolic syndrome at baseline and six months.

Number of metabolic syndrome criteria	Exercise baseline ($n = 35$)	Exercise 6 months ($n = 35$)	Usual care baseline ($n = 30$)	Usual care 6 months ($n = 30$)	Nonadherers baseline ($n = 15$)	Nonadherers 6 months ($n = 15$)	Adherers baseline ($n = 20$)	Adherers 6 months ($n = 20$)
0	4	7	2	3	2	6	2	1
1	5	2	7	8	5	1	0	1
2	2	5	9	6	2	5	0	0
3	10	8	6	4	3	3	7	5
4	7	11	4	7	3	5	4	6
5	7	1	2	2	5	0	2	1
Total	24	20	12	13	11	8	13	12
Percent	69%	57%	40%	43%	55%	40%	87%	80%

effects. Exercise adherers continued to have significant improvement in metabolic syndrome z-score even when change in body fat mass was controlled for (-0.69 ± 0.37 adherers versus 0.70 ± 0.43 nonadherers; $P = .024$). Exercise adherers also had significant improvements in metabolic syndrome z-score when change in lean mass was controlled for (-0.73 ± 0.36 adherers versus 0.76 ± 0.42 nonadherers; $P = .012$).

Table 4 shows change in metabolic syndrome z-score and criteria stratified by exercise adherence. Exercise adherers

Table 3: Six-month change in metabolic syndrome variables in exercise intervention ($n = 35$) versus usual care ($n = 30$).

	Baseline (SD)	Mean change (SE)	Significance (P value)
Waist circumference (cm)			
Exercise	91.7 (12.0)	−1.49 (0.76)	0.508
Usual care	88.6 (15.6)	−0.75 (0.82)	
Systolic blood pressure (mm Hg)			
Exercise	123.1 (12.9)	0.66 (2.25)	0.080
Usual care	123.7 (18.7)	−5.23 (2.43)	
Diastolic blood pressure (mm Hg)			0.304
Exercise	75.2 (6.8)	0.75 (1.16)	
Usual care	76.6 (9.1)	−1.02 (1.25)	
HDL-C (mg/dL)			
Exercise	52.7 (13.2)	0.51 (1.65)	0.325
Usual care	59.1 (15.4)	−1.90 (1.78)	
Triglycerides (mg/dL)			
Exercise	123.7 (53.7)	1.40 (7.1)	0.841
Usual care	117.8 (51.6)	−0.70 (7.7)	
Glucose (mg/dL)			
Exercise	104.9 (12.7)	−1.31 (1.21)	0.029
Usual care	105.1 (10.7)	0.6 (1.3)	
Metabolic syndrome z-score			
Exercise	−1.7 (3.3)	−0.09 (0.39)	0.661
Usual care	−2.2 (4.2)	−0.35 (0.42)	

Note. Negative z-score indicates below cut-off. Negative mean change score indicates improvement in criterion.

Table 4: Six-month change in metabolic syndrome variables in exercise adherers ($n = 20$) versus nonadherers ($n = 15$).

	Baseline (SD)	Mean change (SE)	Significance (P value)
Waist circumference (cm)			
Adherers	89.4 (12.5)	−2.48 (1.05)	0.170
Non-adherers	94.8 (10.9)	−0.18 (1.22)	
Systolic blood pressure (mm Hg)			
Adherers	124.7 (14.4)	−1.99 (2.29)	0.091
Non-adherers	121.0 (10.6)	4.19 (2.65)	
Diastolic blood pressure (mm Hg)			
Adherers	76.2 (6.8)	−0.07 (1.00)	0.226
Non-adherers	73.9 (6.9)	1.84 (1.16)	
HDL-C (mg/dL)			
Adherers	54.8 (14.3)	2.91 (1.42)	0.016
Non-adherers	50.1 (11.5)	−2.67 (1.64)	
Triglycerides (mg/dL)			
Adherers	125.7 (63.2)	−3.13 (7.44)	0.361
Non-adherers	121.0 (39.5)	7.44 (8.60)	
Glucose (mg/dL)			
Adherers	102.6 (12.2)	−1.45 (1.58)	0.898
Non-adherers	107.9 (13.2)	−1.13 (1.83)	
Metabolic syndrome z-score			
Adherers	−1.92 (3.7)	−0.76 (0.37)	0.009
Non-adherers	−1.36 (2.9)	0.80 (0.42)	

WC: waist circumference, HDL-C: high-density lipoprotein cholesterol.

increased HDL cholesterol relative to nonadherers (2.91 ± 1.42 versus −2.67 ± 1.64, $P < .016$). In addition, a decrease in Metabolic Syndrome z-score was greater for the exercise adherers than for the nonadherers (−0.76 ± 0.37 versus 0.80 ± 0.42, $P < .009$). Exercise adherers continued to have significant improvement in metabolic syndrome z-score even when change in body fat mass was controlled for (−0.69 ± 0.37 adherers versus 0.70 ± 0.43 nonadherers; $P = .024$). Exercise adherers also had significant improvements in metabolic syndrome z-score when change in lean mass was controlled for (−0.73 ± 0.36 adherers versus 0.76 ± 0.42 nonadherers; $P = .012$).

4. Discussion

In our study, we observed that over half of our sample of breast cancer survivors were defined as having the metabolic syndrome, putting them at higher risk for other chronic diseases including cardiovascular disease and breast cancer recurrence [2, 25]. In addition, women randomized to the usual care group had higher rates of new onset of metabolic syndrome over the six months. A moderate intensity aerobic exercise program was not associated with an improvement in a metabolic syndrome z-score over six months; however, exercise was associated with a statistically significant decrease in fasting glucose after 6 months. The amount of exercise performed is also of importance, as we observed a decrease in the metabolic syndrome z-score and an increase in HDL cholesterol in women participating in at least 80% of the recommended amount of physical activity (i.e., 120 min/wk) compared with women participating in less than 120 min/wk of exercise. The prevalence rate of metabolic syndrome in this sample (55.4%) of breast cancer survivors who were evaluated at least 6 months after cancer treatment replicates and extends [26] prior findings from Porto and colleagues who found a 59.2% prevalence rate of metabolic syndrome in newly diagnosed breast cancer patients. This finding is particularly salient when compared to the prevalence rate of 37% in age and gender matched individuals in the general population [27]. This also suggests that prevalence rates of metabolic syndrome in breast cancer patients remain similar before and after cancer treatment. Individual components of metabolic syndrome such as higher blood pressure, dyslipidemia, and abdominal obesity are closely related to the etiology and prognosis of breast cancer. Only a few studies have investigated the prevalence of metabolic syndrome in breast cancer survivors and to our knowledge, none have examined the effect of an aerobic exercise intervention on metabolic syndrome criteria and overall metabolic risk score. Further longitudinal investigations are needed to determine whether metabolic syndrome rates increase during the course of treatment and whether exercise prescription may play an important role in decreasing metabolic syndrome risk for this population.

At baseline, both the exercise group and the usual care group had extremely low levels of physical activity (average of 13 and 12 minutes per week, resp.) and 68% of the participants reported no weekly physical activity. Given that 50% of breast cancer survivors are obese [5] and predominantly have low levels of physical activity, this population is further put at risk for cancer recurrence and other comorbid chronic conditions. During the intervention, 20 of the 35 participants met 80% or 120 minutes of exercise per week, which reflects a clinically significant increase in physical activity from baseline. Although the dose of exercise in this intervention is modest, it signifies an obtainable goal for a population that is not likely to participate in physical activity.

Although the exercise intervention did not yield overall changes in metabolic syndrome z-score, it did result in a reduction in fasting blood glucose, which replicates previous beneficial effects of exercise interventions in type II diabetes [28–30]. In other populations (of healthy men and women), exercise has shown the ability to reduce metabolic syndrome criteria. For example, exercise has decreased blood pressure [31], triglycerides [32] fasting blood glucose [28], and increased HDL cholesterol [27, 28] and improved metabolic risk score [23, 24]. Thus, it is surprising that the exercise intervention did not result in changes beyond those in glucose. However, dose and type of exercise may play an important role in understanding this discrepancy. Our findings that meeting 80% of the ACSM weekly exercise guidelines improves HDL and overall metabolic syndrome z-score in postmenopausal breast cancer survivors support the interpretation that dose of exercise is a vital component in reducing metabolic syndrome risk. This finding highlights that exercise, even at very modest amounts, can aid individuals in reducing chronic disease risk. Giving individuals who are not prone to high levels of physical activity an exercise prescription that is obtainable and feasible is an important tool in preventing cancer recurrence and comorbid chronic disease. Given the complexity of comorbid illness in breast cancer survivors and the high prevalence rates of metabolic syndrome in this population, further examination of the dose required to provide beneficial reductions in metabolic syndrome, and the mechanisms by which exercise conveys this benefit, is much needed. Although previous research found that changes in metabolic syndrome resulting from diet and exercise interventions were accounted for by change in fat mass [12, 29], our results suggest that changes in fat mass did not account for the beneficial effects of exercise on metabolic syndrome.

This study demonstrates that sustained aerobic exercise provides health benefits that are relevant to metabolic health in breast cancer survivors. It is important to note that these health benefits are seen by exercising less than the ACSM recommended 220 minutes of exercise per week. This is in line with recent research which has shown a threshold in which further increase of exercise does not necessarily produce additional benefits to outcomes [33, 34]. This suggests a dose-dependent attenuation of these benefits. It is currently unclear what the optimal dose is, as it seems to be related to type of exercise performed, gender of participant, and other individual differences that research has not yet identified [34–38]. The moderate intensity aerobic exercise and the dose performed were well tolerated in these breast cancer survivors. The effects of physical activity on prognosis among breast cancer survivors have been examined by numerous randomized controlled trials and exercise has

been deemed safe and a key factor in improving outcomes for cancer survivors [39]. Further research is now needed on the multitude of benefits from exercise to health status in breast cancer survivors and the optimal dose and type of exercise at which benefits are observed.

A major strength of this study is the use of a continuous score for the metabolic syndrome which replicates previous studies in noncancer survivor samples [18, 19]. The metabolic syndrome z-score allows equal weighting of each risk factor on a dimensional scale and thus is more sensitive to overall change in metabolic syndrome criteria. Additional strengths include the randomized study design and use of a sedentary group of participants, which makes the results generalizable to the clinical population, and supervised exercise to ensure compliance with the study protocol. A limitation in this study is the small sample size which may limit statistical power with regard to some of our stratified analyses. An additional limitation of the present study was that the participants were exercising three times per week in a supervised setting and, thus, these results may not generalize to nonsupervised individuals.

5. Conclusions

In predominantly overweight or obese, physically inactive, breast cancer survivors, adherence to a moderate intensity aerobic exercise intervention was associated with improvements in metabolic syndrome criteria. Given the high prevalence rates observed in this sample, and prior samples, lifestyle interventions are needed to address the ongoing chronic disease issues associated with metabolic dysregulation in breast cancer survivors. Additional randomized control trials with larger sample sizes should examine the dosage and types of exercise that are most beneficial for metabolic syndrome improvements.

Conflict of Interests

The authors have no conflict of interests.

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