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Effects of lifestyle modifications on C-reactive protein: contribution of weight loss and improved aerobic capacity

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Abstract

High-sensitivity C-reactive protein (hs-CRP) is associated with an increased risk of cardiovascular disease and the development of type 2 diabetes mellitus. We analyzed the effects of lifestyle modifications including exercise training on hs-CRP in 47 overweight and obese adults. Subjects were divided into a lifestyle modification group (n = 23) (exercise and diet instruction) and a control group (n = 24) who did not participate in any lifestyle modification. After 3 months, body weight (80.8 ± 11.5 to 73.5 ± 10.7 kg, $P < .01$), total cholesterol (217 ± 38.4 to 178.0 ± 25.6 mg/dL, $P < .01$), low-density lipoprotein cholesterol (151.3 ± 34.9 to 116.7 ± 27.8 mg/dL, $P < .01$), V_{O_2}peak (30.3 ± 5.1 to 37.1 ± 6.9 mL/[kg · min], $P < .01$), and log hs-CRP (0.75 ± 0.4 to 0.56 ± 0.3 mg/dL, $P = .01$) were significantly improved in the lifestyle modification group, but there was no significant improvement in the control group. Changes in log hs-CRP were associated with changes in V_{O_2}peak ($r = -0.41$, $P = .004$) and changes in weight loss ($r = 0.42$, $P = .004$). In stepwise multiple regression analysis, weight loss ($P = .034$) and improved V_{O_2}peak ($P = .039$) were independent predictors of the changes in hs-CRP. When grouped into quartiles according to decreasing weight and increasing V_{O_2}peak, levels of changes in log hs-CRP improved across quartiles of weight loss ($P < .05$) and improved V_{O_2}peak ($P < .01$). Thus, lifestyle changes including regular exercise training in overweight and obese adults decreased hs-CRP, and this was associated with weight loss and improved V_{O_2}peak.

1. Introduction

Regular exercise training has a protective effect on the development of cardiovascular disease (CVD) and type 2 diabetes mellitus, particularly in obese adults [1], but the underlying mechanisms are not completely understood. Although exercise training alters some traditional risk factors, this alone cannot explain the protective effect of exercise [2]. Plasma high-sensitivity C-reactive protein (hs-CRP), an inflammatory marker, is associated with an increased risk of CVD [3] and the development of type 2 diabetes mellitus [4]. Furthermore, inflammation and hs-CRP are linked to both obesity and type 2 diabetes mellitus, possibly representing a "common ground" between these conditions [5,6].

There is some evidence suggesting that increased physical activity [7-9] or high levels of cardiorespiratory fitness [10-12] are related to hs-CRP, thereby contributing to lowering the risk of CVD and type 2 diabetes mellitus by mitigating the inflammatory process in addition to its effect on traditional risk factors. However, these cross-sectional data only demonstrate an association between hs-CRP, fitness, and physical activity.

It is well accepted that weight loss decreases hs-CRP in obese patients [13-15], and this improvement appears to be related to the amount of weight lost. This process may be modulated by reductions in abdominal fat, as abdominal fat

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is related to increased production of inflammatory cytokines [16,17], which in turn stimulate hs-CRP production from the liver [18].

As most physical activity/fitness studies have been cross-sectional in nature [7-12] or have combined exercise with diet interventions designed to produce weight loss [13,14,19,20], it is presently unclear whether exercise training decreases hs-CRP independently of weight loss. As exercise training can affect the abdominal fat depot and insulin resistance even without an overall weight loss [21], it is possible that exercise alone could also decrease hs-CRP without any associated weight loss. Cross-sectional studies have shown an inverse relationship between physical activity [7-9] or cardiorespiratory fitness and hs-CRP even after adjustment for body mass index (BMI) [10,11]. Although intervention studies have documented beneficial reductions in hs-CRP levels after exercise training [22-27], these effects have not been consistently demonstrated after adjustment for changes in body weight [20,28]. Okita et al [22] and Marcell et al [29] showed no relationship either between changes in aerobic capacity and changes in hs-CRP. Thus, it is still unclear whether exercise training is related to positive changes in hs-CRP when also accompanied by substantial weight loss produced with combined lifestyle modification.

Therefore, the purpose of the study was to investigate the effects of exercise training and lifestyle modification on hs-CRP. We also examined whether weight loss and improvements in aerobic capacity after an intervention may independently contribute to changes in hs-CRP. We hypothesized that changes in both aerobic capacity and weight loss would be independently related to changes in hs-CRP.

2. Research design and methods

2.1. Subjects

We recruited 47 (35 males and 12 females, 49.6 ± 6.9 years) healthy, sedentary overweight (n = 4), and obese (n = 43) subjects based on Asia-Pacific criterion [30] from participants who had enrolled in a hospital-sponsored health examination program during a 2-month period in 2002. Subjects were excluded if they had CVD, stroke, type 2 diabetes mellitus, hypertension (or taking any antihypertensive medications), if they were taking aspirin or any other anti-inflammatory medications, or were women on hormone replacement therapy. All subjects signed informed consent and the study was approved by the hospital institutional review board for human research.

2.2. Design

The exercise group consisted of 23 subjects (16 males and 7 females) who enrolled in a lifestyle modification class which included exercise training. The control group consisted of 24 subjects (19 males and 5 females) who chose not to participate in the lifestyle intervention program. Subjects reported to the laboratory in the morning after a 12-hour overnight fast. After a 10-minute period of seated rest, blood samples were obtained from an anticubital vein. Anthropometrics and exercise testing were completed after blood collection. The exercise group was then enrolled in a 3-month lifestyle modification program which consisted of diet education and exercise training, and the control group was provided with information on diet and exercise, but was not instructed to participate in a formal program. After the 3-month intervention, all testing was repeated as described above.

2.3. Exercise testing

Subjects performed symptom-limited exercise testing using the Bruce protocol to determine peak oxygen uptake (VO_2peak) values. Expired gases were collected breath-by-breath using a 1-way valve and analyzed using a metabolic cart (Oxicon Delta, Jaeger Hoechberg, Germany). Data were expressed in 8-second averages. The metabolic system was calibrated using gases of known concentrations, and volume was calibrated using a syringe with a known volume, before each test. Twelve-lead electrocardiograms were obtained throughout the test (Q4500, Quinton, Bothell, WA). Peak effort was considered valid if 2 of the following criteria were present: an respiratory exchange ratio above 1.1, if the subject achieved age-predicted maximal heart rate (MHR), a rating of perceived exertion higher than 17, or if the subject was too fatigued to safely continue walking on the treadmill.

2.4. Anthropometrics and blood pressure

Height and weight were obtained using standard procedures. Body mass index was calculated as weight (kg) divided by height (m^2). Resting blood pressure was measured in sitting position using an automated blood pressure monitor (Dinamap PRO 100, GE, Milwaukee, WI) after at least 5 minutes of quiet rest.

2.5. Blood analyses

Blood samples were collected in the morning (06:00-08:00 AM) after a 12-hour overnight fast. Subjects did not consume alcohol or exercise at least 24 hours before blood draws. Samples were analyzed in the hospital clinical laboratory. High-sensitivity CRP was measured using a CRP (II) Latex X2 turbidimetric method (Hitachi-747, Hitachi, Tokyo, Japan). The intra- and interassay coefficients of variation for hs-CRP were less than 5%. Total cholesterol (TC), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were analyzed enzymatically using a Hitachi 747 analyzer. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Inter- and intra-assay coefficients of variation were less than 5% for all blood lipid variables.

2.6. Lifestyle intervention program

The subjects in the lifestyle intervention group performed home-based regular exercise training with general diet

Table 1
Characteristics of the exercise and control group at baseline

Variables	Lifestyle group (n = 23)	Control group (n = 24)
Age (y)	49.6 ± 7.5	49.7 ± 6.4
Weight (kg)	80.8 ± 11.5	80.7 ± 11.8
BMI (kg/m^2)	28.8 ± 2.0	27.8 ± 2.4
TC (mg/dL)	217.6 ± 38.4	208.8 ± 34.9
HDL-C (mg/dL)	48.7 ± 7.3	48.8 ± 8.3
LDL-C (mg/dL)	151.3 ± 34.9	145.0 ± 31.3
TG (mg/dL)	170.2 ± 106.5	158.9 ± 87.4
TC/HDL-C	4.6 ± 1.0	4.4 ± 1.0
SBP (mm Hg)	130.6 ± 15.3	119.4 ± 15.5*
DBP (mm Hg)	88.1 ± 9.7	84.4 ± 12.3
V_{O_2}peak (mL/[kg · min])	30.3 ± 5.1	31.8 ± 4.9
V_{O_2}peak (L/min)	2.47 ± 0.62	2.57 ± 0.55
MHR (bpm)	157.7 ± 13.9	150.8 ± 14.3
CRP (mg/dL)[a]	0.11 (0.05-0.25)	0.07 (0.04-0.15)
Log CRP (mg/dL)	0.75 ± 0.4	0.61 ± 0.3

Data are expressed as mean ± SD. TC/HDL-C indicates TC/HDL-C ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute.

[a] Median and interquartile range.

* $P < .05$.

education for 3 months. The exercise prescription consisted of aerobic exercise, such as walking, cycling, swimming, and hiking, for 50 to 60 minutes per session, more than 5 times per week. Subjects were asked to exercise at an intensity of 60% to 80% of MHR, or at a rating of perceived exertion of 13 to 15. Every 2 weeks subjects came back to the hospital to meet with an exercise physiologist to check and update their exercise prescription. Their exercise logs and charts were also checked at this time to ensure they adhered to the exercise prescription. Diet education was provided initially and then every 2 weeks by a dietitian, with an aim of reducing total energy intake and providing a healthy diet for weight control. The control group received an initial consultation with both an exercise physiologist and a dietician and also received written educational materials. There was no contact with the control group after the initial consultation until the follow-up 3 months later.

2.7. Statistics

All variables are expressed as mean ± SD. Because the hs-CRP values were not normally distributed, all statistical analyses for hs-CRP were conducted on log-transformed values. Baseline characteristics were compared using a *t* test for independent samples. The response to the lifestyle intervention program was evaluated using 2 × 2 (group by pre- vs postintervention) analysis of variance with repeated measures. To evaluate whether changes in hs-CRP were dependent on changes in body weight or changes in aerobic fitness, 2 × 2 (group by pre- vs. postintervention) analysis of covariance with repeated measures was performed, using change in both weight or change in V_{O_2}peak as the covariate. Pearson correlations were used to evaluate the relationship between changes in hs-CRP and changes in body weight and V_{O_2}peak. To evaluate the independent contribution of changes in body weight and changes in V_{O_2}peak to changes in hs-CRP, partial correlations and stepwise multiple regression analysis were performed. Statistical significance was set at $P < .05$.

3. Results

The physical characteristics of subjects at baseline are shown in Table 1. None of the variables except resting SBP ($P = .02$) were significantly different between exercise and control groups. At baseline, hs-CRP was associated with BMI ($r = 0.35$, $P = .016$) but not V_{O_2}peak ($r = -0.27$, $P = .06$) (Table 2).

3.1. Effects of exercise training and lifestyle modification on hs-CRP

After 3 months of exercise training and lifestyle modification, there were significant reductions in body weight (9%, $P < .01$), BMI (8%, $P < .01$), TC (18%, $P < .01$), LDL-C (23%, $P < .01$), TC/HDL-C (15%, $P < .01$), and hs-CRP (25%, $P < .01$). There was also an increase in V_{O_2}peak (11%, $P < .01$) and MHR (3%, $P = .03$)

Table 2
Correlations among the various parameters at baseline

Variables	Age	Weight	BMI	TC	HDL-C	LDL-C	TG	TC/HDL-C	SBP	DBP	V_{O_2}peak	MHR
Weight	−0.08											
BMI	0.03	0.74**										
TC	0.12	0.03	0.15									
HDL-C	0.09	−0.09	−0.14	0.03								
LDL-C	0.23	−0.01	0.15	0.92**	−0.08							
TG	−0.14	0.21	0.09	0.39**	−0.36*	0.19						
TC/HDL-C	0.03	0.14	0.26	0.75**	−0.63**	0.75**	0.55**					
SBP	0.07	0.43**	0.47**	0.26	0.12	0.23	0.07	0.15				
DBP	−0.06	0.45**	0.42**	0.26	0.08	0.21	0.07	0.16	0.77**			
V_{O_2}peak	−0.14	0.17	0.02	0.02	0.05	−0.05	0.11	−0.02	0.14	0.29*		
MHR	−0.49**	0.15	0.05	−0.03	0.08	−0.15	−0.01	−0.06	0.16	0.22	0.33*	
Log CRP	0.18	0.08	0.35*	0.23	−0.16	0.28	0.05	0.31*	0.21	0.16	−0.27	−0.26

* $P < .05$.

** $P < .01$.

Table 3
Changes in clinical variables before and after exercise training

Variable	Lifestyle group		Control group	
	Pre	Post	Pre	Post
Weight (kg)	80.8 ± 11.5	73.5 ± 10.7*	80.7 ± 11.8	80.1 ± 11.7
BMI (kg/m^2)	28.6 ± 2.0	26.4 ± 2.1*	27.8 ± 2.4	27.7 ± 2.6
TC (mg/dL)	217.6 ± 38.4	178.0 ± 25.6*	208.8 ± 34.9	199.3 ± 25.4
HDL-C (mg/dL)	48.7 ± 7.3	48.1 ± 10.3	48.8 ± 8.3	46.9 ± 10.5
LDL-C (mg/dL)	151.3 ± 34.9	116.7 ± 27.8*	145.0 ± 31.3	130.1 ± 23.5
TG (mg/dL)	170.2 ± 106.5	131.1 ± 93.0	158.9 ± 87.4	147.1 ± 83.8
TC/HDL-C	4.6 ± 1.0	3.9 ± 0.9*	4.4 ± 1.0	4.4 ± 0.9
SBP (mm Hg)	130.6 ± 15.3	123.7 ± 12.5	119.4 ± 15.5	117.6 ± 27.6
DBP (mm Hg)	88.1 ± 9.7	83.9 ± 8.9*	84.4 ± 12.3	86.5 ± 11.0
V_{O_2}peak (mL/[kg · min])	30.3 ± 5.1	37.1 ± 6.9*	31.8 ± 4.9	30.6 ± 4.9
V_{O_2}peak (L/min)	2.47 ± 0.62	2.73 ± 0.65*	2.57 ± 0.55	2.45 ± 0.50
MHR (bpm)	157.7 ± 13.9	163.2 ± 16.2	150.8 ± 14.3	151.7 ± 11.7
CRP (mg/dL)	0.16 ± 0.13	0.09 ± 0.07*	0.10 ± 0.08	0.15 ± 0.17
Log CRP (mg/dL)	0.75 ± 0.4	0.56 ± 0.3*	0.60 ± 0.3	0.70 ± 0.4

Values are means ± SD.
* Significant interaction indicating a greater change in the lifestyle group ($P < .05$).

in the intervention group. There was no change in these variables in the control group (Table 3).

3.2. Correlations of changes in body weight, V_{O_2}peak, and hs-CRP after exercise training

Changes in body weight were associated with changes in hs-CRP ($r = 0.42$, $P = .004$). Changes in V_{O_2}peak were also associated with changes in hs-CRP ($r = -0.41$, $P = .004$), and these changes were still significant after adjustment for changes in weight loss ($r = -0.35$, $P = .04$). The multiple regression analysis showed that changes in body weight ($\beta = .307$, $P = .034$) and changes in V_{O_2}peak ($\beta = -.298$, $P = .039$) were independently associated with changes in hs-CRP (Table 4). The analyses of covariance showed that changes in hs-CRP were not significantly different between groups, after controlling for either changes in body weight or changes in V_{O_2}peak.

To examine the relationship between reduced weight, improved V_{O_2}peak, and changes in hs-CRP, we also constructed weight reduction and V_{O_2}peak improvement quartiles. When grouped into quartiles according to decreasing weight and increasing V_{O_2}peak, levels of changes in hs-CRP improved across quartiles of weight loss ($P < .05$) and improved V_{O_2}peak ($P < .01$) after adjusting for baseline hs-CRP level (Figs. 1 and 2).

4. Discussion

Our results showed that lifestyle modification including aerobic exercise training significantly improved V_{O_2}peak and reduced both hs-CRP and body weight. The present study also found a significant correlation between changes in V_{O_2}peak and hs-CRP when adjusted for changes in weight loss. Similarly, a significant correlation was found between weight loss and changes in hs-CRP when adjusted for changes in V_{O_2}peak after exercise training. Both improved V_{O_2}peak and weight loss were independent predictors of reduced hs-CRP, suggesting that interventions aimed at reducing hs-CRP should focus on improving V_{O_2}peak and reducing body weight.

Table 4
Stepwise multiple regression analysis for changes in hs-CRP

Variables	β coefficient	P
Weight changes	.307	.034
V_{O_2}peak changes	−.298	.039

Included variables were changes in weight, V_{O_2}peak, TC, and LDL-C.

4.1. Effects of weight loss and exercise training on hs-CRP

Previous studies suggest that weight loss significantly decreases hs-CRP in obese patients [13-15]. Present data confirm and extend those findings, showing that weight loss after lifestyle modification was associated with a reduction

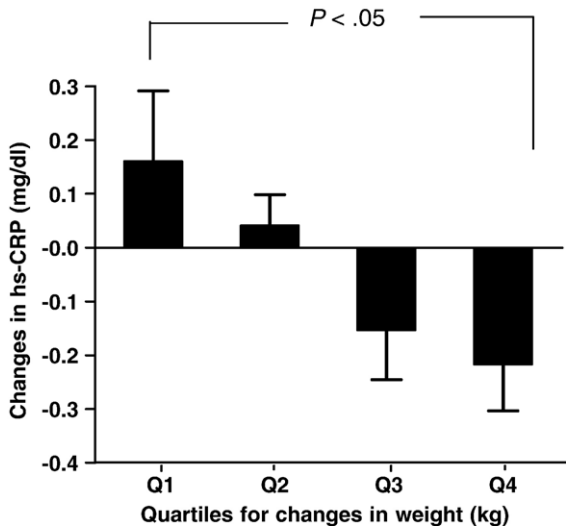

Fig. 1. Mean changes in hs-CRP by quartiles of changes in weight after lifestyle modification (Q1, least amount of changes in weight; Q4, most amount of change in weight).

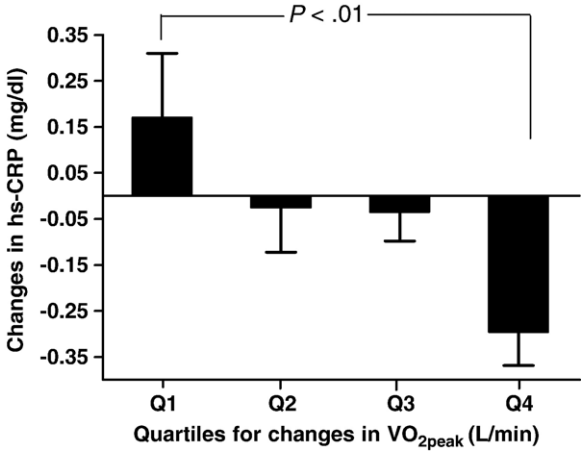

Fig. 2. Mean changes in hs-CRP by quartiles of changes in VO_2peak after lifestyle modification (Q1, least amount of changes in VO_2peak; Q4, most amount of change in VO_2peak).

in hs-CRP and this improvement appears to be related to the amount of weight lost. Diet intervention alone can produce a 15% reduction in body weight and a 26% to 34% decrease in hs-CRP [13-15]. Interestingly, exercise training that produces little change in body weight (1.0-1.5 kg reduction) also significantly reduces hs-CRP [22,25,31].

Although some cross-sectional studies have shown that high levels of cardiorespiratory fitness are associated with reduced levels of hs-CRP in healthy subjects [10-12], these relationships are less clear from longitudinal studies. You et al [19] found that diet plus exercise, but not diet alone, decreased plasma hs-CRP by 34% in obese postmenopausal women. Okita et al [22] reported that supervised aerobic exercise significantly decreased hs-CRP levels by 35%. Ryan and Nicklas [32] also found that 6 months of diet and exercise in overweight and obese postmenopausal women decreased hs-CRP. Similar changes in hs-CRP have been shown in several studies using various exercise and weight loss programs varying in length from 14 days to 6 months [31,33]. However, most of these studies did not include a control group, and it is difficult to discern whether hs-CRP changes were related to exercise training or other lifestyle changes resulting in weight loss.

Two studies suggest that exercise training alone decreases hs-CRP. Milani et al [23] demonstrated a 41% fall in hs-CRP levels in cardiac patients who increased VO_2peak 9% after 3 months of cardiac rehabilitation. However, the cardiac patients in this study [23] may have incorporated lifestyle changes in addition to exercise. Mattusch et al [24] also reported that CRP median fell from 1.19 to 0.82 mg/L after 9 months of endurance training ($P < .05$). It should be noted that the subjects in this study [24] were training for a marathon, thus their exercise training volume was extraordinarily high, making comparisons to other studies difficult. Nevertheless, the findings of the present study are consistent with previous investigations with the present study showing a 25% reduction in hs-CRP accompanied by an 11% improvement in VO_2peak coupled with a 9% weight loss. This reduction in hs-CRP was similar to changes seen with other therapeutic interventions such as statin therapy [34], α-linolenic acid [35], and multivitamin supplementation [36]. Therefore, data from the present investigation suggest that lifestyle modifications coupled with exercise training and weight loss produce comparable changes in hs-CRP as is seen with pharmacological intervention.

Others have reported that exercise training did not have an effect on hs-CRP. Two recent randomized controlled trials [37,38] reported that aerobic exercise reduced hs-CRP, but this reduction was not significantly different from the control group. Nicklas et al [20] and Marcell et al [29] also reported that exercise training did not have a significant effect on hs-CRP. These differences might be a function of diet pattern, subject characteristics, exercise frequency, training period, degree of VO_2peak improvement, and weight loss associated with the program. Further randomized clinical trials are needed to clarify this issue.

Most previous studies, including the present study, were conducted on overweight or obese subjects. Changes in hs-CRP after exercise training in normal weight or lean subjects presently remain unclear. Mattusch et al [24] noted reductions in hs-CRP with exercise training, although they did not report body weight of the subjects. Given that subjects were categorized as healthy marathon "runners," it is reasonable to speculate that subjects were of normal body weight. Future research is needed to evaluate the effect of exercise training on changes in hs-CRP in normal weight vs overweight/obese subjects.

4.2. Relationships between improved VO_2peak and weight loss to reduced CRP

Several epidemiological studies reported that the association between physical activity and hs-CRP was not significant when adjusted for body size [39-41]. Therefore, Bassuk et al [3] suggested that the association between physical activity and hs-CRP was dependent on body weight. In contrast, physical activity [7-9] or cardiorespiratory fitness [10,11] levels were inversely associated with hs-CRP after adjustment for BMI. Thus, cross-sectional evidence for an independent association between hs-CRP and physical activity or physical fitness is unclear.

Okita et al [22] reported that supervised aerobic exercise significantly decreased hs-CRP levels, but the changes in VO_2peak were not significantly related to changes in hs-CRP ($r = 0.04$, $P = .51$). Nicklas et al [20] also reported that there was no significant interaction between weight loss and exercise training on reductions in hs-CRP. However, the study by Nicklas et al was conducted on subjects with osteoarthritis, which might have influenced the relationship between exercise training and changes in hs-CRP.

In contrast, some studies [23,27] suggested changes in hs-CRP were independent of changes in body weight

because similar reductions were found in hs-CRP for both the weight loss and weight gain groups after cardiac rehabilitation with exercise training. Esposito et al [42] demonstrated that after a 2-year lifestyle change intervention, significant associations between changes in hs-CRP and both changes in body weight ($r = 0.31$) and physical activity levels ($r = -0.29$) were revealed. These results are similar to our findings demonstrating that changes in hs-CRP were associated with changes in VO_2peak and weight loss. The stepwise regression in the present study revealed that both changes in body weight and VO_2peak were included as predictors of changes in hs-CRP. This result implies that both changes in body weight and changes in VO_2peak are related to changes in hs-CRP.

Several potential mechanisms may explain the effect of weight loss and improved VO_2peak after lifestyle intervention on reduced hs-CRP levels. First, decreases in hs-CRP may be related to decreases in total adipose tissue. Adipose tissue itself secretes pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, the main stimulus for CRP biosynthesis in liver [18,43]. Many studies suggest that excess body weight is strongly related to body fat mass and CRP levels [5,44]. However, the present study did not measure body fat mass and thus our results cannot directly address this possible mechanism. Second, endothelial dysfunction may facilitate inflammatory processes on the vascular wall [45]. Inflammation has been associated with impaired endothelial function related to decreased nitric oxide release from endothelial cells [45]. Weight loss and improved VO_2peak have been shown to improve endothelial function [46,47], and this may decrease inflammatory markers and CRP production. Third, weight loss and improved VO_2peak are related to decreased glucose levels and insulin resistance [48], and this too may be associated with reduced inflammatory markers. Finally, weight loss and improved VO_2peak may reduce CRP by reducing oxidative stress [49].

Some of the limitations in this study include lack of randomization, raising the possibility of selection bias, although both groups in this study were similar before the intervention. Because we did not have dietary information to evaluate the specific influence of diet, including alcohol intake, we do not know how specific diet alterations influenced hs-CRP. Finally, although exercise prescriptions were adjusted and provided every 2 weeks, exercise training sessions were not supervised. However, because VO_2peak was substantially increased in the intervention group but not in the control group, one may assume reasonable compliance with the home exercise prescription.

In conclusion, we showed that lifestyle modification emphasizing regular exercise training significantly decreased hs-CRP, and the decrease in hs-CRP was associated with both weight loss and improvement in VO_2peak. Therefore, we suggest that both improvements in exercise capacity and reductions in body weight are recommended for reductions in hs-CRP in overweight individuals.

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