Does Aerobic Exercise Training with Weight Loss Affect Serum C-reactive Protein in Asymptomatic Obese Peri-menopausal Women?

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ABSTRACT

Background: *obesity is a major problem especially in the developing countries, the excessive fat activating the pro-inflammatory process and increasing the inflammatory markers that lead to many serious diseases. In perimenopausal period women going through many hormonal changes that leads to decrease the metabolic rate. Purpose of the study: to investigate the effect of aerobic exercise training with weight loss on C - reactive protein (CRP).* ***Methodology:*** *50 obese perimenopausal women with body mass index (BMI) > 30 kg/m^2 randomly assigned into 2 groups, group (A) followed a regimen of restricted diet of 1000-1200 Kcal\day. While, group (B) followed as in group (A) in addition to a program of aerobic exercise training on a treadmill 3 times/week for 40 minutes, both groups followed their program for 3 months.* ***Results:*** *showed a highly significant reduction in CRP level in both groups (P < 0.001 & 0.0001) respectively and it was linear with the highly significant decrease in BMI. But when comparing CRP reduction between groups A&B there was highly significant (P < 0.025) decrease in group (B) in comparison to group (A).* ***Conclusion:*** *aerobic exercise training was effective for weight loss aiming to decrease CRP which is an inflammatory marker and predictor for the incidence of cardiac diseases. So, it is very important that obese women in the perimenopausal period to reduce their weight with both diet reduction and exercise training and later on keep physically active to control body weight and guard against obesity related diseases.*

Key words: *Obesity, CRP, Diet, Exercise.*

INTRODUCTION

Obesity is an independent risk factor for cardiovascular disease[1]. Adipocytes synthesize and secrete several cytokines, including tumor necrosis factor ∞ (TNF∞), interleukin-6 (IL-6), and adiponectin, the latter is a novel adipocytokine with anti-inflammatory and insulin-sensitizing properties[7].

Elevated levels of several pro-inflammatory cytokines, such as (IL-6, IL-8, and TNF∞), as well as the sensitive marker of inflammation C-reactive protein (CRP), have been found associated with elevated body fat body weight and body mass index [BMI] and cardiovascular disease risk factors[4,7].

In fact, obesity may account for a large portion of variation in circulating CRP concentrations; in a population-based study involving healthy, middle-aged women, BMI explained 30% of the variance in CRP concentrations. In an analysis of the Third National Health and Nutrition Examination Survey, the proportion of people with a CRP level above 10 mg/L (the traditional clinical

level suggestive of infection) was 20% in obese women, but only 4% in women whose weight was within the normal range[9,30,31].

CRP is a nonspecific marker of inflammation; it has been implicated in the pathogenesis of chronic diseases including cardiovascular disease, diabetes, and cancer. One of the most important correlates of CRP is adiposity. Large cross-sectional studies have shown that CRP is highly positively associated with measures of adiposity such as BMI, waist circumference, and waist-hip ratio. Previous studies suggesting that weight loss can reduce CRP levels by using different interventions to reduce weight[16,22].

Several roles have been postulated for CRP, including binding to phospholipids of damaged cells to activate complement and enhance uptake of these cells by macrophages as well as activating endothelial cells to express adhesion molecules and decreasing the expression and bioavailability of endothelial nitric oxide synthase[11].

Moreover, it has been suggested that CRP directly and indirectly mediates inflammatory process in atherosclerosis[12], myocardial infarction and stroke in both middle aged and older women. It is positively correlated to age, smoking, obesity, markers of fibrinolytic activity, total cholesterol, triglycerides and glucose. It has an important negative correlation to high density lipoprotein (HDL) cholesterol[2].

Two previous studies demonstrated that CRP levels were reduced in correspondence with diet-induced weight loss in a small sample of obese women. Exercise training is another therapy that can reduce weight and has protective effects against atherosclerosis, and it is more ideal in a clinical situation without muscle wasting compared with caloric restriction alone. However, the effect of regular exercise training on CRP levels is still unclear[26,28].

For women in perimenopause, another weight gain issue is widely fluctuating estrogen levels. As the estrogen production from ovaries falls, the body turns to secondary production sites, are including body fat, skin, and other organs. If the body is struggling to maintain its hormonal balance, body fat becomes more valuable. Often body is balancing estrogen loss with maintaining bone mass, for which it needs additional fat cells[2]. Furthermore, menopause transition results in a reduction in resting metabolic rate, physical activity, energy expenditure, fat free mass and leads to an increase in fat mass and abdominal adipose tissue accumulation. These changes increase the risk of cardiovascular disease. As women near the age of menopause, the tendency to accumulate extra-cellular fluid accompanied by lower metabolic rate, a sedentary life style and a resulting increased difficulty in losing weight and maintaining weight loss[4,7,24].

The purpose of this study was conducted to determine the effect of exercise training with weight reduction on obesity related inflammatory marker (CRP) and conventional cardiovascular risk factors in pre-menopausal women and we hypothized that there was no significant difference.

SUBJECTS, MATERIALS AND METHODS

50 obese peri-menopausal women (BMI > 30 kg\ m^2) their age range from 40-49 years (44±2.6) were recruited from the Out Patient Gynecological Clinic at El Kaser El Aini University Hospitals. Women were sedentary (less than 1 hour/week of physical activity), with no evidence of participation in diet reduction programs within the last 6 months.

Exclusion criteria were type 2 diabetes mellitus, or impaired glucose tolerance, hypertension, cardiovascular disease, peripheral vascular diseases, any symptomatic infectious diseases (including the common cold, pelvic inflammatory diseases, genital prolepses and hepatitis), current or previous smoking, any orthopedic limitation, and no pregnancy before the study by 6 months or during the study. All participants were signed a written informed consent before starting the study.

All participants were divided randomly into 2 groups, group (A): 25 women were following a low caloric diet with allowed calories 1000-1200 kcal/day which was divided as following 50-60% carbohydrates, 20% protein, > 30% total fat and 18 gm of fiber \1000 Kcal. They were revised every 2 weeks for any modification in their diet regimen within the allowed calories. Group (B): 25 women were following a low calorie diet as in group (A) and in addition to a program of aerobic exercise training, both groups followed their program for 3 months.

Evaluative procedures

Fasting venous blood sample was collected at the same time in the morning, after subjects had obstained from all food and drink, except water and from any vigorous activity for at least 12 hours, to estimate the serum level of CRP, this parameter in addition to BMI were measured at the beginning of the study, after 6 weeks then at the end of the 3 months by the following equation BMI= (Weight) Kg/(Height) ^{2}(m^2).

Exercise training for Group (B)

Each woman in group (B) was participated at exercise training program for 3 months (3 times per week) each exercise session was hold for 40 minutes. Each woman should be instructed not to eat for 3 hours before the exercise session.

The exercise training program was in the form of walking on treadmill, and asking each woman not to tightly grasp the rails because this action reduces the workload at any stage of exercise. To overcome this problem each woman was asked to remove their hands from rails, close their fists, and place one finger on the rails to maintain balance after they accustomed to walking on the treadmill.

The exercise session was started by 5 minutes warm up which involved walking with no resistance and no inclination at the walk way of the treadmill followed by 30 minutes of walking with 15 degrees inclination at the walk way of the treadmill and adjusted speed to reach (20-40% of target heart rate (THR) in the first 6 weeks of the study then the speed was increased till reach (40-60% THR) in the second 6 weeks of the study.

The THR= [(maximal heart rate – resting heart rate)] + resting heart rate [8].Maximum heart rate (MHR) was detected according to the equation MHR= 220-age. Then the session is ended by 5 minutes of cool down in which the intensity of the exercise was reduced to the level of the warm up.

Statistical Analysis

All values were calculated by mean ± standard deviation (SD) for covariates analyzed as quantitative data. For all the statistical testes done, the threshold of significance was fixed at the 5% level (P-value). P-value >0.05 indicated non significant results. P-value < 0.05 indicated highly significant results. Using student t-test to compare between subjects in both groups at each time of readings while, one way ANOVA to compare intra subjects in the three times of readings[23].

RESULTS

45 women who continued till the end of the current study, 5 subjects didn't complete (3 women in group A with no apparent reason and 2 women in group B because they developed knee pain that limited the exercise program). In concerning CRP level, group (A) who followed a diet reduction regimen, CRP showed a linear reduction with the time of the study as the highly significant (F= 6.34 & P < 0.001) decrease was observed after 12 weeks of the intervention with a mean value 2.17 ±0.79 mg\L. In group (B), who followed a diet reduction regimen in addition to aerobic training program, the same observation was noted at the end of the study as showed the highly significant (F= 12.09 & P < 0.0001) decrease of CRP with a mean value 1.72 ±0.55 mg\L(table 1& fig 1). When comparing the changes of CRP level along the study between both groups, there was non significant differences at the beginning and post 6 weeks of the study (P < 0.717 & P < 0.146) respectively. While, after 12 weeks of the intervention, group (B) showed a highly significant decrease (P < 0.025) in comparison to group (A).

Table (1): CRP level at the beginning, after 6 & 12 weeks of the study in both groups.

	CRP (mg/L)					
	Group (A)			Group (B)		
	Pre-training	Post 6 weeks	Post 12 weeks	Pre-training	Post 6 weeks	Post 12 weeks
Mean	5.68	3.38	2.17	5.51	3.00	1.72
S.D. ±	1.52	1.01	0.79	1.65	0.76	0.55
F. value	6.34			12.09		

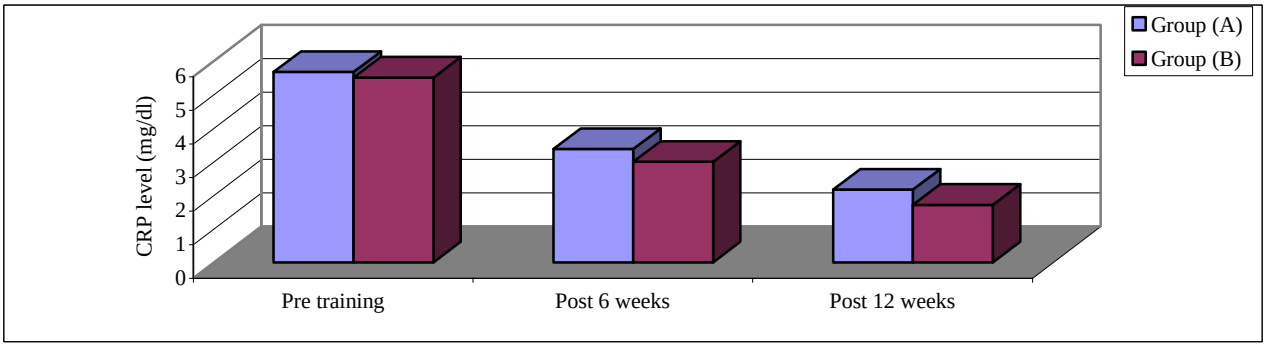

Fig. (1): Level of CRP in both groups (A & B) at different times of measurements.

For the BMI, there was a continuous reduction in both groups all through the study and when comparing to the pre treatment readings of BMI, after 12 weeks of intervention showed the highly significant decrease (F= 8.35 & P < 0.001) in group (A) and (F= 12.2 & P < 0.0001) in group (B) (table 2 & fig. 2).In comparing between group (A) & (B), at the beginning of the study there was non significant difference in BMI (P < 0.906). While, there was a highly significant decrease (P < 0.001 & P < 0.0001) of BMI after 6 and 12 weeks of the intervention respectively.

Table (2): BMI at pre, after 6 & 12 weeks of the study in both groups (A & B).

	Group (A)			Group (B)		
	Pre-training	Post 6 weeks	Post 12 weeks	Pre-training	Post 6 weeks	Post 12 weeks
Mean	32.4	30.57	29.49	32.37	29.58	27.89
S.D. ±	0.89	1.03	0.01	1.00	0.86	0.83
F-value	8.45			12.2		
P-value	< 0.001			< 0.0001		

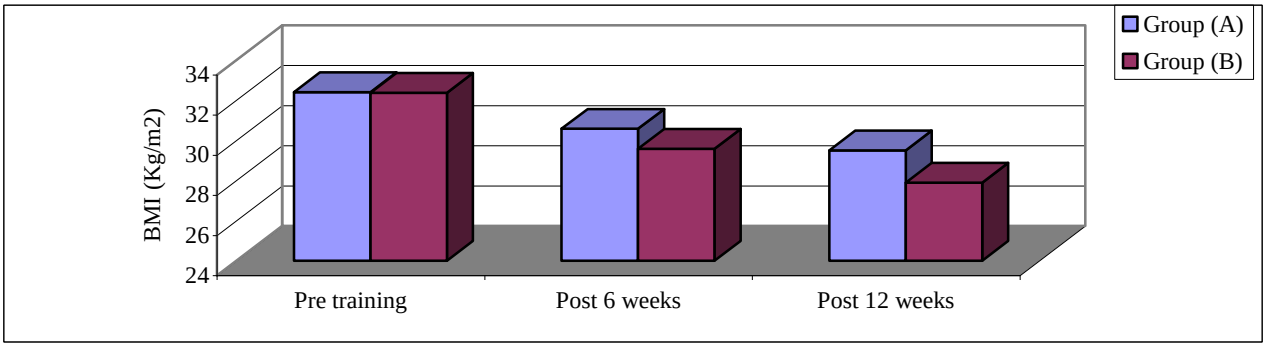

Fig. (2): BMI in both groups (A & B) at different times of measurements.

DISCUSSION

Knowledge on the relationship between physical activity and serum C-reactive protein levels is mainly derived from large observational and cross-sectional studies[7,11,13,15,16,17,18]. There are yet few prospective controlled studies on the effect of exercise intervention on C-reactive protein but the outcomes are not equivocal[29].

Adipose tissue may be directly involved in the production and regulation of inflammatory cytokines that induce CRP production, and it has been suggested that inflammation may represent one of the mechanisms by which lifestyle changes and weight loss reduce the risk of cardiovascular disease. Several findings over the last decade suggest that weight loss could directly lead to reductions in CRP levels. In particular, adiposities produce cytokines that regulate CRP production. Interleukin 6, a key proinflammatory cytokine and principal regulator of hepatic CRP production, may be particularly important in mediating the increases in CRP levels associated with greater adiposity. Thus, a reduction in body weight is likely to have important consequences for circulating levels of CRP[6,10,22].

In the present study, all subjects in both groups showed a highly significant ($P < 0.001$ & $P< 0.0001$) decrease in CRP, but in group (B) who followed a program of aerobic training in addition to diet reduction regimen for 3 months showed more significant ($P < 0.025$) reduction in CRP when compared to group (A). For BMI, there was significant reduction in both groups and it was proportionally with the decrease in CRP level.

The results of this study were in agreement with Bastard et al., 2000[3], who reported that after the exercise training program, body weight and the CRP levels were significantly reduced. It has been demonstrated that obesity is related to CRP levels, and that adipose tissue is likely a factor modulating CRP levels.

In addition to Nicklas et al. (2005)[17], who reported about an inverse association between markers of inflammation and physical activity. They concluded that dietary weight loss plus exercises is likely more effective than weight reduction alone in reducing inflammation.

Many studies found a good percentage of reduction in CRP level after a program of exercise training but did not reach the significance level that can be explained through (a) the subject criteria who were either marathon training[13], subjects with high risk of cardiovascular diseases[26], or patients with intermittent claudications[29]. Also, (b) due to the length of the study which was ranged from nine months up to two years[11,13,26].

In contrast, Raurama et al. (2004)[21] reported a non-significant decrease in C-reactive protein level after a 6-year randomized trial of aerobic physical exercise in a population sample of 140 middle aged men. The differences in outcome of this study are understood by the design, the included population, length, intensity, and supervision of the exercise training or other factors?

Most of the dietary weight-loss studies showed the magnitude of decrease in inflammatory markers to be linearly related to the amount of weight lost. This suggests there may be a dose–response effect between the degree of weight loss and its capacity to attenuate chronic inflammation[7,28].

This was confirmed as weight loss associated with a decline in CRP level with linear relationship reach for each 1 kg of weight loss, the overall mean change in CRP was –0.13 mg/L. It can be concluded that on average, the largest changes in weight are likely to produce the highest magnitude of change in CRP level[25].

In contrast, Changes in CRP concentrations were unassociated with changes in body weight or percent body fat, which provided compelling evidence that the exercise training effect was independent of body fat loss[15].

The results of this study can be explained as aerobic exercise and dietary weight loss affected the immune system by reducing the number of mononuclear cells in the peripheral blood, which are a source of pro-inflammatory cytokines (such as IL-6 and TNF). A reduction in adipose tissue wouldn't only reduce the number of endothelial cells and macrophages that reside there. These cells produce many pro-inflammatory mediators as CRP and cytokines. Weight loss through diet and exercise may also increase the expression of anti-inflammatory mediators. The resulting circulatory changes could, in-tern, cause the liver to contribute by decreasing its production of fibrinogen and other pro-inflammatory mediators[3,17].

This was supported with a multidisciplinary lifestyle program for obese women, including caloric restriction and physical training, reduced cytokine production [interleukin-6 (IL-6) and TNF-alpha] was observed. This diminishes C-reactive protein levels as hepatic C-reactive protein production is stimulated by IL-6[5,24].

This is in disagreement with Okita et al. (2004)[18], who reported that the high pace of weight reduction did not necessarily reduce CRP levels. There might be some strong adverse effects that cancelled improvement in CRP levels during high paced weight reduction with exercise.

The previous results contrast with ours because n the current study all subjects performed mild intensity of exercises for 6 weeks then moderate intensity for the 6 weeks of the study. For instance, it has been reported that strenuous exercise can lead to muscle damage and thereby increase inflammation[4]. In

addition, important adverse effects of exercise training related to overtraining associated with oxidative stress and free-radical formation have been indicated and might act as an inflammatory stimulus [12]. Likewise, some studies reported that acute strenuous exercise could raise CRP levels[14].

C-reactive protein levels respond differently to acute or chronic physical exercise. Acute heavy physical exercise leads to an inflammatory response with a marked rise in C-reactive protein levels, suggesting muscular damage proportional to the amount of exercise and muscles engaged. However, longer term exercise training (which resembles to this study that lasted for 3months) produces an opposite effect, as a parallel protective anti-inflammatory counter response in cytokine production occurs during the course of the training[19].

Physical training reduces peripheral inflammatory markers associated with endothelial dysfunction, such as soluble intracellular and vascular adhesion molecules, and macrophage chemo attractant protein-1 in patients with heart failure[1]. Regular physical activity also improves endothelial function preserving nitric oxide availability[27]. Although exercise acutely increases oxidative metabolism and thereby induces oxidative stress, there is evidence that long-term physical activity increases antioxidant defenses through the up-regulation of antioxidant enzymes[20]. Furthermore, this antioxidant effect of exercise reduces the susceptibility of low-density lipoprotein (LDL) to oxidation which in turn helps further prevention of endothelial injury and inflammation. In summary, it is likely that exercise training reduces CRP both directly by reducing cytokine production in fat, muscle, and mononuclear cells and indirectly by increasing insulin sensitivity, improving endothelial function, increase LDL and reducing body weight.

In conclusion, it can be recommended that regular aerobic training in addition to diet reduction regimen would be a safe and effective method to reduce CRP so reducing with a great percentage the risk factor of cardiovascular disease (CVD) in asymptomatic obese peri-menopausal women. Furthermore, according to the recent European guidelines on CVD prevention, healthy persons are recommended to choose enjoyable physical activities which fit into their daily routine with moderate intensity for 30-45 minutes /3-4 times per week can lower C-reactive protein values[19].

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الملخص العربي

هل للتمرينات الهوائية مع تقليل الوزن تأثير على مستوى (البروتين الفعال 2) في السيدات البدينات في فترة ما قبل انقطاع الدورة الشهرية ؟

تعتبر السمنة من اكبر المخاطر على صحة الإنسان لما لها من تأثير كبير على أجهزة الجسم المختلفة .كذلك السمنة تزيد من نسبة دلالات الالتهابات في الدم مما له تأثير كبير على القلب و من ثم فقد كان هدف هذه الدراسة معرفة تأثير التمرينات الهوائية على تقليل الوزن ومن ثم تقليل دلالات الالتهابات في الدم (البروتين الفعال 2). اشتركت في تلك الدراسة 50 سيدة تتراوح أعمارهن ما بين 40-49 سنة ويزيد معامل كتلة أجسامهن عن 30 كجم\متر2 وقسمن عشوائيا إلى مجموعتين متساويتين. مجموعة (أ): تتكون من 25 سيدة خضعن لنظام غذائي محدود السعرات الحرارية ما بين 1000-1200 ك كالورى\يوميا لمدة 12 أسبوع و بالنسبة للمجموعة (ب) فكانت 25 سيدة خضعن لنظام غذائي محدود السعرات مثل مجموعة (أ) بالإضافة إلى برنامج من التمرينات الهوائية بشدة 20-40% من نبض القلب المستهدف لمدة 40 دقيقة على جهاز التريدميل لمدة 6 أسابيع ثم تزيد الشدة إلى 40-60 % من نبض القلب المستهدف لمدة 6 أسابيع الأخرى من الدراسة . وقد أظهرت النتائج انخفاض ذو دلالة إحصائية عالية في (سى ريأكتف بروتين) في كلتا المجموعتين و لكن الانخفاض في المجموعة (ب) أكثر من المجموعة (أ) وكان ذلك الانخفاض متلازما مع انخفاض ذو دلالة إحصائية عالية في معامل كتلة الجسم . في نهاية تلك الدراسة من الضروري نصح السيدات البدينات بتقليل أوزانهن عن طريق نظام غذائي وممارسة الرياضة بانتظام 3-4 مرات أسبوعيا للحفاظ على صحتهن من مخاطر أمراض القلب.

الكلمات الدالة: السمنة ، (البروتين الفعال 2) ، الحمية الغذائية ، التمرينات