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# The effect of eight weeks of combined exercise on interleukin-6, C-reactive protein, and lipid profile in patients with coronary artery disease

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**Abstract:**

**Background:** Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide, claiming approximately 17.9 million lives annually. Given the role of physical activity in the prevention and management of cardiovascular diseases, investigating the impact of exercise on inflammatory markers is of particular importance. Therefore, this study was conducted to evaluate the effect of eight weeks of combined exercise on interleukin-6, C-reactive protein, and lipid profile in individuals with coronary artery disease.

**Method**: In a randomized clinical trial, 24 patients with coronary artery disease, overweight or obesity, and an average age of 59 ± 8 years with a body mass index of 27.76 ± 0.42 were randomly assigned to two groups: combined exercise training and control. The training group followed a specific exercise protocol for eight weeks, with three sessions per week. Venous blood samples were collected before and after the intervention. For data analysis, the Shapiro-Wilk test was used to assess normality, while analysis of covariance and Bonferroni post hoc test were applied to compare mean values between groups. The final analysis was conducted using SPSS version 22.

**Results**: The results showed that combine exercises led to a significant decrease in the levels of inflammatory response protein (CRP) (p=0.025) and IL-6 (p=0.011) compared to the control group. Also, despite the decrease in the mean TG, TC, LDL indices and the increase in HDL, the changes were not significant (P>.05).

**Conclusion**: The results show that 8 weeks of combine training can reduce inflammatory markers and reduce the risk of cardiovascular disease.

**Keywords:** combine training, interleukin-6, C-reactive protein, lipid profile, cardiovascular disease

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**Introduction**

Cardiovascular diseases (CVD) is a broad term encompassing various disorders that affect the heart and blood vessels (1). One of the prominent diseases in this category is coronary artery disease (CAD), which plays a significant role in CVD-related mortality (1,2. CAD occurs due to impaired blood supply, oxygenation, and nutrient delivery to the heart muscles, primarily caused by the accumulation of fatty deposits in the walls of the coronary arteries, a condition known as atherosclerosis. Several key risk factors contribute to the development of atherosclerosis, including smoking, high blood pressure, diabetes mellitus (DM), dyslipidemia, obesity, physical inactivity, and stress (3).

Epidemiological studies confirm that physical fitness is strongly associated with reduced cardiovascular mortality and lower hospitalization rates due to cardiovascular diseases (4,5). Over the past two decades, the approach to post-heart attack recovery has shifted significantly, with patients now encouraged to engage in exercise programs shortly after a cardiac event (5). Research highlights that the beneficial effects of exercise are independent of genetic background and are most effective when sustained over a longer duration. Regular physical activity has been shown to improve heart and lung function, reduce metabolic dysfunction, and lower the risk of cardiovascular diseases. To maximize the benefits of exercise in healthcare, future efforts should focus on increasing adherence to physical activity by offering engaging and effective exercise programs. Studies suggest that structured exercise interventions can significantly reduce the risk of sudden cardiac death and improve overall cardiovascular health (6).

According to the World Health Organization, one person in the United States dies from cardiovascular disease every 33 seconds (National Center for Health Statistics, 2023) (7). Considerable evidence has proven the value of high levels of physical activity (PA), exercise training, and cardiorespiratory fitness (CRF) in the prevention and treatment of cardiovascular disease, and the main threat to health in the 21st century is clearly inadequate levels of physical activity (8). In the Middle East, and especially in Iran, it is observed that the incidence of cardiovascular disease and its mortality rate are increasing at an alarming rate. Cardiovascular diseases account for almost half of all deaths, comprise 20-23% of the disease burden, and account for about 24% of all years of life lost in Iran (9, 10).

Physical activity can improve insulin sensitivity, reduce plasma dyslipidemia, modulate hypertension, reduce blood viscosity, enhance endothelial nitric oxide production, and improve leptin sensitivity to protect the cardiovascular system (11). It is widely accepted that regular physical activity is beneficial for cardiovascular health. Frequent exercise is strongly associated with reduced cardiovascular mortality as well as the risk of cardiovascular disease. Physically active individuals have lower blood pressure, higher insulin sensitivity, and more favorable plasma lipoprotein profiles (12).

To identify risk factors for cardiovascular diseases, in addition to diagnostic tests such as echocardiography and electrocardiography, some inflammatory factors and lipid profiles are also examined, one of which is called interleukin-6 (IL-6). IL-6 is a glycoprotein located on chromosome 7 that has anti-inflammatory and pro-inflammatory functions at the level of circulating structures. (13) Elevation of this biomarker can increase the risk of atherosclerotic plaque instability and rupture and increase mortality in patients with coronary artery disease (CAD). (14,15) Elevated levels of IL-6 have been shown to increase the risk of CAD and are associated with CVD mortality. (16) This is largely because it is a cause of the early phase of inflammation in the endothelial wall (17). Another inflammatory factor evaluated in clinical laboratories is C-reactive protein (CRP), an acute phase protein synthesized by the liver in response to the secretion of several inflammatory cytokines, including IL-6, IL-1, and tumor necrosis factor. CRP was the first acute phase protein to be described and accepted in clinical laboratories as a highly sensitive systemic marker of inflammation and tissue damage. (18) Exercise and activity Physical activity may be associated with reduced levels of inflammatory markers, including (CRP) and (IL-6), which can reduce disease progression, functional decline, and the risk of cardiovascular outcomes in patients with PAD (peripheral artery disease) (19). High serum concentrations of total cholesterol, LDL, HDL, and triglycerides are also known as risk factors for cardiovascular disease (20, 21). Numerous studies have emphasized the importance of reducing saturated fatty acid intake in these patients, as high intake of these fats can lead to increased LDL levels and ultimately death (22).

The foundations of combine training can be traced back to the early 1980s, when Dr. William Hickson conducted pioneering studies on the effects of combine strength and endurance training. (23) Today, these training is widely used as an effective approach for diverse groups in society.The effect of combine exercise training has been associated with a reduction in total cholesterol and LDL cholesterol (bad cholesterol) levels in pregnant women (24,25). Studies have shown that combine and aerobic training were both effective in reducing pro-inflammatory markers. Simultaneous training was more effective in reducing BMI, body fat composition, and CRP than aerobic and resistance training. Also, middle-aged women benefited from aerobic training to reduce IL-6 levels.

The result of one study showed that the combination of aerobic and resistance training not only has a positive effect on body composition, but also through anti-inflammatory mechanisms, it reduced inflammatory markers by 23% in CRP levels and 18% in IL-6 levels and also improved metabolic health in young women (26). In addition, it has been showed that combine training (aerobic + resistance) in one session significantly improved functional capacity and muscle performance in elderly patients with heart failure. Exercise interventions, especially combine exercises, significantly reduce inflammatory markers CRP, IL-6, TNF-α in obese patients with heart failure (27). This reduction in inflammation is associated with improved body composition and cardiorespiratory function (28) Also, examining the effect of 12 weeks of combine training compared to combined training (separate sessions), has a superior effect on reducing inflammation:

a 25% reduction in CRP in the combine exercise in one session and an increase in muscle strength. (29)

Overall, although many studies have been conducted on the effect of exercise training on cardiovascular indicators, fewer studies have been conducted on the combined training model, especially on the levels of inflammatory factors IL-6 and CRP, as well as the lipid profile in cardiovascular patients. However, to understand the extent to which exercise duration affects the desired inflammatory indicators in people at risk of cardiovascular disease, it is important to address this gap because it is necessary to discover the optimal duration and frequency of combined training and protocols that maximize the positive effects in the shortest time for the target population.

## Material and method

This study included 24 adults (10 women and 14 men) aged 51 to 66 years with coronary artery disease, a history of myocardial infarction or prior therapeutic interventions, including coronary artery bypass surgery and coronary angioplasty. Participants were either overweight or obese and were referred to the designated cardiac rehabilitation clinic in Tehran based on the recommendation and diagnosis of a cardiologist. None of the participants had contraindications for exercise. The sample size was determined using G*Power software version 3.1.9.2, with a mean body mass index (BMI) of 27.76 ± 0.42 kg/m². All participants had a sedentary lifestyle, defined as not adhering to aerobic or resistance training guidelines in the past three months. The primary selection criteria included non-smoking status, abstinence from alcohol, and no use of medications affecting study variables. Additional exclusion criteria included individuals who smoked and those who planned to be absent for more than two weeks during the intervention period. Before the intervention, each participant signed an informed consent form.

### Study Design

Participant recruitment was completed between June and July 2024. To improve adherence, participants underwent a screening session before enrollment. After confirming eligibility criteria, they attended two educational sessions to minimize dropout rates. Participants were then randomly assigned by a study statistician to one of two parallel groups with a 1:1 ratio:Control group (no exercise) and experimental group (a combination of aerobic and resistance training). Baseline assessments included echocardiographic Doppler imaging and an exercise test. Additionally, a 5 mL venous blood sample was collected from the superficial arm vein for evaluation. Blood samples were stored in serum separation tubes and analyzed externally in a laboratory. After eight weeks of training, participants completed post-test assessments to evaluate the effects of the intervention.

**Assessments**

Body mass index (BMI) was calculated using measured weight and height. Body composition was analyzed through multi-frequency bioelectrical impedance analysis (BIA) using an 8-electrode touch system (InBody 720, Biospace Co., Ltd., Seoul, South Korea), providing values for body fat percentage, fat mass, and lean mass. Cardiorespiratory fitness was assessed using a submaximal treadmill exercise test following the modified Balke & Ware protocol. All participants reached 70% of their heart rate reserve before completing the test. Cardiorespiratory fitness was estimated using the American College of Sports Medicine (ACSM) formula; [(slope*Spee*1.8}+ (0.1*speed) + 3.5].

**Exercise Intervention**

The warm-up consisted of two five-minute phases. The first phase involved light walking and cycling with a gradual increase in intensity to prepare the muscles for exercise. Each stretch was held for 10 to 15 seconds to enhance flexibility and reduce injury risk. In the aerobic training phase, the first week started with treadmill exercises at 60–65% of maximum heart rate for 20 minutes. As participants' physical condition improved, both duration and intensity gradually increased. The main exercise duration extended by one minute per session, while intensity increased by approximately 4% of maximum heart rate per week. Throughout the sessions, heart rate, blood pressure, and potential changes in electrocardiogram readings were monitored before and during exercise. In addition to aerobic exercises, participants performed resistance training twice a week for 15 minutes per session. This involved lifting 1–2 kg weights, completed in two sets per session with 10–20 repetitions. Between weeks four and seven, the weight was progressively increased by 0.5 kg per body weight. Resistance exercises included shoulder abduction and overhead weight lifting in a seated position, as well as horizontal shoulder flexion in a lying position. The cool-down phase aimed to gradually reduce heart rate, slow movement speed, and restore the body to a resting state. Stretching exercises were incorporated to minimize muscle soreness after exercise. The complete cool-down process lasted 10 minutes (30).

**Statistical Method**

Statistical data analysis was performed using SPSS version 22. The ANCOVA model was applied for between-group comparisons, while paired t-tests were used to assess within-group changes. Additionally, the Bonferroni post hoc test was conducted to determine the significance threshold. The significance level was set at $p < 0.05$.

## Results

The demographic characteristics in both the training and control groups are presented in Table 1.

The results of this study indicated that after group homogenization, C-reactive protein (CRP) levels significantly decreased in the training group following eight weeks of combine exercise compared to the control group ($p = 0.001$). However, no significant changes in CRP levels were observed in the control group ($p = 0.025$).

**Table 1.** Mean and standard deviation of general and physiological characteristics of the participants.

| variables | Groups | |
|---|---|---|
| | Control | Training |
| **Age** | 60±4 | 58±4 |
| **Wieght** | 84.17 ± 6.71 | 84.25 ± 6.15 |
| **BMI** | 28.22 ± 0.54 | 28.45 ± 0.55 |
| **VO2peak** | 36.0 ± 1.5 | 32.0 ± 5 |
| **%FAT** | 19.82 ± 2.50 | 21.72 ± 1.40 |
| **BPsystol** | 131 ± 16 | 131 ± 14 |
| **BPdiastol** | 83±10 | 80±9 |
| **HR.rest** | 72±0.58 | 70±0.58 |

Additionally, interleukin-6 (IL-6) levels showed a significant reduction in the training group compared to the control group ($p = 0.001$), while no significant changes were observed in the control group (Table 2).

Lipid profile indices did not show statistically significant differences between the groups.
Although the mean levels of LDL, TC, and TG decreased non-significantly in the training group, HDL levels exhibited a non-significant increase p.

**Table 2.** presents the mean and standard deviation of the research variables in both the training and control groups before and after the exercise intervention.

| Variables | Groups | pre | post | P value |
|---|---|---|---|---|
| **CRP** | **Training** | 7.80±3.50 | 6.95 ± 3.40 | 0.025* |
| | **Control** | 7.25± 3.20 | 7.30 ± 3.22 | 0.96 |
| **IL-6** | **Training** | 7.20 ± 1.5 | 6.95 ± 1.55 | 0.001* |
| | **Control** | 6.90 ± 1.30 | 6.85 ± 1.35 | 0.90 |
| **TG** | **Training** | 249.6 ±30.01 | 242.0 ±23.39 | 0.75 |
| | **Control** | 281.7±25.3 | 279.0 ± 23.89 | 0.71 |
| **TC** | **Training** | 266.9 ±32.2 | 260.5 ± 28.9 | 0.79 |
| | **Control** | 294.2 ±24. 1 | 291.2 ± 23.7 | 0.67 |
| **LDL** | **Training** | 162.30 ±30.10 | 160.0 ± 28.5 | 0.94 |
| | **Control** | 169.8±11.3 | 170.0 ± 10.9 | 0.95 |
| **HDL** | **Training** | 45.83 ± 7.23 | 47.5 ± 8.0 | 0.88 |
| | **Control** | 55.75± 5.48 | 56.0 ± 5.64 | 0.88 |

* Indicates a significant difference between data before and after training.

## Discussion

The findings of this study indicate that eight weeks of combine exercise led to a significant reduction in C-reactive protein (CRP) and interleukin-6 (IL-6) levels among cardiac patients, while the control group, which did not engage in any physical activity, showed no significant changes. These results align with previous research. Consistent with this study, Sobhani et al. (2024) found that an eight-week combined exercise program in elderly women significantly reduced IL-6 levels (31)., suggesting that such programs may have anti-inflammatory effects in this population Similarly, Maleki et al. (2023) reported that combined exercise training significantly lowered IL-6 levels and metabolic indicators in men with metabolic syndrome (32). The reduction in IL-6 levels observed in the combine exercise group in this study may be attributed to several factors: Enhanced cardiovascular function, which improves circulation and reduces systemic inflammation; Improved metabolic efficiency, leading to better regulation of inflammatory markers; Reduced adipose tissue, as training has been shown to decrease fat mass, which is a major source of inflammatory cytokines. Additionally, research suggests that exercise intensity and duration play a crucial role in modulating inflammatory responses (33).

Regarding the CRP index, the study by Orange et al. (2023) found that combined exercise significantly reduces CRP levels in physically inactive adults (34). A decrease in CRP indicates reduced systemic inflammation, which is associated with improved cardiovascular and metabolic health. Similarly, Silva et al. (2024) observed that combined exercise lowers pro-inflammatory cytokines, leading to a reduction in CRP production (35). Higher physical fitness is linked to lower CRP concentrations, demonstrating a direct relationship between exercise and inflammation reduction. This effect may be due to the anti-inflammatory properties of combined exercise on pro-inflammatory cytokines like IL-6, which decreases, and anti-inflammatory cytokines like IL-10, which increase—ultimately reducing CRP production. Additionally, improved adipose tissue function due to exercise leads to a reduction in visceral fat, which is a primary source of inflammatory cytokines, thereby lowering CRP levels (36).

On the other hand, improved adipose tissue function due to exercise reduces visceral fat, a major source of inflammatory cytokines, which in turn reduces CRP levels. Also, improved metabolic health (improved insulin sensitivity and lipid metabolism) reduces systemic inflammation and CRP levels (37). Furthermore, Pedersen et al. concluded that simultaneous strength and aerobic training improves body composition in overweight and obese women. However, it did not significantly affect glucose homeostasis or the lipid profile, suggesting that simultaneous exercise did not affect the lipid profile (38).

In contrast to our study (Pérez et al. 2022) showed that in sedentary postmenopausal women with obesity, serum IL-6 increased after a 12-week combined exercise intervention (39). This increase may be due to the inflammatory response to moderate- or vigorous-intensity physical activity, which results from mechanical and metabolic stress on the muscles. Also, in a study of 32 obese women who performed combined, resistance, and high-intensity endurance training interventions, it was shown that all three types of combined exercise intensities increased the levels of myokines, such as irisin and IL-6 (40). The results of a 16-week combined exercise study (41) in untrained subjects decreased the fat profile, which may be due to the high intensity of the exercises. Also, the effect of 12 weeks of high-intensity combined exercise intervention on 12 obese men resulted in a significant reduction in the change in lipid profile levels (total cholesterol, HDL-C, LDL-C, and TGs) between groups and other biochemical parameters, such as CRP and leptin, indicating the role of combine exercise intensity (42). In other words, the lack of significant changes in lipid profiles in our study could be due to the intensity or duration of combined exercise.

Overall, our study showed that moderate-intensity combine exercise improves inflammatory markers while causing no significantly reductions in other factors influencing cardiovascular disease (CVD) development. This supports the recommendation of combine exercise for the greatest overall benefits of exercise training in middle-aged adults at risk of cardiovascular disease. Limitations of the present study include the estimation of cardiorespiratory fitness using the submaximal treadmill test and the lack of complete control over participants' diet, rest quality, and stress. However, further research with larger sample sizes and longer interventions is necessary to explore the overall cardiovascular benefits, different exercise modalities, and optimal combinations of training programs.

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**Ethical considerations**

This study was approved by the Ethics Committee of the Islamic Azad University under the registration ID IR.IAU.VARAMIN.REC.1403.030.

**Conflict of Interest**

The authors have no conflicts of interest to report.

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