Inflammatory Markers and Adipocytokine Responses to Exercise Training and Detraining in Men Who Are Obese

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[1]Department of Physical Education and Sport Sciences, Ilam Branch, Islamic Azad University, Ilam, Iran; [2]Clinical Microbiology Research Center, Ilam University of Medical Sciences, Ilam, Iran; [3]Department of Physical Education and Sport Sciences, Tarbiat Modares University, Tehran, Iran; and [4]Department of Sport and Exercise Physiology, Faculty of Physical Education, Shahid Beheshti University, Tehran, Iran

Abstract

Nikseresht, M, Sadeghifard, N, Agha-Alinejad, H, and Ebrahim, K. Inflammatory markers and adipocytokine responses to exercise training and detraining in men who are obese. *J Strength Cond Res* 28(12): 3399–3410, 2014– The purpose of this study was to compare the effects of nonlinear resistance training (NRT) and aerobic interval training (AIT), and detraining on selected inflammatory markers in men who are middle aged and obese. Subjects first were matched by aerobic capacity, age, and percentage body fat and then randomly assigned to NRT ($n = 12$), AIT ($n = 10$) and, control (CON, $n = 11$) groups. The experimental groups performed 3 weekly sessions for 12 weeks followed by a 4-week detraining period. Nonlinear resistance training consisted of 40–65 minutes of weight training with flexible periodization. Aerobic interval training consisted of running on a treadmill (4 × 4 minutes at 80–90% maximal heart rate, with 3-minute recovery intervals). Compared with CON, serum levels of interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF-α) did not significantly change after training, but adiponectin (ADPN) increased significantly only with AIT (5.09 ± 2.29 vs. 4.36 ± 0.84 $\mu g \cdot ml^{-1}$). No significant changes in CRP and TNF-α occurred in both training groups after detraining, but ADPN (NRT: 3.6 ± 1.2 and AIT: 3.4 ± 1.7 vs. CON: 4.7 ± 1.2 $\mu g \cdot ml^{-1}$) and IL-6 (NRT: 5.8 ± 3.3 and AIT: 5.5 ± 2.9 vs. CON: 2.3 ± 1.2 $pg \cdot ml^{-1}$) worsened significantly. Both the AIT and NRT were equally effective at reducing soluble intercellular cell adhesion molecule 1 (NRT: 187.2 ± 117.5 and AIT: 215.2 ± 142.4 vs. CON: 416.2 ± 205.9 $ng \cdot ml^{-1}$) and insulin (NRT: 4.0 ± 1.0 and AIT: 4.8 ± 2.7 vs. CON: 7.4 ± 3.0 $\mu U \cdot ml^{-1}$) levels, but these variables returned to the pretraining levels after detraining. The practical applications are that both the AIT and NRT and detraining had similar effects on most inflammatory markers in men who are obese, but the AIT seems to have better anti-inflammatory effects (as indicated by ADPN) compared with NRT.

Key Words nonlinear resistance training, aerobic interval training, inflammation, cytokine, obesity

Introduction

Chronic systemic inflammation is an important risk factor for several major clinical diseases, such as cardiovascular disease (CVD) and diabetes mellitus. Circulating levels of inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) are elevated with obesity (4,43). Conversely, the adipocyte-derived molecule adiponectin (ADPN), which seems to have both anti-inflammatory and antiatherogenic properties, has been shown to be lower in individuals who are obese compared with lean controls (3). This obesity-mediated reduction in ADPN levels is also inversely related with the upregulation of soluble intercellular cell adhesion molecule 1 (sICAM-1) (31). Elevated serum levels of sICAM-1 are associated with increased severity of atherosclerosis and risk for myocardial infarction (14). However, ADPN acts indirectly to decrease levels of CRP and IL-6 through a dose-dependent reciprocal inhibition of TNF-α (30). Increased levels of circulating IL-6 stimulate CRP synthesis in the liver (4). Both CRP and IL-6 have been shown to play independent roles in the development of atherothrombosis and thus may represent a mechanistic link between obesity and the development of coronary heart disease and overall CVD (6).

Regular exercise training lowers indicators of CVD and diabetes mellitus disease risk including some inflammatory cytokines (26). Also, recent evidence supports that regular exercise training such as aerobic and resistance training (RT)

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Table 1. Nonlinear resistance training protocol.*

Exercises	Very light	Light	Moderate	Heavy	Very heavy
Knee extension	40/20 × 1†	60/15 × 2	75/10 × 3	90/4 × 3	95/2 × 4
Bench press	40/20 × 1		75/10 × 3	90/4 × 3	95/2 × 4
Incline bench press		60/15 × 2			
Seated row	40/20 × 1	60/15 × 2	75/10 × 3	90/4 × 3	95/2 × 4
Dead lift	40/20 × 1	60/15 × 2	75/10 × 3	90/4 × 3	95/2 × 4
Pulley crunches	1 × 20	2 × 20	3 × 15	3 × 18	3 × 20
Lat pull-downs		60/15 × 2			
Calf raise	40/20 × 1	60/15 × 2	75/10 × 2	90/4 × 2	
Hamstring curl	40/20 × 1	60/15 × 2	75/10 × 2	90/4 × 2	
Press behind neck	40/20 × 1	60/15 × 2	75/10 × 2	90/4 × 2	
Upright row	40/20 × 1	60/15 × 2	75/10 × 2	90/4 × 2	
Arm curl	40/20 × 1	60/15 × 2	75/10 × 2	90/4 × 2	

*Length of rest period: very light = 1 minute; light and moderate = 1–2 minutes; heavy = 3–4 minutes; and very heavy = 5–7 minutes.
†1 set × 20 repetitions, 40% 1 repetition maximum.

reduces chronic inflammation, especially in individuals who are obese with high levels of inflammatory markers undergoing a longer term intervention (5). However, there is limited research directly comparing different types of training. Some studies have demonstrated a decrease in TNF-α after exercise training in patients with chronic heart failure (1), IL-6 in elderly people (27), and CRP in sedentary and healthy men (41); however, other studies have not found reductions in some of these inflammatory markers in sedentary and healthy subjects (11,22,23). Recently, Donges et al. (11) compared the effects of 10 weeks of resistance and endurance training in sedentary healthy subjects on inflammatory markers related to CVD risk; they verified reductions only in CRP with RT, with no change in IL-6 in both training groups. Interestingly, there are more contradictions in ADPN levels. For example, Ahmadizad et al. (2) reported no changes in ADPN levels in response to 12 weeks of resistance and endurance training in healthy middle-aged men, whereas other studies showed rises in ADPN after RT in older adults with type 2 diabetes mellitus (7), and in women who are overweight (29).

Physiological responses to aerobic exercise training, as well as inflammatory responses, differ from RT (18). In addition, the inflammatory responses may vary according to the type of exercise, intensity, duration, and recovery between exercise bouts and also depends on the training status (25). Different forms of RT induce different physiological adaptations. Nonlinear resistance training (NRT) is a form of RT that produces greater day-to-day variation in the training stimuli and induces less muscle damage (20). It is important because the inflammatory response to damaging exercise is in addition to the inflammatory response to exercise without damage. Also, the NRT is at least as effective or possibly more effective than the linear periodization for maximal strength gains. No previous study has investigated the effects of this type of training on inflammatory markers. We also used the intensive aerobic interval training (AIT) because it has been shown that moderate long-term exercise seems to have no effect on adipokine gene expression (i.e., TNF-α) nor on plasma levels except for leptin (32). Racil et al. (34) demonstrated that high-intensity interval training positively

Table 2. Mesocycle with emphasis on endurance and general preparation.*†

Week		1	2	3	4	5	6	7	8	9	10	11	12
Workout sequence	Day 1	L	L	M	VL	M	L	VL	H	L	M	L	VL
	Day 2	M	VL	H	H	M	M	M	VL	L	M	M	H
	Day 3	L	H	L	L	L	H	L	M	VH	VL	VL	L

*L = light-intensity workout; M = moderate-intensity workout; VL = very light–intensity workout; H = heavy-intensity workout; VH = very heavy–intensity workout.
†An active rest day was used after any workout.

Table 3. Comparison of the physical characteristics for the obese and lean subjects at baseline.*†

Groups	$\dot{V}O_2$max ($ml \cdot kg^{-1} \cdot min^{-1}$)	Body weight (kg)	Percentage body fat (%)	Waist circumference (cm)	WHR (ratio)
Obese ($n = 33$)	41.0 ± 4.5	91.1 ± 6.3	30.3 ± 1.5	100.3 ± 5.6	0.96 ± 0.5
Lean ($n = 11$)	42.4 ± 2.8	68.7 ± 8.6	16.5 ± 2.0	80.1 ± 6.2	0.83 ± 0.5
p	0.237	0.001‡	0.001‡	0.001‡	0.001‡

*WHR = waist-to-hip ratio.
†Data are presented as mean ± *SD*.
‡Significant difference between groups ($p \leq 0.05$).

changes ADPN levels in adolescent girls who are obese, compared with moderate-intensity exercise.

Recently, it has been shown that chronic inflammation is reduced by increasing physical activity (5). Also, lifestyle interventions, such as changes in diet and physical activity, may have clinically significant benefits for improving inflammation (5). Thus, exercise training programs lead to an increase in energy expenditure, which will likely improve

Table 4. Baseline, after the training and detraining within- and between-group comparison of the physical characteristics for the NRT, AIT, and CON.*†

Variables	NRT ($n = 12$)	AIT ($n = 10$)	CON ($n = 11$)	p			ES	SP
				i	t	i × t		
Body weight (kg)								
Baseline	88.9 ± 6.8	90.2 ± 5.7	94.2 ± 5.2	0.030	0.020	0.003	0.25	0.90
After training	88.0 ± 7.2	87.3 ± 5.2^{c,r}‡§	95.7 ± 5.3					
Detraining	88.3 ± 7.5	87.7 ± 5.6^{c}‡§	95.2 ± 5.5					
Percentage body fat (%)								
Baseline	30.7 ± 1.8	30.4 ± 1.5	29.7 ± 1.2	0.513	0.001	0.001	0.46	0.98
After training	28.4 ± 1.9^{c}‡§	28.0 ± 1.7^{c}‡§	30.1 ± 1.7					
Detraining	28.9 ± 1.8^{c}‡§	28.7 ± 1.2^{c}‡§	29.6 ± 1.4					
Waist circumference (cm)								
Baseline	99.9 ± 4.8	102.6 ± 6.6	94.2 ± 5.2	0.083	0.001	0.001	0.39	0.99
After training	94.2 ± 5.1^{c}‡§	95.6 ± 4.8^{c}‡§	95.7 ± 5.3					
Detraining	95.6 ± 5.2‡	97.4 ± 5.1^{c}‡§	95.2 ± 5.5					
WHR (ratio)								
Baseline	0.95 ± 0.04	0.97 ± 0.04	0.95 ± 0.05	0.535	0.033	0.049	0.22	0.79
After training	0.93 ± 0.03‡	0.92 ± 0.03^{c}‡§	0.96 ± 0.04					
Detraining	0.95 ± 0.03	0.93 ± 0.04‡	0.96 ± 0.05					
$\dot{V}O_2$max ($ml \cdot kg^{-1} \cdot min^{-1}$)								
Baseline	41.4 ± 4.2	39.4 ± 4.6	42.1 ± 4.9	0.816	0.001	0.001	0.47	0.99
After training	44.2 ± 2.8^{c}‡§	45.6 ± 4.6^{c,r}‡§	41.6 ± 4.7					
Detraining	42.5 ± 2.4	43.5 ± 4.5^{c}‡§	41.8 ± 4.7					
1RM bench press (kg)								
Baseline	46.7 ± 12.0	51.5 ± 8.3	53.9 ± 11.3	0.213	0.001	0.001	0.29	0.87
After training	74.5 ± 11.0^{c,a}‡§	53.9 ± 9.2	50.5 ± 8.3					
Detraining	71.7 ± 8.9^{c,a}‡§	52.9 ± 11.2	51.8 ± 10.1					
1RM knee extension (kg)								
Baseline	23.7 ± 4.3	25.3 ± 5.9	27.9 ± 6.2	0.001	0.001	0.001	0.40	0.96
After training	47.3 ± 7.3^{c,a}‡§	32.5 ± 6.2^{c}‡§	28.5 ± 6.1					
Detraining	44.5 ± 7.2^{c,a}‡§	31.7 ± 5.3^{c}‡§	28.3 ± 5.2					

*c = control; r = NRT group; a = AIT group; NRT = nonlinear resistance training; AIT = aerobic interval training; CON = control group; i = intervention; t = time; ES = effect size; SP = statistical power; 1RM = 1 repetition maximum; WHR = waist-to-hip ratio.
†Data are presented as mean ± *SD*.
‡Significant difference within groups compared with baseline ($p \leq 0.05$).
§Significant difference between groups ($p \leq 0.05$).

Table 5. Comparison of the inflammatory biomarkers for the obese and lean subjects at baseline.*†

Groups	CRP ($mg \cdot L^{-1}$)	TNF-α ($pg \cdot ml^{-1}$)	IL-6 ($pg \cdot ml^{-1}$)	Adiponectin ($\mu g \cdot ml^{-1}$)	sICAM-1 ($ng \cdot ml^{-1}$)
Obese ($n = 33$)	2.34 ± 0.46	3.05 ± 0.77	2.84 ± 0.95	4.90 ± 1.54	426.3 ± 195.6
Lean ($n = 11$)	1.95 ± 0.83	2.54 ± 0.92	2.22 ± 1.24	7.34 ± 2.66	294.8 ± 115.1
p	0.169	0.079	0.093	0.013‡	0.042‡

*CRP = C-reactive protein; TNF-α = tumor necrosis factor alpha; IL-6 = interleukin 6.
†Data are presented as mean ± *SD*.
‡Significant difference between groups ($p \leq 0.05$).

several inflammatory markers. Furthermore, it has been reported that weight loss leads to reductions in inflammatory markers after a very low–carbohydrate diet and a low-fat diet in men who are overweight (38). It is hypothesized that an intervention using NRT (with energy expenditure similar to AIT) will improve markers of inflammation similar to AIT in men who are obese with a normal diet.

Although a number of studies examined effects of regular exercise training with different protocols on inflammatory markers in men who are obese, it is still not clear what type of training is most appropriate. In addition, there is a lack of information on adaptations caused by cessation of the training stimulus (detraining). Therefore, this study was designed to determine and compare the effects of 12 weeks of NRT and AIT (with similar energy expenditure), and a subsequent 4-week period of detraining, on serum TNF-α, IL-6, CRP, sICAM-1, ADPN, and insulin concentrations in men who are middle aged and obese. An additional aim was to compare the inflammatory markers between the age-matched subjects who are lean and obese at baseline.

Methods

Experimental Approach to the Problem

This study was undertaken to compare the effects of 12 weeks of NRT and AIT, and a subsequent 4-week period of detraining on selected inflammatory markers, body composition, and functional capacity in men who are middle aged, sedentary, and obese. Subjects who are obese first were matched by aerobic capacity, age, and percentage body fat and then randomly assigned to NRT, AIT, and control (CON) groups. An age- and physical activity–matched control group of lean men were also recruited for baseline comparison. To examine a relatively long-term scenario, we used a period of 12-week training under carefully monitored conditions. After completion of the training programs, subjects in NRT and AIT groups were instructed to resume their normal lifestyles and avoid any type of regular exercise for 4 weeks. Subjects in the CON group maintained a sedentary lifestyle throughout the whole periods. The volume of training was matched for energy expenditure using a heart rate monitor (Polar RCX 5 sd Run; Polar Electro Inc., Hyde

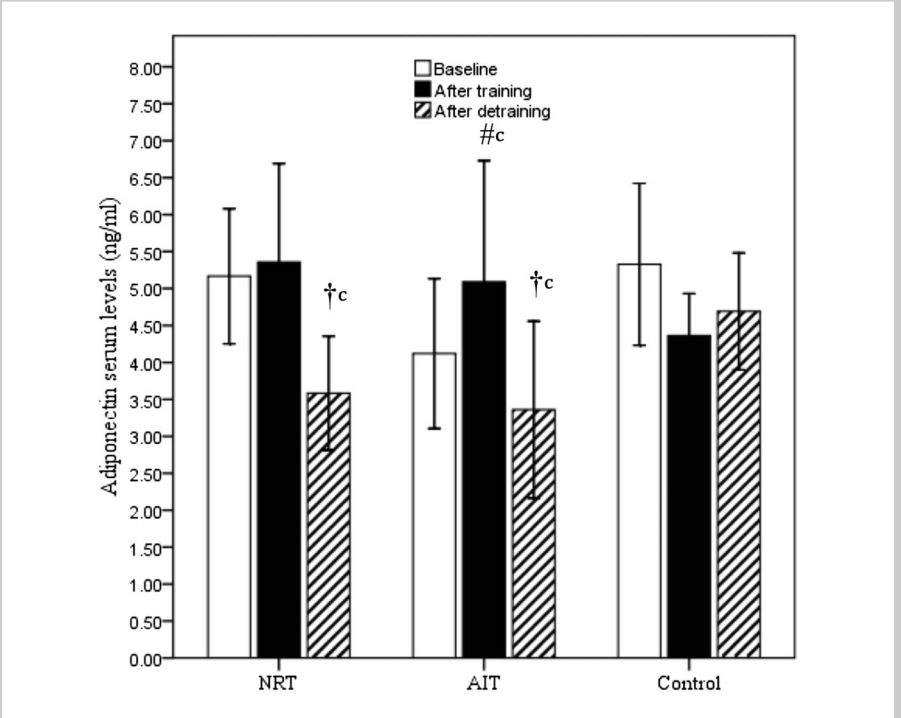

Figure 1. Serum levels of adiponectin (mean ± *SD*) at baseline, after the training and detraining periods. #Significant ($p \leq 0.05$) difference between groups (comparing baseline and after training); †Significant ($p \leq 0.05$) difference between groups (comparing after training and detraining). Effect size = 0.27 and statistical power = 0.93. NRT = nonlinear resistance training; AIT = aerobic interval training; C = control group.

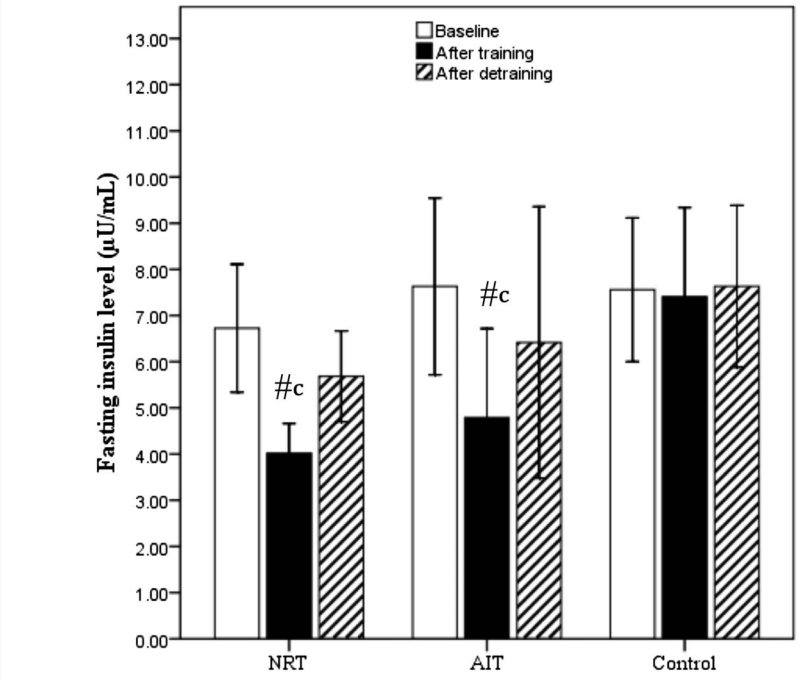

Figure 2. Fasting insulin levels (mean ± *SD*) at baseline, after the training and detraining periods. #Significant ($p \leq 0.05$) difference between groups (comparing baseline and after training). Effect size = 0.16 and statistical power = 0.77. NRT = nonlinear resistance training; AIT = aerobic interval training; C = control group.

Park, NY, USA), to ensure identical training loads in the 2 training programs. The algorithm used in this software for the energy expenditure estimation is based on type of exercise, $\dot{V}O_2$max, physical activity level, age, gender, and body mass index. Blood samples were collected to determine serum TNF-α, IL-6, CRP, sICAM-1, ADPN, and insulin concentrations at baseline and the end of the training and detraining periods.

Subjects

All subjects were informed as to the experimental procedures and provided signed informed consent and completed medical history forms in adherence with the human subjects' guidelines of the Ilam University of Medical Sciences, before any data collection. Eligible subjects (33 obese and 11 lean men) aged 34–46 years participated in this study and were allocated to the following groups: NRT (age = 40.4 ± 5.2 years, $n = 12$), AIT (age = 39.6 ± 3.7 years, $n = 10$), CON (age = 38.9 ± 4.1 years, $n = 11$), and lean (age = 39 ± 5.9 years, $n = 11$). The inclusion criteria were sedentary (less than 60-minute physical activity per week), nonsmokers, no regular exercise for at least the past 6 months, no regular consumption of medication, no special diet (i.e., low-carbohydrate diet, low fat, and vegetarian, etc.), percentage body fat for obese >25% and lean <18%, and no history of any kind of medical condition that would prevent them from participating in the exercise intervention. Overall, 3 people in NRT and 5 people in AIT were excluded because only the subjects who performed more than 89% of the training sessions were included in this study.

Procedures

All subjects were asked to complete a personal health and medical history and lifestyle evaluation questionnaires, which served as a screening tool. Subjects were familiarized with all testing procedures before the start of the testing. A maximal oxygen uptake ($\dot{V}O_2$max) test, maximal strength and body composition assessments, measurement of serum inflammatory markers (TNF-α, IL-6, CRP, sICAM-1, and ADPN), and fasting insulin levels were done before, after the 12 weeks of training, and after 4 weeks of detraining. All measurements were performed at the same time of day for each subject. This study was conducted during the months of October and February.

Maximal Strength and $\dot{V}O_2$max Assessments. After familiarization, subjects were asked to report to the laboratory for an additional test session designed to determine 1 repetition maximum (1RM) for the bench press and knee extension. After the warm-up, subjects performed the 1RM test using the Brzycki method (20). Measures of 1RM were obtained within 3 attempts. Accepted 1RM included the greatest resistance the subject could lift through a full range of motion using proper technique. The warm-up consisted of riding a stationary bicycle for 10 minutes, 2 sets of progressive resistance exercises similar to the actual exercises used in the main experiment, and 3 minutes of rest accompanied by some light stretching exercises. $\dot{V}O_2$max was estimated using the Bruce treadmill protocol (8) 2 days after the maximum strength tests. In addition, these tests were retested to eliminate the effects of learning and fatigue after 4 days.

Anthropometric. Each subject's body mass was measured after a 12-hour fast while they were wearing underclothes on a balance scale (700 Mechanical Column Scales; Seca, United Kingdom) calibrated to the nearest 0.1 kg. Then, waist circumference was measured midway between the lowest rib and the iliac crest. The hip circumference was measured at the widest part of the gluteal region. The waist-to-hip ratio (WHR) was then calculated. Subcutaneous skinfold thickness

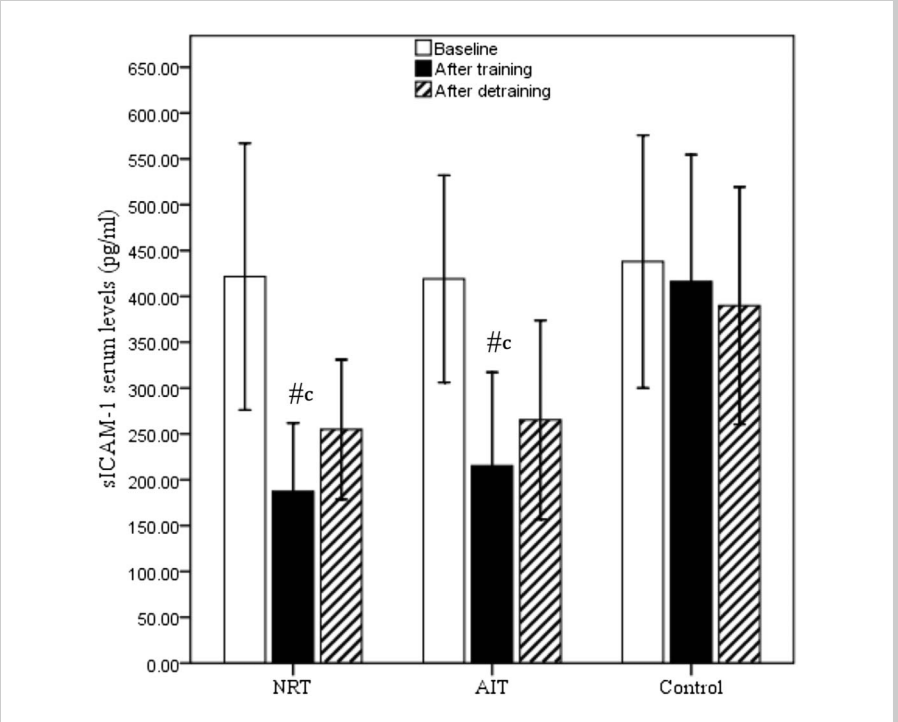

Figure 3. Serum levels of sICAM-1 (mean ± *SD*) at baseline, after the training and detraining periods. #Significant ($p \leq 0.05$) difference between groups (comparing baseline and after training). Effect size = 0.20 and statistical power = 0.82. NRT = nonlinear resistance training; AIT = aerobic interval training; C = control group.

was measured sequentially, in triplicate, at the chest, abdominal, and thigh using a skinfold caliper (Lange; Country Technology, Gays Mills, WI, USA), and standard technique. The average of 3 measures for each skinfold was used. Then, percentage body fat was estimated using the equation of Jackson and Pollock (17). The same investigator performed all skinfold and girth measurement assessments.

Estimate of Dietary Energy Intakes. Before blood sampling, the subjects were told to record a 2-day dietary intake to determine the composition of their normal diet. Therefore, the subjects were provided instructions to have a normal diet (50–60% carbohydrate, 20–30% fat, and 10–15% protein) and were instructed to maintain their normal energy intake throughout the duration of the study.

Blood Analyses. On the day of blood sampling, subjects began by reporting to the laboratory in the morning (7:00–8:00 AM). They assumed a supine position for 20 minutes. After a 12-hour overnight fast and 8 hours of sleep, blood samples (~10 ml) were obtained from the antecubital vein at baseline, after the training and detraining periods. The subjects were asked to avoid from strenuous physical activity for at least 4 days before blood sampling. The subjects were also asked whether they had experienced any symptoms of illness in the past 4 days or had taken any medication in this period. If a subject indicated that this was the case, a new appointment was made 4 days later. In addition, the subjects were asked to consume a similar diet for at least 48 hours before blood sampling at baseline, after the training and detraining periods. Posttraining blood samples from subjects in the training groups were obtained 4 days after their last exercise session. Whole blood was allowed to clot for 60 minutes centrifuged at 1,000 rpm (4° C), and the serum was removed and stored at −20° C until subsequent analysis.

Biochemical Analyses

Serum samples were used to measure IL-6, ADPN, sICAM-1, CRP, TNF-α, and insulin levels. The concentrations were measured in duplicate by enzyme-linked immunosorbent assay according to the specifications of the manufacturer (Quantikine High Sensitivity Kit; R&D Systems, Minneapolis, MN, USA, for IL-6; AviBion, Orgenium Laboratories Unit, Vantaa, Finland, for TNF-α; Boster Biological Technology Ltd, USA, for ADPN and sICAM-1; Binding Site Group Ltd, Birmingham, United Kingdom, for CRP and INSULIN Q-1 kit, DIAPLUS Inc., NY, USA, for insulin). The intra- and interassay coefficients of variation were less than 7.4% for all variables. The minimum detectable concentrations were less than 0.7, 15, 10, and 10 $pg \cdot ml^{-1}$ for IL-6, TNF-α, ADPN, and sICAM-1, respectively. The assay sensitivity was 0.5 $\mu U \cdot ml^{-1}$ and 0.01 $mg \cdot L^{-1}$ for insulin and CRP, respectively.

Training Programs

Nonlinear Resistance Training. The NRT program was with emphasis on endurance and general preparation and consisted of 40–65 minutes of weight training per day, 3 days per week, for 12 weeks (Tables 1 and 2). This training program consisted of weight training at different intensities (10 exercises, 1 set/20 repetitions, 40% 1RM for 7 sessions; 11, 2/15, 60% 1RM for 12; 10, 3/10, 75% 1RM for 10; 10, 3/4, 90% 1RM for 6 and 5, 4/2, 95% 1RM for 1). This training has already been proposed presented by Nikseresht et al. (27) and the details are shown in Tables 1 and 2.

Aerobic Interval Training. The AIT program consisted of running on a treadmill, consisting of 4 times 4 minutes each of running at an exercise intensity of 80–90% of maximal heart rate separated by period of 3-minute jogging at 55–

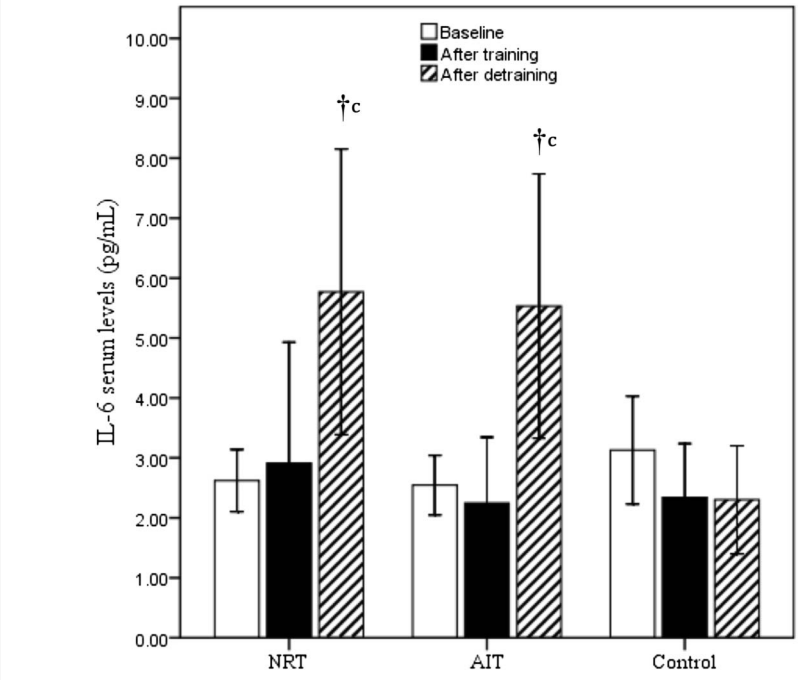

Figure 4. Serum levels of IL-6 (mean ± *SD*) at baseline, after the training and detraining periods. †Significant ($p \leq 0.05$) difference between groups (comparing after training and detraining). Effect size = 0.22 and statistical power = 0.86. NRT = nonlinear resistance training; AIT = aerobic interval training; C = control group; IL-6 = interleukin 6.

65% of maximal heart rate, 3 days per week, for 12 weeks. The exercise intensity was controlled by the authors, using a heart rate monitor (Polar RCX5sd-Run). In both training groups, each training session was commenced with a general warm-up and a cool-down was completed after the session. The training sessions were performed in the University laboratory and were supervised by the researchers.

Statistical Analyses

All data analysis was performed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). Values are expressed as mean ± *SD*. Normality of distribution was tested using the Kolmogorov-Smirnov test. To determine differences between obese ($n = 33$) and lean ($n = 11$) subjects for baseline comparison, unpaired *t*-tests were used. A 2-factor repeated-measure analysis of variance (ANOVA) was used to determine the differences between interventions and across time. The first factor was "intervention" (between-group factor) and had 3 levels (AIT, NRT, and CON), and the second factor was "time" (repeated-measure factor) and had 3 levels (baseline, after training, and detraining). When the ANOVA detected significant interactions among mean values (intervention/time), the Bonferroni analysis was used post hoc to identify where those differences occurred. The statistical power was calculated to help protect against type II error. To determine the meaningfulness of the intervention effects, the effect sizes were calculated for the intervention/time interactions. To assess for within-group reliability of the dependent variables, intraclass correlation coefficients were calculated for each group in the 3 measurement points. Intraclass correlation ranged between 0.61 and 0.97 for all variables except IL-6 in NRT (0.06) and AIT (0.13) in the after detraining. The level of significance was set at $p \leq 0.05$ for all statistical comparisons.

Results

Anthropometric and Functional Capacity

Subjects' physical characteristics in obese and lean subjects are shown in Table 3. Significant differences were noted at baseline between the groups for body mass, percentage body fat, waist circumference, and WHR (all, $p \leq 0.05$), but not for $\dot{V}O_2$max ($p = 0.23$). Anthropometric characteristics and $\dot{V}O_2$max of the subjects in 3 conditions (NRT, AIT, and CON) at baseline, after 12 weeks of training and detraining period are shown in Table 4. After the training period, significant differences in body mass, percentage body fat, waist circumference, WHR, and $\dot{V}O_2$max were detected by ANOVA. There was a significant reduction in body mass (3.3%) at the end of AIT, compared with the NRT ($p = 0.01$) and control ($p = 0.001$) groups, and in percentage body fat at the end of AIT (7.8%) and NRT (7.4%), compared with the CON (both $p < 0.001$). After 4 weeks of detraining, body mass and percentage body fat had not returned to the baseline values. Compared with the CON, the AIT and NRT resulted in a significant ($p = 0.001$ and $p = 0.005$, respectively) reduction in waist circumference at the end of training and returned to baseline values after 4 weeks of detraining in NRT but not with AIT. The AIT resulted in a significant ($p = 0.02$) reduction in WHR at end of training compared with the CON and returned to pretraining levels after detraining.

There were significant increases in $\dot{V}O_2$max for both training groups compared with the CON (both, $p < 0.01$), but the increase was significantly higher with AIT than with NRT ($p = 0.004$). After detraining, $\dot{V}O_2$max was significantly decreased in both training groups (both, $p < 0.001$); however, these values were still higher in the AIT compared with

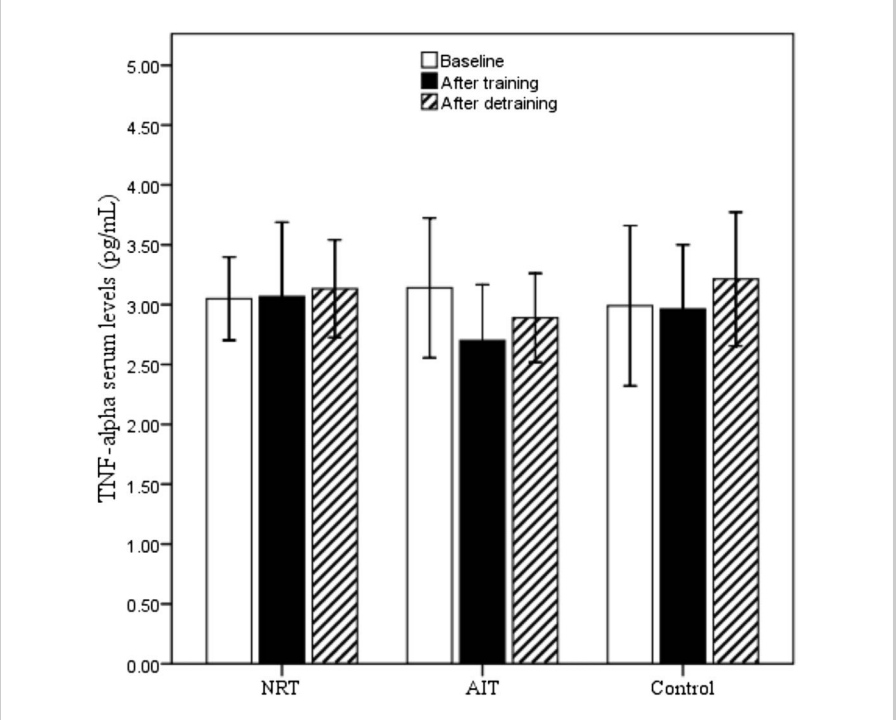

Figure 5. Serum levels of TNF-α (mean ± *SD*) at baseline, after the training and detraining periods. Effect size = 0.09 and statistical power = 0.39. NRT = nonlinear resistance training; AIT = aerobic interval training; TNF-α = tumor necrosis factor alpha.

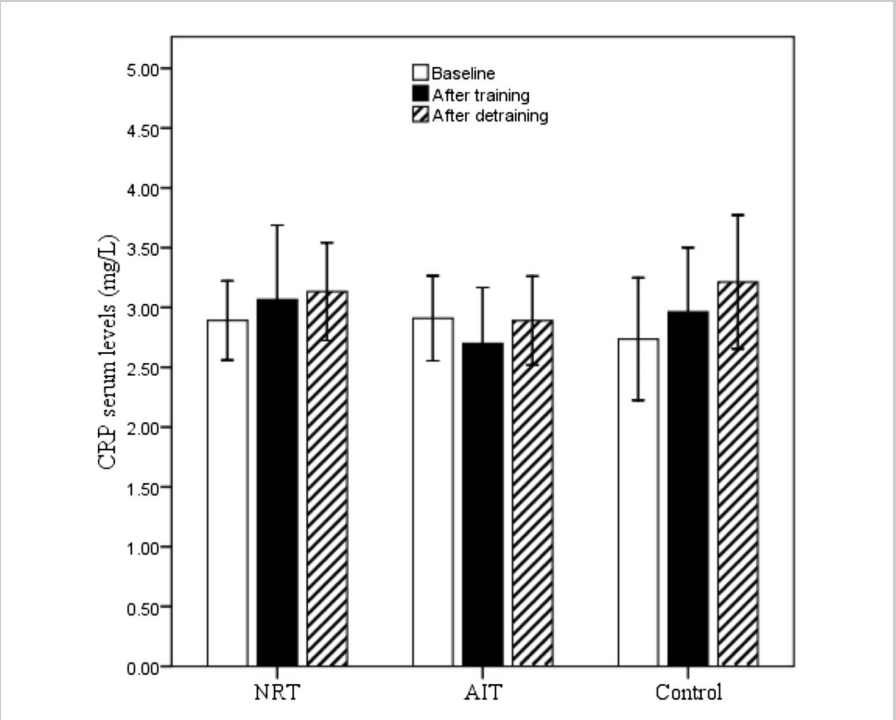

Figure 6. Serum levels of CRP (mean ± *SD*) at baseline, after training and detraining. Effect size = 0.03 and statistical power = 0.17. NRT = nonlinear resistance training; AIT = aerobic interval training; CRP = C-reactive protein.

the CON ($p = 0.003$), but it returned to pretraining levels in the NRT ($p = 0.72$). Maximal strength for bench press and knee extension were significantly increased with NRT compared with the other groups (all, $p < 0.001$); however, the AIT induced a significant increase only in knee extension ($p = 0.001$). Interestingly, these improvements persisted in the NRT and AIT after detraining.

Serum Biochemistry

Significant differences were noted at baseline between obese and lean subjects for ADPN ($p = 0.013$) and sICAM-1 ($p = 0.042$), but not for IL-6, CRP, and TNF-α ($p > 0.05$) (Table 5). After the training period, although there were no significant intervention effects ($p = 0.57$ and $p = 0.10$), there were significant time effects (both, $p = 0.001$) and intervention/time interaction ($p = 0.002$ and $p = 0.023$) for ADPN and insulin, respectively. Compared with the CON, 12 weeks of AIT lead to a significant increase in ADPN levels (23.7%, $p = 0.03$), but there was no significant change with NRT ($p = 0.29$). After detraining, ADPN levels decreased significantly (comparing after training and detraining) in both training groups (both $p < 0.001$) (Figure 1). Both the AIT and NRT were equally effective at reducing fasting insulin levels (both, $p \leq 0.05$) compared with the CON, but returned to the pretraining levels in both training groups after the detraining period (Figure 2). Repeated-measure ANOVA identified a significant time effect ($p = 0.001$) and intervention/time interaction ($p = 0.01$), but no significant intervention effect

($p = 0.42$) for sICAM-1. There was a significant decrease in sICAM-1 after 12 weeks of AIT (49%) and NRT (56%) compared with the CON ($p = 0.04$ and $p = 0.01$, respectively). After detraining, sICAM-1 had returned to the pretraining levels (Figure 3). Similarly, repeated-measure ANOVA identified a significant time effect ($p = 0.001$) and intervention/time interaction ($p = 0.008$), but no significant intervention effect ($p = 1.00$) for IL-6. Twelve weeks of AIT and NRT did not cause significant changes in IL-6. Interestingly, the serum concentration of this cytokine was significantly increased after 4 weeks of detraining with AIT ($p = 0.01$) and NRT ($p = 0.01$) groups when compared with the CON (Figure 4). Repeated-measure ANOVA determined no significant intervention effects, time, and intervention/time interaction for CRP ($p = 0.08$, $p = 0.8$, and $p = 0.70$, respectively) and TNF-α ($p = 0.76$, $p = 0.06$, and $p = 0.13$, respectively) (Figures 5 and 6).

Discussion

This is the first study to compare the effects of different exercise training programs (NRT and AIT) and detraining on selected inflammatory markers in men who are middle aged, healthy, and obese. In this study, both the AIT and NRT (with similar energy expenditure) were equally effective at reducing sICAM-1 and insulin levels, but the variables returned to the pretraining levels after detraining. Serum levels of IL-6, CRP, and TNF-α did not significantly change after training, but ADPN increased significantly with AIT. No significant changes in CRP and TNF-α occurred in both training groups after detraining, but ADPN and IL-6 worsened significantly.

At baseline, the men who are obese had significantly lower ADPN and higher sICAM-1, respectively compared with lean controls, but there were no significant differences between the groups for IL-6, CRP, and TNF-α. At baseline, all anthropometric measures were moderately and inversely correlated with ADPN (all, $r > -0.38$) and percentage body fat was moderately and positively correlated with sICAM-1 ($r = 0.30$) (data not shown). According to this finding, it seems that the obesity indices are main factors for regulation of ADPN and sICAM-1 levels. Also, the lack of significant differences for IL-6, CRP, and TNF-α between the obese and lean subjects might be due to the similar status in general health and aerobic capacity.

In this study, the 3 months of AIT induced an increase in ADPN levels. This finding is in accordance with the study of Racil et al. (34) investigating the effects of high-intensity interval aerobic training in obese individuals. In contrast, other studies showed that ADPN levels remained unchanged after prolonged aerobic training with low-to-moderate intensity, 3–5 exercise sessions per week for 8–24 weeks in healthy overweight or obese individuals (2,16,19,32). However, the NRT did not induce any significant change in ADPN, which is in accordance with the findings of Fatouros et al. (13). This study reported significant increases in ADPN after 6 months of moderate- and high-intensity RT but not after low-intensity RT. Brooks et al. (7) showed a significant increase in ADPN after 14 weeks of high-intensity RT in older adults with type 2 diabetes mellitus. In this study, more than 80% of the NRT regimen was performed at low-to-moderate intensity. Thus, it seems that the intensity is a determinant for a significant increase in ADPN in both training groups. In this study, the AIT caused a significant improvement in body mass and $\dot{V}O_2$max compared with the other groups. Yang et al. (44) showed that the increase in ADPN levels have been associated with weight loss due to dietary restrictions. In addition, studies have shown that there is a significant positive correlation between ADPN and $\dot{V}O_2$max (13,35). Therefore, it seems likely that the reduction in body mass or an increase in $\dot{V}O_2$max, or a combination of these could explain at least part of the increase in ADPN levels.

Another possible mechanism for the increase in ADPN is an increase in mitochondrial biogenesis. It was shown that induction of increased mitochondrial biogenesis augmented ADPN synthesis in adipocytes, whereas impairment of mitochondrial function decreased it. One family of transcriptional regulators in particular, the peroxisome proliferate-activated receptor γ coactivator family (PGCs: PGC-1α, PGC-1β) is important in driving mitochondrial biogenesis (37). The activity as well as the expression of PGCs is rapidly increased after a single bout of aerobic exercise. Interestingly, Terada et al. (42) reported that high-intensity exercise increases PGC activation more than low-intensity exercise. However, this study did not measure any index of mitochondrial function, but it was suggested that the AIT has lead to an increase in ADPN levels through mitochondrial biogenesis.

Twelve weeks of NRT and AIT did not change serum IL-6, TNF-α, and CRP concentrations, but sICAM-1 and insulin levels decreased significantly. These results were consistent with previous studies indicating no significant changes in IL-6, TNF-α (22,23), and CRP (23) after resistance and endurance training in similar subject groups to those in this study. However, some studies demonstrate a decrease in IL-6 (28,33), TNF-α (1), and CRP (24,41) after different exercise training protocols in elderly people or cardiac patients. Recently, Donges et al. (11) demonstrated significant decreases in CRP concentration after 10 weeks of moderate RT but not for aerobic exercise training in sedentary and subjects who are overweight. There are few studies that investigated the sICAM-1 responses to chronic exercise training. For example, sICAM-1 levels were significantly reduced after aerobic exercise training in patients with chronic heart failure and peripheral arterial diseases, respectively (1,36). These results are in agreement with our study. In contrast, Olson et al. (29) reported that 1 year of moderate RT did not a significantly change this marker in women who are overweight. These investigators also reported that the subjects did not have overt clinical manifestation of atherosclerosis and demonstrated relatively normal levels of adhesion molecules at baseline. As an explanation for this result,

we suggest that baseline levels of data should be considered. In this study, the initial mean level of sICAM-1 was 426 ± 196 $ng \cdot ml^{-1}$, which was higher than the values reported in the study of Olson et al. In conclusion, these discrepant results may be attributed to differences in timing in blood sampling, training programs, subject populations, and diet. In addition, factors such as aging, obesity, physical inactivity, and the most important CVD and diabetes mellitus have increased levels of these inflammatory markers. Therefore, it is possible that regular exercise training is most effective at reducing the levels of these inflammatory markers in individuals with elevated levels to begin with.

In this study, IL-6 and ADPN levels worsened significantly after 4 weeks of detraining in both training groups, also sICAM-1 and insulin levels had returned to initial baseline levels. Data are limited regarding the effects of detraining on biomarkers of inflammation in men who are trained and obese. Dixon et al. (10) recently revealed that no changes in IL-6, CRP, TNF-α, sICAM-1, and ADPN after reduced physical activity for 7 days in active and overweight middle-aged men. These discrepant results may be attributed to difference in the detraining time periods (4 weeks vs. 1 week). Krogh-Madsen et al. (21) reported that insulin stimulates IL-6 gene expression in human subcutaneous adipose tissue. However, IL-6 expression and secretion increases in the adipose tissue of subjects who are obese and is negatively associated with ADPN (15). Thus, the insulin stimulation of IL-6 gene expression in adipose tissue might play a role in the reduction of ADPN. Proinflammatory cytokines such as IL-6 and TNF-α activate several pathways, including the Janus kinase/signal transducers and activators of transcription (JAK/STAT) and extracellular signal-regulated kinase 1/2 pathways, which have a major role in ADPN regulation (39). Thus, it is possible that increase in IL-6 after the detraining in both experimental groups might be responsible for decrease in ADPN levels. Moreover, the expression levels of ADPN also decrease during oxidative stress and are negatively correlated with the production of reactive oxygen species. During oxidative stress, the expression of ADPN mRNA is inhibited by glucose oxidase (40). It seems that H_2O_2 markedly suppresses ADPN mRNA expression and protein secretion, while it enhances plasminogen activator inhibitor 1 and IL-6 production in mature adipocytes. ADPN expression was reduced by H_2O_2 through the Akt and JAK/STAT pathway. Increased fat mass results in a hypoxic microenvironment, which has been associated with the decreased levels of ADPN (9). Fatouros et al. (12) reported that endurance training may attenuate basal and exercise-induced lipid peroxidation and increase protection against oxidative stress by increasing total antioxidant capacity and glutathione peroxidase activity in older men. However, detraining may reverse these training-induced adaptations (12). Thus, this study suggested that the increase in ADPN after the AIT is probably due to an increase in antioxidant capacity and the reduction after detraining is associated with reduction in it.

It has been shown that adipose tissue oxygen levels are reduced with obesity, possibly due to a decreased angiogenesis, an increased vasoconstriction and a decreased blood flow (45). It is not clear whether the hypoxia state of adipose tissue contributes to the elevated inflammatory state with obesity. However, it is likely that hypoxia triggers the recruitment of inflammatory macrophages, increases the ratio of proinflammatory M1-type to anti-inflammatory macrophages within adipose tissue, and leads to increased local and systemic inflammation. In addition, hypoxia was associated with a decreased expression of ADPN and anti-inflammatory proteins in adipose tissue (46). According to these data, it can be suggested that an effective training program to improve hypoxia in adipose tissue may result in a better anti-inflammatory effect. Thus, the AIT (due to a greater increase in $\dot{V}O_2max$) may have a more beneficial effects compared with NRT and perhaps a greater increase in $\dot{V}O_2max$ with NRT (equal to AIT) can lead to similar effects.

Practical Applications

In conclusion, this study demonstrates that 3 months of NRT and AIT improve sICAM-1 and insulin levels and that these do return to the baseline levels after 4 weeks of detraining. The AIT induced a significant increase in ADPN; however, this variable worsened significantly in both training groups after detraining. Twelve weeks of AIT and NRT did not cause significant changes in serum levels of IL-6, TNF-α, and CRP, but IL-6 significantly worsened after 4 weeks of detraining with the AIT and NRT. It seems like both types of training are beneficial overall (e.g., all improvements listed above) but AIT is the only one that had some effects on one (ADPN) of the anti-inflammatory markers. These findings do not fully support the idea that the NRT regimen has similar beneficial effects to the AIT on systemic inflammation in men who are healthy, middle-aged, and obese. Therefore, men who are obese can use both the AIT and NRT to reduce metabolic syndrome, although it seems that the AIT may have better anti-inflammatory effects. Also, detraining in both training groups had comparable results. Thus, it is strongly recommended that the training programs should not be discontinued to prevent worsening of inflammatory conditions.

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