Journal of the American College of Cardiology Vol. 45, No. 10, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.12.077

STATE-OF-THE-ART PAPER

The Effects of Physical Activity on Serum C-Reactive Protein and Inflammatory Markers

A Systematic Review

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Physical activity is associated with a reduced incidence of coronary disease, but the mechanisms mediating this effect are not defined. There has been considerable recent interest in inflammation in the pathogenesis of cardiovascular disease. Some of the beneficial role of physical activity may result from its effects on the inflammatory process. We searched PubMed for articles published between 1975 through May 2004 using the terms exercise, physical activity, or physical fitness combined with C-reactive protein, inflammation, inflammatory markers, or cytokines. The review revealed 19 articles on the acute inflammatory response to exercise, 18 on cross-sectional comparisons of subjects by activity levels, and 5 examining prospectively the effects of exercise training on the inflammatory process. Exercise produces a short-term, inflammatory response, whereas both cross-sectional comparisons and longitudinal exercise training studies demonstrate a long-term "anti-inflammatory" effect. This anti-inflammatory response may contribute to the beneficial effects of habitual physical activity. (J Am Coll Cardiol 2005;45:1563–9) © 2005 by the American College of Cardiology Foundation

There is increasing evidence that inflammation contributes to the atherosclerotic process (1). Several cytokines and acute-phase reactants have been examined as predictors of disease. High-sensitivity C-reactive protein (CRP) has the analyte and assay characteristics that are most conducive for clinical use and has shown a dose-response relationship to coronary heart disease that is independent of other major risk factors (2). 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 (3–5).

It is well documented that physical activity has a role in preventing coronary heart disease (6), mediated, in part, by changes in inflammation. This review examines the effects of physical activity on serum CRP and explores possible underlying mechanisms.

METHODS OF LITERATURE REVIEW

English-language articles on CRP and exercise published between 1975 and May 2004 were identified via a PubMed search and from references in other articles using the terms exercise, physical activity, or physical fitness in sequence with the terms CRP, inflammation, inflammatory markers, or cytokines. Articles examining the effects of exercise on CRP and inflammation were examined. The review identified 19 articles on the acute inflammatory response to exercise, 18 cross-sectional comparisons of subjects by activity levels, and 5 prospective studies of exercise training and the inflammatory process.

ACUTE PHASE RESPONSE (APR) AFTER STRENUOUS EXERCISE

Several studies have examined the APR to strenuous exercise (Table 1) (7–12). A study (7) of 70 male and 20 female runners demonstrated marked but transient increases in the white blood cell count (+160%, $p < 0.01$) and CRP (+2,000%, $p < 0.01$) immediately and 24 h after a 42-km marathon race. There also were significant increases in interleukin (IL)-1 (+48%, $p < 0.01$) and creatinine kinase (CK) (+800%, $p < 0.01$) 24 h after exercise, suggesting that cytokines and/or muscle injury contribute to the inflammatory response. Values returned to baseline two to six days after exercise. Another study (8) evaluated the hematologic and APRs of 18 athletes to 21 km of canoeing, 97 km of cycling, and 42 km of running. C-reactive protein increased 266% ($p < 0.05$) 24 h after the race and returned to baseline by 48 h. There were parallel increases after the race in cortisol (+195%), white cell count (+158%), lactoferrin (+100%), and CK (+1,200%) ($p < 0.05$, for all). A study (9) of 55 runners in the 1996 and 1997 Boston marathons noted increases in CRP (+122%), fibrinolytic activity (+184%), von Willebrand factor (+113%), and D-dimer (+199%) within 4 h after the event ($p < 0.001$ for all).

This APR to exercise seems to be proportional to the amount of activity and muscle injury. In 38 trained runners

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Manuscript received July 29, 2004; revised manuscript received October 21, 2004, accepted December 13, 2004.

JACC Vol. 45, No. 10, 2005
May 17, 2005:1563–9

Abbreviations and Acronyms

APR = acute phase response
BMI = body mass index
CK = creatine kinase
CRP = high-sensitivity C-reactive protein
IL = interleukin
NHANES = National Health and Nutrition Examination Survey
PRINCE = Pravastatin Inflammation/CRP Evaluation study
TNF = tumor necrosis factor

competing in races of 15 to 88 km, the APR, as assessed by CRP concentrations, increased with increasing race duration and serum CK levels (13). The APR also may be related to the type of exercise and the muscle mass involved. A study of 14 subjects found no increase in inflammatory markers after eccentric exercise using the elbow flexors, despite 100-fold increases in serum CK levels (14).

Exercise training appears to reduce the APR to strenuous activity. The APR to 2 h of running in three men was examined before and after nine weeks of endurance training (15). Post-run CRP, haptoglobin, and alpha-1 acid glycoprotein were reduced by 40%, 30%, and 60%, respectively, after training, although the distances that were run after training were 10%, 12%, and 20% longer.

The mechanisms mediating the APR to exercise are not defined. Interleukin-1, IL-6, and tumor necrosis factor (TNF)-alpha are involved in the APR. These cytokines, with the possible exception of TNF-alpha, temporarily increase during and shortly after prolonged exercise (16–18). Interleukin-6 stimulates hepatic CRP synthesis and increases as much as 100-fold (18,19) after strenuous exercise (16–21). This increase in IL-6 is the earliest and most prominent of the cytokine responses to exercise (Fig. 1) (21).

Exercise also produces an acute increase in various anti-inflammatory mediators, including the cytokine inhibitors, IL-1 receptor antagonist, TNF receptors, IL-10 and IL-8, and macrophage inflammatory proteins 1-alpha and -beta (17,18,21,22), whereas leukocyte adhesion molecules, such as beta-1 and -2 integrins, decrease (23). Thus, there is a parallel "protective" anti-inflammatory counter-regulation that also is part of the APR to exercise.

Exercise-induced muscle injury has been thought to be the primary stimulus for the IL-6 response. Recent studies suggest that complex intramuscular signaling stimulates the exercised muscle to release IL-6 (20,21), independently of muscle damage. Subsequently, muscle damage per se elicits a repair response, including macrophage entry into the muscle, causing further IL-6 production. This injury-induced IL-6 response is delayed and smaller than the IL-6 production related to muscle contraction. This difference in injury versus contraction-induced IL-6 also may explain the observation that the IL-6 response is more pronounced, occurs earlier, and is shorter in duration after concentric compared with eccentric muscle contractions. During eccentric exercise, the muscle contracts while lengthening, producing greater muscle damage (20). Apart from the type of muscle contraction, the increase in IL-6 is directly related to exercise intensity, duration, and mass of muscle recruited (21). The role of muscle-derived IL-6 is under investigation, but it appears to act like a hormone, assisting glucose homeostasis and lipolysis during exercise, whereas it also may have immune regulatory effects by inhibiting TNF-alpha production (20,24).

EFFECTS OF REGULAR PHYSICAL ACTIVITY ON SERUM CRP LEVELS

Cross-sectional studies demonstrate an inverse relationship between regular physical activity and the serum concentration of inflammatory markers (Table 2). In the earliest report (25), baseline CRP levels in 356 male and 103 female athletes were compared with those from 45 male and 40 female untrained control subjects. Interestingly, in the athletes, the effects of exercise training on CRP varied with the type of exercise, and values were significantly lower than control subjects in swimmers (−80% for males and −72% for females, $p < 0.001$ for both) and rowers (−48%, $p < 0.01$ in males and −28%, but not significant in females), whereas in soccer players, CRP did not differ significantly from control subjects.

Table 1. Studies of Serum CRP After Strenuous Exercise

Study	Participants	Type of Exercise	Baseline Mean CRP Before Exercise†	Maximum Mean CRP After Exercise*	p Value
Weight et al. (7)	70 ♂ and 20 ♀ trained runners	Marathon race, 42 km	1.1 ± 4.4	22.7 ± 15.9	<0.01
Taylor et al. (8)	18 ♂ trained athletes	160-km triathlon	13.9 ± 6.7	50.8	<0.05
Siegel et al. (9)	55 ♂ marathon runners	Marathon race, 42 km	0.343 ± 0.611	0.762 ± 0.973	<0.001
Fallon (10)	7 ♂ and 1 ♀ trained runners	6-day ultramarathon	1.9	37.5	<0.005
Castel et al. (11)	20 ♂ trained runners	Marathon race, 42 km	3.3	15	0.05
Drenth et al. (12)	7 ♂ and 3 ♀ trained runners	5-km race	0.2	0.5	0.0115
Strachan et al. (13)	38 trained runners	15- to 88-km races	<3	27†	—
Leisen et al. (15)	8 ♂ subjects	3-h run	2	12	—

*CRP in mg/l. CRP assay techniques account for the variation in values among studies. Maximum CRP was observed 24 to 48 h after exercise. †Maximum mean CRP after the 88-km race.
CRP = C-reactive protein.

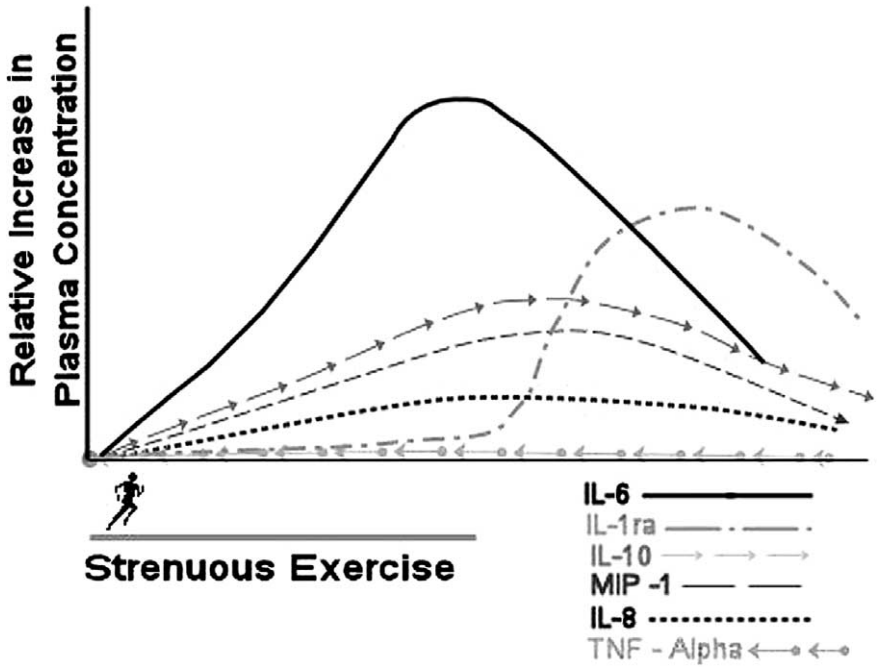

Figure 1. Plasma cytokine response to strenuous exercise. Adapted from Febbraio and Pedersen (21) with permission. IL = interleukin; IL-1ra = interleukin-1 receptor antagonist; MIP = macrophage inflammatory protein; TNF = tumor necrosis factor.

The effects of various forms of exercise on inflammatory markers also were examined in 4,072 participants in the National Health and Nutrition Examination Survey (NHANES) III (26). Using bivariate analyses to compare different forms of exercise and after adjusting for confounding factors, joggers (odds ratio [OR] = 0.33) and aerobic dancers (OR = 0.31) were significantly less likely to have elevated inflammatory markers compared with cyclists (OR = 1.30), swimmers (OR = 0.62), and weightlifters (OR = 0.83). The amount of leisure-time physical activity also was inversely associated with CRP levels ($p < 0.001$) in 13,748 adults in NHANES III (27). This association remained significant after adjusting for such potential confounders as age, gender, ethnicity, education, occupation, smoking, hypertension, body mass index (BMI), waist-to-hip ratio, high-density lipoprotein cholesterol, aspirin use, chronic diseases affecting CRP, and

Table 2. Cross-Sectional Studies on the Effects of Regular Physical Activity on Baseline Serum CRP

Study	Participants	Average CRP in Lowest Physical Activity Levels*	Average CRP in Highest Physical Activity Levels*	p Value
Dufaux et al. (25)	459 athletes/95 untrained controls ♂ and ♀	♂: 0.502 ♀: 0.396	♂: 0.102 ♀: 0.110	<0.001
King et al. (26)	4,072 adult ♂ and ♀	286	69	<0.01
Ford (27)	13,748 adult ♂ and ♀	21%†	8%†	<0.001
Albert et al. (28)	2,833 adult ♂ and ♀	2.6	1.68	<0.001‡
Abramson et al. (29)	3,638 adult ♂ and ♀	15.1%§	6.5%§	<0.001
Geffken et al. (30)	5,888 elderly ♂ and ♀	2.24	1.82	<0.001
Taaffe et al. (31)	880 elderly ♂ and ♀	0.74¶ 0.76‖	0.44¶ 0.53‖	<0.001¶ 0.11‖
Wannamethee et al. (32)	3,810 elderly ♂	2.29	1.43	<0.0001
Tomaszewski et al. (33)	67 ♂ athletes/63 sedentary ♂	0.9	0.4	0.0013
Koenig et al. (34)	936 adult ♂	1.82	1.23	0.001
Pitsavos et al. (35)	891 ♂ and 965 ♀	14.7	9.1	0.02
Rohde et al. (36)	1,172 adult ♂	1.4	1.2	<0.01
Verdaet et al. (38)	892 adult ♂	1.05¶ 0.88‖	0.68¶ 0.81‖	0.02¶ 0.46‖
Aronson et al. (39)	892 adult ♂ and ♀	1.62	2.37	<0.0001
Church et al. (40)	722 adult ♂	2.29	0.52	<0.001
LaMonte et al. (41)	135 adult ♀	4.3	2.3	0.002**
Isasi et al. (42)	205 ♂ and ♀ age 6–24 yrs	1.9	1.1	<0.01†

*CRP in mg/l. CRP assay techniques account for the variation in values among studies. †% participants with CRP >85th percentile. ‡Significant only in ♂, but not in ♀ after adjustment. §% participants with CRP >7 mg/l. ¶Before and ‖after adjustment for confounding factors. **p significant in Native American and Caucasian but not in African-American women.

CRP = C-reactive protein.

serum insulin. Similarly, among 1,732 men and 1,101 women in the Pravastatin Inflammation/CRP Evaluation (PRINCE) study (28), strenuous aerobic activity was associated with lower CRP values in men after adjustment for confounders ($p = 0.007$) but not in women ($p = 0.38$). The reason for this gender-related discrepancy is unclear, but may be related to less physical activity in women.

Other cross-sectional studies (29–36) also consistently demonstrate an inverse association between physical activity and CRP (Table 2). One of these studies (32) examined changes in physical activity over the course of 20 years and showed that inactive men who became active had CRP values approaching those of men who remained at least lightly active. Conversely, those who became inactive had CRP levels similar to those who remained inactive, suggesting that physical activity has to be continuous to maintain its effect on CRP, whereas taking up physical activity later in life can still alter CRP levels.

Two recent studies failed to confirm an independent inverse relationship between chronic physical activity and inflammation. In a longitudinal study (37) of 109 healthy men and women, BMI, but not current or previous-year physical activity, was significantly related to CRP. Similarly, a cross-sectional study (38) of 804 men found no relationship between leisure-time physical activity and CRP, fibrinogen, and serum amyloid A, after correction for BMI and current smoking status. One explanation for the absence of an exercise effect in these studies may be the high proportion of sedentary subjects. Also, physical activity remains an important correlate of CRP in multiple studies after adjustment for possible confounders, including BMI and smoking status (26–33,39–42).

Self-reported data, such as that cited in Table 2, are subject to recall and reporting biases, which undermine the accurate classification of physical activity. To eliminate reporting bias, several studies examined the relationship of cardiorespiratory fitness to CRP. A cross-sectional survey (39) of 892 middle-aged men and women noted that cardiorespiratory fitness was inversely related to CRP levels in a stepwise fashion ($p < 0.0001$). For each 1-U increase in metabolic equivalents, the geometric mean of CRP decreased by 0.061 mg/l (95% confidence interval, 0.034 to 0.089 mg/l). This inverse relationship also has been observed in other studies after adjustment for potential confounders (40–42). Among children and young adults (42), increased cardiorespiratory fitness was associated with decreased CRP levels in boys ($r = -0.32$, $p < 0.01$) but not in girls ($r = -0.15$, $p =$ NS), again suggesting a different relationship between CRP and physical activity by gender (28,42).

Few studies have prospectively examined the effect of exercise training on CRP (Table 3). A randomized trial of 39 patients with intermittent claudication demonstrated that both CRP and serum amyloid-A levels were significantly reduced after three and six months of supervised exercise compared with controls (43). Similarly, nine months of marathon training ($n = 12$) reduced CRP levels by 31% ($p < 0.05$) versus no change in non-training control subjects ($n = 10$) (44). A 35%, albeit nonsignificant, reduction in CRP also was observed among 43 subjects at high risk of ischemic heart disease after six months of supervised exercise training (45). These prospective intervention trials support the concept that exercise training reduces CRP levels by altering the inflammatory process.

MECHANISMS OF REDUCTION IN BASELINE CRP LEVELS WITH REGULAR PHYSICAL ACTIVITY

How exercise training reduces inflammation and suppresses CRP levels is not well defined. Physical activity is related to several confounders that are independently associated with lower CRP levels. For example, physical activity is inversely related to age, smoking, hypertension, BMI, and waist-to-hip ratio, total and non–high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B concentrations, whereas these factors are directly related to CRP concentrations (27). Similarly, physical activity is directly related to the proportion of white participants, education level, insulin sensitivity, alcohol consumption, and fruit and vegetable intake, all factors that are inversely associated with CRP (27). Despite the overlap between factors associated with physical activity and CRP, higher CRP levels persist in more active subjects in most studies even after adjustment.

Hepatic CRP production is stimulated by IL-6 and, to a lesser extent, by IL-1 and TNF-alpha. Individuals who are obese and/or hyperinsulinemic have increased adipocyte production of inflammatory markers, including CRP, IL-6, and TNF-alpha (46,47). A multidisciplinary program to reduce body weight in obese women through lifestyle changes, including a low-calorie diet, and increased physical activity, reduced IL-6, IL-18, CRP, and insulin resistance, whereas adiponectin levels increased (48). Adiponectin is a novel adipocytokine with anti-inflammatory and insulin-sensitizing properties (49). Evidence also exists that leptin

Table 3. Prospective Studies of Physical Training and Serum CRP

Study	Participants	Intervention	Duration	CRP Before*		CRP After*		p Value
				Exercise Group	Control Group	Exercise Group	Control Group	
Tissi et al. (43)	39 ♂ and ♀†	Exercise/observation	3 months	5.3	5.6	4.4	4.8	<0.05‡
Mattusch et al. (44)	22 ♂	Endurance training/control	9 months	1.19	0.77	0.82	1.55	<0.05‡
Smith et al. (45)	43 ♂ and ♀	Supervised exercise	6 months	48.1	—	31.3	—	0.12

*CRP in mg/l. CRP assay techniques account for the variation in values among studies. †Patients with intermittent claudication. ‡Significant only for the exercise group.
CRP = C-reactive protein.

levels are reduced in physically active individuals independent of BMI (33) and that leptin is associated with CRP (50). Moreover, in centrally obese individuals, omental adipocytes produce more IL-6 than do abdominal subcutaneous adipocytes (51). Consequently, physical activity could decrease resting levels of IL-6 and TNF-alpha and, ultimately, CRP production, by reducing obesity and leptin and increasing adiponectin and insulin sensitivity (52). Once again, however, the relationship between increased physical activity and lower CRP persists even after adjusting for BMI, waist-to-hip ratio, and fasting insulin concentration (26–33,39–42), suggesting that other factors contribute to the exercise-related anti-inflammatory effect.

Some of this effect may be mediated by modification of cytokine production from other sites, besides adipose tissue, such as skeletal muscles (53) and mononuclear cells (45). Exercise training reduces skeletal muscle TNF-alpha, IL-1-beta, and IL-6 expression in patients with heart failure (53). Furthermore, long-term exercise attenuates mononuclear cell production of atherogenic cytokines (IL-1-alpha, TNF-alpha, and interferon gamma) while augmenting the production of atheroprotective cytokines (IL-4, IL-10, and transforming growth factor-beta-1) (45). Thus, these multifocal effects of exercise drive the resting cytokine balance to an "anti-inflammatory" state.

Physical activity may also mitigate inflammation by improving endothelial function. Endothelial cells are known to secrete IL-1 and IL-6, whereas activated endothelial cells can increase the production of ILs and adhesion molecules inducing inflammation (54). Physical training reduces peripheral inflammatory markers associated with endothelial dysfunction, such as soluble intracellular and vascular adhesion molecules, granulocyte-macrophage colony-stimulating factor, and macrophage chemoattractant protein-1 in patients with heart failure (55). Regular physical activity also improves endothelial function preserving nitric oxide availability (56). 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 (57). Furthermore, this antioxidant effect of exercise reduces the susceptibility of low-density lipoprotein to oxidation (58), which in turn helps further prevent endothelial injury and inflammation (59,60). 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, and reducing body weight.

LIMITATIONS OF PRESENT DATA AND FUTURE RESEARCH OPPORTUNITIES

Acute effects of strenuous exercise. Most of the studies demonstrating that exercise transiently increases the APR have examined trained athletes. Only one study of three untrained subjects indicates that exercise training blunts the APR (15). Further prospective studies are needed to evaluate the APR in previously untrained subjects after training. The effect of genetic variability on the APR and on the effects of exercise training also warrants examination. A recent report examined the influence of the +1444C>T variant of the human CRP gene on CRP and its response to physical activity in 250 army recruits (61). Subjects homozygous for the +1444TT gene had higher baseline CRP and a greater increase after physical activity than did carriers of the C-allele. Larger study cohorts, including women, are needed to confirm these findings.

Chronic effects of physical activity. C-reactive protein levels are consistently lower in cross-sectional studies (Table 2). Only three small prospective studies (43–45) have demonstrated a reduction in CRP with the initiation of physical activity. Further prospective randomized studies of exercise and inflammation are needed. Additionally, future research is necessary to delineate the mechanisms by which physical activity affects the inflammatory process.

Conclusions. There is a short-term, transient increase in serum CRP after strenuous exercise, produced by an exercise-induced APR, mediated by the cytokine system and mainly IL-6. Exercise training may blunt this response, whereas there is also a homeostatic, anti-inflammatory counter-APR after strenuous exercise. Chronic physical activity reduces resting CRP levels by multiple mechanisms, including a decrease in cytokine production by adipose tissue, skeletal muscles, endothelial and blood mononuclear cells, improved endothelial function and insulin sensitivity, and possibly an antioxidant effect.

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