Effect of Regular Aerobic Training on Serum C-Reactive Protein and IL-6 Levels in Obese Women

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Objective: This study's objective was to evaluate interleukin-6 (IL-6) and C-reactive protein (CRP) responses and performance changes in obese women after 8 weeks of aerobic training with an intensity of 50 to 60% of their individual maximum oxygen uptake ($\dot{V}O_2$).

Methods: A total of 18 sedentary women with an average age of 44.3 (± 1.9) years volunteered for this study. Over a period of 8 weeks, in 4 40-minute sessions per week, the participants walked at an exercise intensity that caused their heart rates to increase to levels corresponding to 50 to 60% of their $\dot{V}O_2$peaks. Blood samples were collected from the participants, both when they were at rest and a couple of minutes after the end of the 1st exercise session. Sampling was repeated in the 4th and 8th weeks, before and after the last training sessions.

Results: The participants' body mass indices and weights decreased significantly by the end of the 8th week, while their maximum running speeds and $\dot{V}O_2$peaks increased significantly. There were no differences in CRP or IL-6 concentrations between the pre- and post-training sessions, but most of the participants' IL-6 levels dropped below 10 pg/ml after 8 weeks of training.

Conclusion: Although no significant changes were observed in CRP or IL-6 concentrations, it is important to note that in response to aerobic training, the IL-6 levels of most of the participants fell to what is generally considered acceptable. [*P R Health Sci J 2021;40:81-86*]

Key words: Exercise, Inflammation, Weight loss, Aerobic capacity

Obesity can be defined as a chronic and low-grade non-infectious disease with an increasing prevalence worldwide (1,2,3). In previous studies, it has been shown that, with increased adipose tissue mass elevates plasma concentrations of acute phase reactants such as interleukin-6 (IL-6) and C-reactive protein (CRP) and activates inflammatory signal pathways (2,4). Adipocytes and macrophages that infiltrate the adipose tissue cause the upregulation of related cytokines and chemokines. Furthermore, it is known that many tissues other than adipose tissue release those cytokines. It is thought that skeletal muscles cells are one of the sources of increased IL-6 and that increased IL-6 production is a response to exercise (5). Consequently, systemic inflammation secondary to weight gain might increase the risk of comorbidities that affect the cardiovascular system and, the metabolism.

Aerobic training has a key role in the treatment of metabolic diseases, including obesity. However, the concentrations of some inflammatory markers in the circulation change following exercise. In some studies, reduced CRP levels following aerobic exercise have been seen (6,7), while in others, reduced levels of IL-6 without any change in CRP levels have been found (8). Further, numerous studies support the notion that exercise affects IL-6 levels (9). The different findings regarding the reduction of CRP vs. IL-6 levels following aerobic exercise might be due to the variable responses (anti-inflammatory or pro-inflammatory) of cytokines to exercise (including the type and intensity of same).

Exercises whose intensities range from 40 to 70% of maximal oxygen uptake ($\dot{V}O_2$max) are defined as being low- to moderate-intensity exercises (10). Fats are accepted as a predominant fuel source for exercises whose intensities are below 65% $\dot{V}O_2$max (11). Reductions in adipose tissue mass that occur at such exercise intensities might decrease possible sources of inflammation. For obese individuals, the main reasons for losing weight are to deal with metabolic issues and to break the

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vicious cycle of chronic inflammation. However, considering the scarcity of studies on the effects of low- to moderate-intensity physical activity on obese middle-aged women's cytokine responses, this population deserves further investigation.

It has been shown that obesity is associated with chronic inflammation and that regular exercise has a profound effect on the immune system's normal functioning. Thus, we hypothesized that regular low- to moderate-intensity physical activity would reduce CRP and IL-6 levels in obese middle-aged women. In this study, we aimed to evaluate the effects of 8 weeks of aerobic training (at an intensity of 50 to 60% $\dot{V}O_2max$) on cytokine responses in obese middle-aged women.

Methods

A total of 18 sedentary females with an average age of 44.3 (± 1.9) years volunteered for this study. After having received a detailed explanation of the study, each participant was asked to sign an informed consent. Measurements were made after obtaining the Çukurova University Medical Faculty Ethics Committee's approval (number: 30.06.2011/17) and were carried out under the Declaration of Helsinki. All the tests were conducted at the sports physiology research and analysis laboratory of the Physiology Department of Çukurova University Medical Faculty. Participants with a history of any disease or of drug use were excluded from the study.

Anthropometric measurements

Before exercising, each participant had her anthropometric measurements taken; a single individual performed this task with all the members of the study sample For each participant, body mass and height were determined with a scale and stadiometer (Sport Expert, Professional Sport Technologies, Tümer, Turkey). A non-elastic measuring tape was used to make circumference measurements. Body-fat estimates were made using the method developed by Siri (12). Body density, which was used in the Siri formula, was calculated (13). Muscle mass was calculated according to Cattrysse et al. (14). The anthropometrical measurements were repeated before the 1st test and at the end of the 8-week training program.

Exercise protocol and indirect calorimetry

A maximal cardiopulmonary exercise test was performed on a treadmill (H/P/Cosmos, Nussdorf – Traunstein, Germany). Breath-by-breath gas measurements were taken throughout the exercise test using an indirect calorimetry system (Quark b2, COSMED, Rome, Italy). The system's volume and gas were calibrated using a 3 L calibration syringe and calibration gases, respectively (16% O_2 and 5% CO_2). Using a heart rate monitor (COSMED, Rome, Italy), each participant's heart rate was continuously recorded by telemetry.

The participants started the test walking at 3 km/h. The speed was increased by 0.5 km/h every min until exhaustion. A given individual's test was discontinued if she reached (or exceeded) 90% of her estimated maximum heart rate (per the 220-minus-age formula), achieved a plateau in oxygen consumption, or reached and maintained a non-protein respiratory quotient of 1.15 or higher (15).

Maximal cardiopulmonary exercise tests were performed before the 1st session of the training program (pre-training), at the end of the 4th week, and after the last session of the 8-week training program. When an individual participant's physical capacity showed improvement, that person's training intensity was adjusted according to the performance test performed in the 4th week of the training period.

Training program

Individual exercise intensity was determined from the maximal cardiopulmonary test. During the training period, the participants walked at an exercise intensity that caused their heart rates to increase to levels corresponding to a $\dot{V}O_2peak$ of 50 to 60%. The training program had an 8-week duration with 4 sessions consisting of 40 min/week.

Blood analysis

Blood was collected from the participants at rest and a couple of minutes following the end of the 1st exercise session. Sampling was repeated at the 4th and 8th weeks, before and after the last training sessions. Venous blood samples were centrifuged at 3500 rpm for 5 min. CRP was analyzed in serum collected from 5 ml of blood with an assay utilizing rate nephelometry (IMMAGE 800, Beckman Coulter, Brea, CA, USA). The rest of the samples were stored at -80 °C. After samples were collected from all the subjects, IL-6 was analyzed with the chemiluminescence method (IMMULITE 2000, Siemens Healthineers, Erlangen, Germany).

Statistical analysis

Results are expressed as means ± SEM. The software Statistical Package for the Social Sciences, version 22.0, for Windows (IBM SPSS Statistics, Inc, Chicago, IL) was used for statistical analysis. The normality of values was assessed with the Shapiro–Wilk test. Normally distributed data were compared with a paired t-test. Nonparametric data were compared with Friedman test and the Wilcoxon signed-rank test. The P values were checked with the Benjamini–Hochberg procedure. An α value of .05 was used to determine statistical significance.

Results

The participants' physical and performance characteristics before and at the end of the 4th and 8th weeks of the aerobic training program are given in Table 1. Exercise intensity was kept constant at 50 to 60% of the participants' peak oxygen uptake (56.9 ± 4.1%) throughout the training period. The participants trained at an average speed of 4.04 (± 0.11) km/h for 8 weeks. The participants' body weights and body mass indices (BMIs) had decreased significantly by the 4th and 8th weeks, whereas their maximal running speed during the maximal cardiopulmonary exercise test had increased significantly. Additionally, each individual's peak V̇O2 at the end of the 8 weeks of training was significantly higher than it had been before starting the program ($P<0.05$). The participants' body fat percentages had decreased significantly by the end of 8 weeks ($P<0.001$), and their fat-free mass had increased significantly ($P<0.001$).

Table 1. Physical characteristics and maximal cardiopulmonary test values of the participants before and after aerobic training (n = 18)

	Pre-training	4th week	8th week
Body mass (kg)	86.2 ± 3.5	85.2 ± 3.5&	83.5 ± 3.5*
Body mass index (kg/m^2)	34.2 ± 1.2	33.2 ± 1.2&	33.1±1.2&
Body fat percentage (%)	35.0 ± 0.6	-	31.5 ± 0.9*
Fat-free mass (%)	65.0 ± 0.6	-	68.5 ± 0.9*
Peak V̇O$_2$ (ml/min/kg)	19.1 ± 0.8	20.9 ± 0.8	21.2 ± 0.9&
Maximal heart rate (bpm)	156.1 ± 4.5	153.1 ± 3.9	158.7 ± 3.3
Maximal speed (km/h)	6.8 ± 0.2	7.6 ± 1.2&	8.0 ± 0.2*

Results are expressed as means ± SEM. *p<0.001 and &p<0.05; significantly different than pre-training levels.

The changes in the mean cytokine levels (in response to exercise) are given in Table 2. Although the mean IL-6 level had almost doubled by the end of the 1st exercise session, this difference was not significant. The post-training IL-6 level at the end of the 4th week had decreased by almost half compared to the post-training level for the 1st week. The decreases in the IL-6 response to exercise in the post-training values in the 1st and 4th weeks were not significant. Even though post-training IL-6 levels had decreased slightly more by the end of the last training session in the 8th week, this change was not significant. It was found that IL-6 levels might reach 10 pg/ml or more in obese individuals (9). Figure 1 shows that 16 people were above this level in the 1st week before the training (the IL-6 levels of 2 people were both found to be 0 pg/ml). The number of people above this level had decreased to 5 before the last training session at the end of the 8th week.

The pre-training and post-training levels of CRP did not show any significant differences in the 1st, 4th, and 8th weeks. Similar to what was the case with IL-6, a CRP level higher than 0.70 mg/dl was accepted as high (2), and no significant changes were found in response to training (Figure 2).

Table 2. Mean cytokine levels before and after 8 weeks of aerobic training

	1st Week		4th Week		8th week	
	Pre-training	Post-training	Pre-training	Post-training	Pre-training	Post-training
IL-6 levels (pg/ml)	10.8 ± 1.2 (0–20.5)	19.3 ± 4.4 (8.9–80.0)	10.5 ± 0.8 (3.1–17.1)	9.6 ± 1.2 (0–19.9)	12.4 ± 5.1 (0–94.9)	8.6 ± 2.5 (0–35.9)
CRP levels (mg/dl)	0.7 ± 0.2 (0.1–2.9)	0.7 ± 0.1 (0.1–2.6)	0.7 ± 0.2 (0.1–3.1)	0.7 ± 0.2 (0.1–3.2)	0.7 ± 0.1 (0.1–2.7)	0.7 ± 0.1 (0.1–2.7)

Results are expressed as means ± SEM. Minimum and maximum values are in parentheses.

Discussion

The main finding of this study was that even though class I obese women experienced statistically significant changes in their BMIs, body fat percentages, and exercise performances as a result of 8 weeks of aerobic training performed at 50 to 60% of their peak V̇O$_2$, their cytokine levels did not undergo any significant changes. Although no significant changes were observed, it is important to note that the IL-6 levels of most of those participants who began the intervention at 10 pg/ml or greater had fallen to below that mark after 8 weeks of training.

It is well known that chronic and low-grade inflammatory processes are related to various diseases, such as obesity, diabetes, and metabolic disorders. The presence of an inflammatory condition may trigger many physiological and pathological processes including the immune response. As a part of these processes, abnormal cytokine responses increase acute phase reactants; the activation of inflammatory signal pathways has been discussed in the literature (16,17,18,19). Many triggering factors, such as a fat-enriched diet and a high plasma leptin concentration, have been shown to affect T cell function and activate macrophages present in adipose tissue (16,20). In addition, factors such as monocyte chemoattractant protein that released from adipose tissue may activate macrophages (21). In addition, it has been shown that preadipocytes gain macrophage-like activity, and all these events cause cytokine responses (16,18). Many studies discovered that even though IL-6 and CRP inflammatory responses were found to be higher in obese individuals than in lean subjects, the degree of inflammation was not similar (16). For instance, these same studies found that plasma IL-6 concentrations tend to be below 1 pg/ml in healthy individuals at rest, but may reach as much as 10 pg/ml in obese individuals (9). Additionally, in a study in which 1830 women older than 20 years participated, Ford et al. found a median CRP value of 0.22 mg/dl, after excluding CRP concentrations above 1 mg/dl (22). Some studies also define elevated CRP levels as a plasma concentration of CRP 0.70 mg/dl or more (23). Given the previous and congruent with the scientific literature, many of the cytokine levels we saw in our study can justifiably be called high.

Apart from during resting conditions, it is noteworthy to mention that post-exercise cytokine responses show considerable variation. For example, in some studies where blood was collected just after the exercise, the IL-6 levels showed an increasing trend (24), whereas some studies claim that the immune response might have been suppressed due to glucocorticoids triggered by acute exercise stress, which in turn led to a decrease in cytokine release (21). In our study, the pre-training and post-training IL-6 levels were not significantly

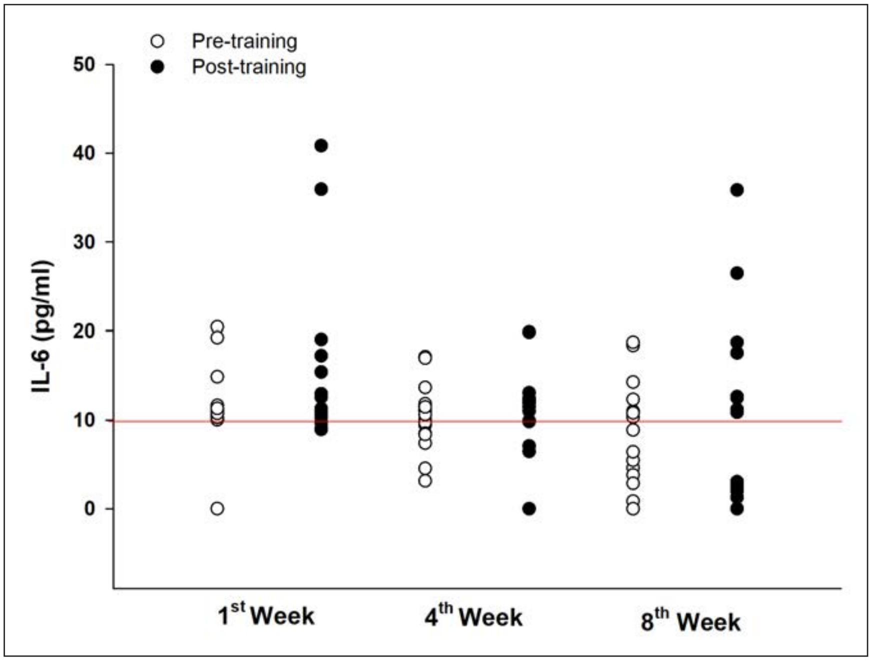

Figure 1. Pre- and post-training IL-6 values for the 1st, 4th, and 8th weeks.

the first and last sessions of training might be related to the possible changes in autonomic nervous system activity.

There were no significant differences in pre-training and post-training CRP concentrations. In this study, blood samples were collected before and immediately after each exercise session, and changes in CRP concentrations in the time periods that followed were not evaluated. As was the case in our study, Kelly et al. could not find any significant changes in the CRP concentrations of their participants (subjects with BMIs of 30 kg/m2 or greater) in response to 8 weeks of cycling exercise performed at 50 to 80% of $\dot{V}O_2$ peak (31). Thus, our exercise protocol's intensity or duration might not be enough to affect CRP levels.

The limitations of our study may include the small sample size, the relatively short duration of the training period, and the discontinuation of blood sampling after exercise.

different. Even though there was a decreasing trend in the average IL-6 values, the high variation between the maximal and minimal values might have caused nonsignificant differences between the groups. Studies reported in the literature show that plasma cytokine levels have variations without any noteworthy changes in response to aerobic training in obese women (2,25). Moreover, we did not classify our participants according to their fat distribution. As is currently known, the release pattern and properties of cytokines might differ in subcutaneous and visceral obesity (26). What is more, even though there were no significant differences in cytokine responses throughout the training period, it was shown that a noticeable number of participants' IL-6 levels fell to what is generally considered acceptable in response to aerobic training.

Given the normal cytokine response to regular exercise, it is thought that the beta-adrenergic system and its agonists play an important role in cytokine release from adipocytes (27,28,29). Although we did not evaluate autonomic nervous system activity in our study, an improvement in parasympathetic activity following regular, moderate intensity exercise has previously been shown (30). With this improvement in mind, we believe that the reduction in IL-6 concentration that occurred in the period between

The general view of the literature is that aerobic training effectively modulates cytokine responses (19). Cytokines have many paracrine and/or autocrine functions, such as energy expenditure regulation and insulin sensitivity (32). It might be important to adopt training intensities that aim to decrease fat tissue and thereby reduce the area in which said tissue becomes the source or trigger of inflammation. BMIs, fat percentages, peak oxygen uptakes, and maximal speeds showed significant

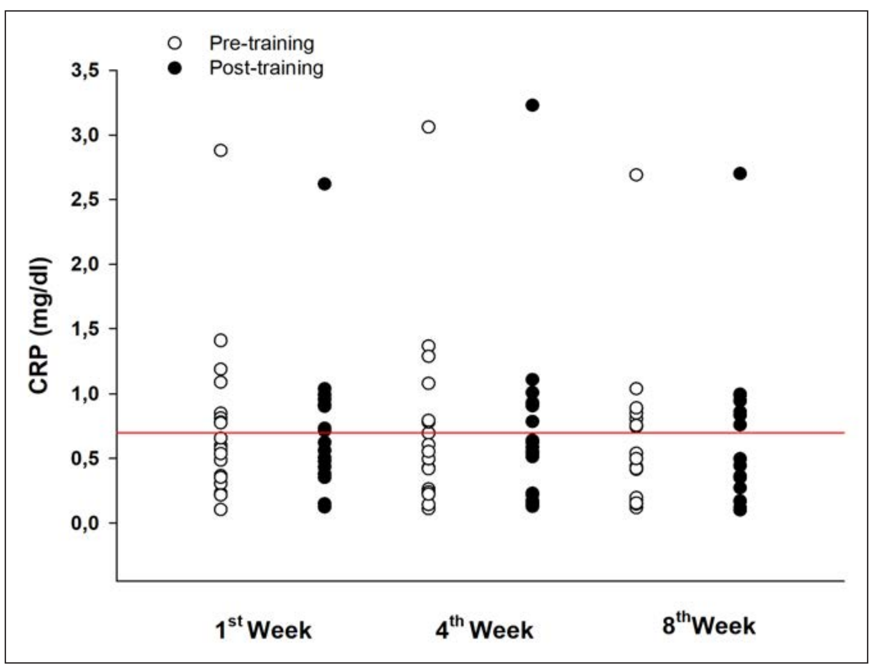

Figure 2. Pre- and post-training CRP values for the 1st, 4th, and 8th weeks.

changes in response to the mentioned workloads. These changes are expected from aerobic training. The reduction of CRP and IL-6 concentrations indicate a possible effect of low- to moderate-intensity training on immune regulation. The response of inflammatory cytokines to different training modalities and their relationship to adipose tissue mass changes should be addressed in future studies.

Resumen

Objetivo: El objetivo de este estudio fue evaluar las respuestas de la interleucina-6 (IL-6) y la proteína C reactiva (PCR) y los cambios en el rendimiento en mujeres obesas después de 8 semanas de entrenamiento aeróbico con una intensidad del 50 al 60% de su oxígeno máximo individual. absorción ($\dot{V}O_2$). Métodos: Un total de 18 mujeres sedentarias con una edad promedio de 44,3 (± 1,9) años se ofrecieron como voluntarias para este estudio. Durante un período de 8 semanas, en 4 sesiones de 40 minutos por semana, los participantes caminaron a una intensidad de ejercicio que provocó que su frecuencia cardíaca aumentara a niveles correspondientes al 50 al 60% de sus VO2picos. Se recolectaron muestras de sangre de los participantes, tanto cuando estaban en reposo como un par de minutos después del final de la primera sesión de ejercicio. El muestreo se repitió en la cuarta y octava semanas, antes y después de las últimas sesiones de entrenamiento. Resultados: Los índices de masa corporal y los pesos de los participantes disminuyeron significativamente al final de la octava semana, mientras que sus velocidades máximas de carrera y $\dot{V}O_2$ picos aumentaron significativamente. No hubo diferencias en las concentraciones de CRP o IL-6 entre las sesiones previas y posteriores al entrenamiento, pero la mayoría de los niveles de IL-6 de los participantes cayeron por debajo de 10 pg / ml después de 8 semanas de entrenamiento. Conclusión: Aunque no se observaron cambios significativos en las concentraciones de CRP o IL-6, es importante señalar que en respuesta al entrenamiento aeróbico, los niveles de IL-6 de la mayoría de los participantes cayeron a lo que generalmente se considera aceptable.

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