

Effect of Aerobic Training Program on Serum C-reactive Protein Levels

Mojtaba Eizadi,¹ Shahram Sohaily,^{2,*} Davood Khorshidi,³ and Hamidreza Samarikhalaj³

¹Department of Physical Education and Sport Sciences, Islamshahr Branch, Islamic Azad University, Tehran, IR Iran

²Department of Physical Education and Sport Sciences, Islamic Azad University, Shahr-e-Qods Branch, Tehran, IR Iran

³Department of Physical Education and Sport Sciences, Islamic Azad University, Saveh Branch, Saveh, IR Iran

*Corresponding author: Shahram Sohaily, Department of Physical Education and Sport Sciences, Islamic Azad University, Shahr-e-Qods Branch, Tehran, IR Iran. Tel: +98-9193551960, E-mail: shahramsohaily@yahoo.com

Received 2015 September 20; Revised 2015 October 30; Accepted 2015 October 31.

Abstract

Background: Smoking is an established risk factor for cardiovascular diseases and metabolic syndrome.

Objectives: Here we aimed to assess the effect of 3-month aerobic training on C-reactive protein (CRP) level and total antioxidant capacity (TAC) in male smokers.

Patients and Methods: A total of 34 male cigarette smokers aged 35 – 45 years participated in this study by accessible sampling and were divided randomly into experimental and control groups. Pre- and post-training CRP and TAC data were collected in both groups and compared by Student's t-test.

Results: Aerobic training resulted in a significantly increased TAC ($P < 0.001$), but CRP remained unchanged ($P = 0.96$).

Conclusions: Despite a lack of CRP change, long-term aerobic training is associated with anti-oxidative effects.

Keywords: Aerobic Training, Smoking, Stress Oxidative, Inflammation

1. Background

The oxidative stress condition that follows an increased production of reactive oxygen species or free radicals in response to smoking is associated with symptoms such as stimulation of DNA breakage, inactivation of specific proteins, and breakage of biological membranes (1). In smokers, the antioxidant defense capability, or total antioxidant capacity (TAC), against free radicals and other oxidants is reduced. In fact, increased oxidative stress, as a consequence of reduced defense capacity or capability of antioxidants in the immune system against the increased oxidants, plays a significant role in the pathogenesis of smoking-related diseases such as cancer, cardiovascular diseases, metabolic syndrome, hypertension, and type 2 diabetes (2). The literature supports the role of oxidative stress in the pathogenesis of 100 different diseases (3). Studies show that the lung epithelial cells are the primary targets of the inflammatory damage caused by smoking. Cigarettes are known to contain > 4,700 chemicals and oxidants (4), which comprises an important etiological factor in the development and severity of respiratory diseases such as chronic obstructive pulmonary disease (COPD).

Activated inflammatory cells secrete and produce various inflammatory mediators in response to smoking; among them, inflammatory cytokines are the most important. Some recent studies have identified the correlation between smoking and increased inflammatory biomark-

ers such as C-reactive protein (CRP), fibrinogen, and increased numbers of white blood cells and other inflammatory cytokines such as interleukin (IL)-6 (5). Changes in the levels of such inflammatory cytokines not only occur in smokers' lungs and airways but also in their circulation (6).

In this regard, one study showed that the serum CRP levels of smokers were significantly higher than those of non-smokers (7). Its connection to the surface of microorganisms activates the complement pathway as part of the immunological response, which subsequently creates a primary defense mechanism against infection and protects active tissue in the body against toxins. However, its increased serum or plasma levels increased inflammation in smokers, stressing the harmful effects of cigarette smoking on the immune system (8). Researchers also suggested that increased CRP levels in smokers compared to non-smokers increases the risk of atherosclerosis (9). Smoking has also been shown to cause oxidative stress and dysfunction in the inflammation profile in the airways and alveolar epithelium, both of which are important in the pathogenesis of smoking-related diseases (10). Thus, understanding the mechanisms responsible for the effects of smoking on the inflammatory profile as well as oxidant and antioxidant levels has been the focus of health scientists. In this respect, although studies on the responses of CRP or oxidative stress indexes are limited to a variety

of exercise trainings, findings in other healthy or patient populations are also more or less contradictory and inconsistent, as some studies showed beneficial effects (11-13), whereas others showed ineffectiveness (14-16) of exercise on the TAC or CRP levels of healthy or patient populations.

2. Objectives

Given the contradictory findings in other populations as well as the limited studies on smokers in the field, this study aimed to determine the effect of 3 months of aerobic exercise on serum CRP levels and TAC in male smokers. We also queried whether changes in CRP in response to training are associated with changes in TAC. Obtaining the answer to this question is also a main objective of the present study.

3. Patients and Methods

In this quasi-experimental study, the effects of 3 months of aerobic exercise on serum CRP levels and TAC were measured in male smokers with a sedentary lifestyle. The study population consisted of 36 male smokers aged 35 - 45 years in Saveh who were randomly divided into the experimental (participation in aerobic training for 3 months) and control (no exercise) groups. After being informed by the researchers of the study objectives, consent forms were completed and signed by the participants.

3.1. Inclusion and Exclusion Criteria

Smoking at least 10 cigarettes a day for at least 3 years was the smoking criterion (17). The studied subjects were non-athletes, meaning that during the last 6 months, they had not participated in any regular exercise. Their weight had not fluctuated more than 1 kilogram in the preceding 6 months. A history of metabolic or chronic inflammatory disorders such as type 2 diabetes, asthma, cancer, and cardiovascular or liver disease was the health-related exclusion criterion.

3.2. Measurements of Anthropometric Indices

Anthropometric indices and body fat percentages were measured at the study start and end. Heights were measured using a wall stadiometer after the subjects removed their shoes with an accuracy of 0.1 cm. Body mass index (BMI) was calculated by dividing weight in kilograms by the height in meters squared. Body fat percentage was measured by a body composition measurement device (HFB590; Omron, Finland). Waist and hip circumferences were measured in the thickest area using an inelastic tape measure. Abdominal to hip circumference ratio (AHR) was calculated by dividing waist circumference by hip circumference.

3.3. Measurement of Clinical Markers Training Protocol

Blood samples were obtained in the fasting condition before exercise program and 48 hours after the last training session. Subjects were asked to be present in the laboratory between 8 and 9 am after an overnight fast (10 - 12 hours). Subjects were prohibited from participating in any physical activity for 48 hours before the blood samples were drawn. After each subject entered the lab and rested for 20 minutes, venous blood samples were collected via the cannulated antecubital vein. Serum isolation was performed immediately thereafter, and the samples were stored at -76°C until use. CRP levels were measured by enzyme-linked immunosorbent assay (High-Sensitivity CRP [Hs-CRP] ELISA; Diagnostics Biochem Canada Inc.). The Hs-CRP assay sensitivity was 10 ng/mL, while the intra- and inter-assay coefficients of variation were 5.0 and 9.5%, respectively. Plasma TAC was measured by the FRAP assay.

The aerobic exercise training was conducted in 45- to 60-minute sessions three times a week for 3 months at each subject's 60% - 80% maximum heart rate. The first session had the least duration and intensity, while the duration and intensity increased as the last session was approached. Each session started with a warm-up phase followed by continued aerobic activities in the form of running on a flat surface and group aerobic exercise and ended with cooling down. Target heart rate was controlled and recorded using a heart pulse meter (POLAR, Finland) (18).

3.4. Statistical Analysis

The statistical analysis was conducted in SPSS 15. The Kolmogorov-Smirnov test was used to determine the data distribution. The independent t-test was used to compare the pre-tests between the experimental and control groups. The paired t-test was used to determine the significance level of the differences of each pre- versus post-test variable value. The correlation between serum CRP level and TAC was determined using the Pearson correlation test. Values of $\alpha < 0.05$ were considered significant.

4. Results

Here we investigated the effect of 3 months of aerobic training on serum CRP and TAC in male smokers. Pearson correlation data showed a significant inverse correlation between serum CRP and TAC at baseline ($P = 0.001$, $r = -0.55$; Figure 1). The patterns of these two variables (Figure 1) show that a reduced serum CRP level was associated with increased TAC in the studied smokers.

The pre- and post-training of physical characteristics and clinical variables of the two groups are shown in Table 1. Based on the independent t-test, no significant dif-

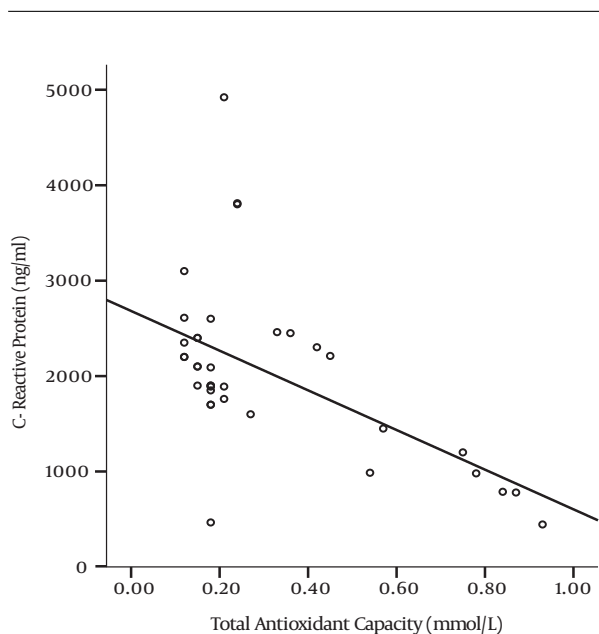


Figure 1. The correlation between total antioxidant capacity and C-reactive protein patterns in the studied male smokers is significant and inverse.

ference was observed in any anthropometrical marker between the two groups at baseline ($P > 0.05$). There were no statistically significant differences between the exercise and control groups with regard to TAC at baseline ($P = 0.92$). No significant difference was also found in serum CRP between two groups at baseline ($P = 0.96$).

According to the paired sample t-test findings, the aerobic training program resulted in a significant decrease in all anthropometrical markers, including weight, AHR, BMI, and body fat percentage compared with pre training ($P < 0.001$).

The effect of aerobic training on serum CRP and TAC in smoker men were main aims of present study. Compared to pre-training, TAC increased significantly after exercise program ($P = 0.001$) but this clinical variables was not changed in control subjects. On the other hand, serum CRP did not change with aerobic training program in exercise group ($P = 0.96$).

5. Discussion

In this study, aerobic exercise significantly increased the TAC in male adult smokers but serum CRP levels did not change significantly. However, a significant correlation was observed between changes in TAC and those in CRP levels in response to training, which is clinically interesting.

Oxidative stress plays an important role in the pathogenesis of many diseases, including COPD, lung cancer, and atherosclerosis. Cigarette smoke also increases oxidative stress by producing reactive oxygen radicals and reducing the body's antioxidant defense system. This also leads to chronic diseases such as type 2 diabetes, hypertension, and metabolic syndrome as well as malignant diseases (19).

It was once believed that the ability and role of smoking in producing oxidative stress in the alveolar epithelial cells are not associated with the release of pro-inflammatory cytokines (20). These studies even reported the ineffectiveness of smoking on the release of pro-inflammatory cytokines in airway cells. However, more recent studies have pointed out to the close association between pro-inflammatory cytokines and oxidative stress or antioxidants (21). Researchers believe that oxidative stress caused by smoking leads to the destruction of alveolar walls and airway resistance. On the other hand, increased oxidative stress results in the impairment and increase in the pro-inflammatory cytokines in the lungs of smokers and COPD patients (22). In this respect, the findings of this study showed the significant negative correlation between TAC and serum CRP level as a pro-inflammatory cytokine, which supports the close correlation between oxidative stress and inflammatory profile in smokers.

The literature has revealed that the epithelium of the airways and the upper parts of the lungs is the main target of the inhalants that play an important role in the release of pro-inflammatory mediators. This release plays an important role in the development of tissue damage during inflammatory processes or inflammatory diseases, representing or reflecting the role of the epithelium in the airways or lungs in the pathogenesis of inflammatory respiratory diseases such as COPD (10). Laboratory findings in previous studies revealed that smoking increases the release of pro-inflammatory cytokines in the lungs of smokers and tobacco chewers (23). However, the precise molecular mechanisms by which cigarettes affect the release of pro-inflammatory cytokines, particularly in the alveolar cells or airways, are not yet fully understood. Previous studies have shown that the toxic effects of cigarettes (24) occur mainly due to their chemical components, such as acrolein, nicotine, benzopyrene, and N-nitrosamines (25). On the other hand, these findings clearly show that smoking is toxic to the alveolar cells and plays a role in the development of smoking-related lung diseases (24).

Despite the limited availability of studies on the response of antioxidants or antioxidants as well as inflammatory mediators to exercise in smokers, in this study, 3 months of aerobic training significantly increased the TAC in adult male smokers who previously led an inactive

Table 1. Mean and Standard Deviation of Anthropometrical and Clinical Characteristics in Pre- and Post-Training of the two Study Groups^a

Variables	Experimental Group			Control Group		
	Pre-Training	Post-Training	P Value	Pre-Training	Post-Training	P Value
Age, y	42 ± 4.8	NA	NA	41 ± 3.9	NA	NA
Height, cm	175 ± 2.9	NA	NA	175 ± 2.4	NA	NA
Weight, kg	91.8 ± 5.1	88.2 ± 5.1	< 0.001	91 ± 2.6	91 ± 5.7	0.79
AC, cm	101 ± 6	97 ± 5	< 0.001	100 ± 6.4	100 ± 5.8	0.86
HC, cm	102 ± 4.9	97 ± 4.3	< 0.001	100 ± 5.6	100 ± 5.8	0.58
BMI, kg/m ²	29.9 ± 2.11	28.7 ± 2.09	< 0.001	29.6 ± 1.91	29.6 ± 1.94	0.80
BF, %	29 ± 2.01	27.3 ± 1.77	< 0.001	28.8 ± 1.79	29 ± 1.91	0.20
TAC, mmol/L	0.32 ± 0.26	0.44 ± 0.26	< 0.001	0.31 ± 0.27	0.31 ± 0.15	0.87
Hs-CRP, ng/ml	2028 ± 1077	2040 ± 749	0.96	2044 ± 749	2087 ± 665	0.74

Abbreviations: AC, abdominal circumference; BF, body fat; BMI, body mass index; HC, hip circumference; Hs-CRP, high-sensitivity C-reactive protein percentage; NA, not available; TAC, total antioxidant capacity.

^aData are presented as men ±SD.

lifestyle. This finding indirectly supports the reduced intensity of oxidative stress in smokers in response to long-term exercise training. Improved TAC along with reduced oxidative damage induced by training has also been reported by other studies (26). However, in a recent study, despite a significant increase in superoxide dismutase activity and reduced malondialdehyde level following 8 weeks of progressive resistance training in male non-athletes, glutathione peroxidase activity and TAC were not significantly changed (27). In addition to training type and measurement tool, the inconsistencies in these findings appear related to differences in the studied populations since most studies that reported unchanged levels of oxidants or antioxidants in response to physical activity were performed in healthy athletes or non-athletes (26, 27). However, not all of those studies of patient populations or those somehow influenced by external stimuli suggested improved antioxidant capacity or oxidative stress (12, 13). Overall, antioxidant supplementation to increase the internal antioxidant capacity reduces exercise-induced reactive oxygen species (28).

A significant increase in the TAC in male smokers in response to training was observed, whereas serum CRP levels were not affected. However, a significant correlation between serum CRP level and TAC was observed before the exercise training. In fact, the finding of an unchanged CRP level despite significant TAC improvement is somewhat controversial. However, some studies have reported the ineffectiveness of long-term exercise training on CRP level in other healthy or patient populations. For example, in a recent study, 3-month-long exercise was not associated with changes in inflammatory markers such as CRP in patients

with chronic heart disease (14). In another study, 6 months of aerobic exercise significantly changed the levels of inflammatory markers such as CRP, IL-6, and tumor necrosis factor- α in postmenopausal obese or overweight women (29). In contrast, in two other studies, exercise training in the form of 24 weeks of fast walking 5 times a week (11) and 3 and 6 months of intensive aerobic and resistance exercise (30) significantly reduced the serum CRP levels and cardiovascular risk factors in patients with multiple sclerosis or inflammatory rheumatic disorder. In another study, 3 months of moderate aerobic exercise led to improvements in the oxidative stress reagents such as superoxide dismutase and inflammatory profile and decreased insulin resistance in obese men (31).

However, the unchanged CRP level despite significant TAC improvement through aerobic exercise remains controversial. It is also possible that serum CRP in response to training or other interventions such as quitting smoking has a delayed response or requires a long period of time. Most studies that have measured CRP levels in smokers have reported a lack of reduction in its levels immediately after quitting, which suggests the involvement of deep tissue damage caused by smoking and the long-term recovery required (6). In this regard, a longitudinal study reported higher CRP levels in smokers than in non-smokers. It also showed that even 5 years after smoking cessation, the difference is still significant, and full recovery to or normal CRP levels have been reported in those who have not smoked in 20 years (32). In that study, after not smoking for 30 – 55 years, CRP levels decreased from 1.92 mg/L in the initial state to 1.25 mg/L (32).

According to the findings of this study, although exer-

cise training is associated with increased TAC and insignificant changes in serum CRP levels, it does not affect serum CRP level as an inflammatory cytokine in male smokers. However, a clinically important inverse correlation was observed between their changes in response to exercise training. These findings somehow support the fact that reduced oxidative stress or increased TAC is associated with an improved inflammatory profile. Further studies with larger sample sizes that measure other oxidant and antioxidant agents are recommended to confirm our findings.

Acknowledgments

We express our gratitude to all of the study participants. We thank the Research Deputy of Islamic Azad University, Islamshahr Branch, for the financial support of and cooperation in implementing this project.

Footnote

Authors' Contribution: Mojtaba Eizadi and Shahram Sohaily, conceived of and designed the study as well as drafted the manuscript; Davood Khorshidi and Hamidreza Samarikhalaj, performed the statistical analysis and provided administrative, technical, and material support.

References

- Durak I, Elgun S, Kemal Bingol N, Burak Cimen MY, Kacmaz M, Buyukkocak S, et al. Effects of cigarette smoking with different tar content on erythrocyte oxidant/antioxidant status. *Addict Biol.* 2002;7(2):255-8. doi: [10.1080/135562102200120505](https://doi.org/10.1080/135562102200120505). [PubMed: [12006222](https://pubmed.ncbi.nlm.nih.gov/12006222/)].
- Therriault MJ, Proulx LI, Castonguay A, Bissonnette EY. Immunomodulatory effects of the tobacco-specific carcinogen, NNK, on alveolar macrophages. *Clin Exp Immunol.* 2003;132(2):232-8. [PubMed: [12699410](https://pubmed.ncbi.nlm.nih.gov/12699410/)].
- Baek KJ, Thiel BA, Lucas S, Stuehr DJ. Macrophage nitric oxide synthase subunits. Purification, characterization, and role of prosthetic groups and substrate in regulating their association into a dimeric enzyme. *J Biol Chem.* 1993;268(28):21120-9. [PubMed: [7691806](https://pubmed.ncbi.nlm.nih.gov/7691806/)].
- Cotgreave IA, Gerdes RG. Recent trends in glutathione biochemistry-glutathione-protein interactions: a molecular link between oxidative stress and cell proliferation?. *Biochem Biophys Res Commun.* 1998;242(1):1-9. doi: [10.1006/bbrc.1997.7812](https://doi.org/10.1006/bbrc.1997.7812). [PubMed: [9439600](https://pubmed.ncbi.nlm.nih.gov/9439600/)].
- Frohlich M, Sund M, Lowel H, Imhof A, Hoffmeister A, Koenig W. Independent association of various smoking characteristics with markers of systemic inflammation in men. Results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). *Eur Heart J.* 2003;24(14):1365-72. [PubMed: [12871694](https://pubmed.ncbi.nlm.nih.gov/12871694/)].
- Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. *Chest.* 2007;131(5):1557-66. doi: [10.1378/chest.06-2179](https://doi.org/10.1378/chest.06-2179). [PubMed: [17494805](https://pubmed.ncbi.nlm.nih.gov/17494805/)].
- Bashtam M, Shahparyan M, Abaszadeh M, Bashtam M, Rangamiz F. Comparison of serum CRP level, Uric acid in active and non-active smokers with non-smokers. *Isfahan Med Uj.* 2003;21(69-70):41-4.
- Henriksen T, Mahoney EM, Steinberg D. Enhanced macrophage degradation of biologically modified low density lipoprotein. *Arteriosclerosis.* 1983;3(2):149-59. [PubMed: [6838433](https://pubmed.ncbi.nlm.nih.gov/6838433/)].
- Rouzbahani R, Asgary S, Naderi GA, Nejad MD, Rezaei F. Comparison of Plasma Lipid Peroxidants, Glycosylated Hemoglobin, Conjugated Dienes and CPR Level in Smokers and Non-smokers Men. *J Isfahan Med School.* 2009;27(93):115-21.
- Kode A, Yang SR, Rahman I. Differential effects of cigarette smoke on oxidative stress and proinflammatory cytokine release in primary human airway epithelial cells and in a variety of transformed alveolar epithelial cells. *Respir Res.* 2006;7:132. doi: [10.1186/1465-9921-7-132](https://doi.org/10.1186/1465-9921-7-132). [PubMed: [17062156](https://pubmed.ncbi.nlm.nih.gov/17062156/)].
- Di Raimondo D, Tuttolomondo A, Butta C, Casuccio A, Giarrusso L, Miceli G, et al. Metabolic and anti-inflammatory effects of a home-based programme of aerobic physical exercise. *Int J Clin Pract.* 2013;67(12):1247-53. doi: [10.1111/ijcp.12269](https://doi.org/10.1111/ijcp.12269). [PubMed: [24246205](https://pubmed.ncbi.nlm.nih.gov/24246205/)].
- Shahandeh M, Roshan VD, Hosseinzadeh S, Mahjoub S, Sarkisian V. Chronic exercise training versus acute endurance exercise in reducing neurotoxicity in rats exposed to lead acetate. *Neural Regen Res.* 2013;8(8):714-22. doi: [10.3969/j.issn.1673-5374.2013.08.006](https://doi.org/10.3969/j.issn.1673-5374.2013.08.006). [PubMed: [25206718](https://pubmed.ncbi.nlm.nih.gov/25206718/)].
- Pinho RA, Chiesa D, Mezzomo KM, Andrades ME, Bonatto F, Gelain D, et al. Oxidative stress in chronic obstructive pulmonary disease patients submitted to a rehabilitation program. *Respir Med.* 2007;101(8):1830-5. doi: [10.1016/j.rmed.2007.02.004](https://doi.org/10.1016/j.rmed.2007.02.004). [PubMed: [17376663](https://pubmed.ncbi.nlm.nih.gov/17376663/)].
- Ahmad T, Fiuzat M, Mark DB, Neely B, Neely M, Kraus WE, et al. The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. *Am Heart J.* 2014;167(2):193-202 e1. doi: [10.1016/j.ahj.2013.10.018](https://doi.org/10.1016/j.ahj.2013.10.018). [PubMed: [24439980](https://pubmed.ncbi.nlm.nih.gov/24439980/)].
- Tong TK, Kong Z, Lin H, Lippi G, Zhang H, Nie J. Serum oxidant and antioxidant status following an all-out 21-km run in adolescent runners undergoing professional training—a one-year prospective trial. *Int J Mol Sci.* 2013;14(7):15167-78. doi: [10.3390/ijms140715167](https://doi.org/10.3390/ijms140715167). [PubMed: [23880864](https://pubmed.ncbi.nlm.nih.gov/23880864/)].
- Leonardo-Mendonca RC, Concepcion-Huertas M, Guerra-Hernandez E, Zabala M, Escames G, Acuna-Castroviejo D. Redox status and antioxidant response in professional cyclists during training. *Eur J Sport Sci.* 2014;14(8):830-8. doi: [10.1080/17461391.2014.915345](https://doi.org/10.1080/17461391.2014.915345). [PubMed: [24803271](https://pubmed.ncbi.nlm.nih.gov/24803271/)].
- Abbasi F, Farin HM, Lamendola C, McLaughlin T, Schwartz EA, Reaven GM, et al. The relationship between plasma adiponectin concentration and insulin resistance is altered in smokers. *J Clin Endocrinol Metab.* 2006;91(12):5002-7. doi: [10.1210/jc.2006-0419](https://doi.org/10.1210/jc.2006-0419). [PubMed: [17003098](https://pubmed.ncbi.nlm.nih.gov/17003098/)].
- Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. *Diabetes Care.* 2004;27(10):2518-39. [PubMed: [15451933](https://pubmed.ncbi.nlm.nih.gov/15451933/)].
- Axelsen M, Eliasson B, Joheim E, Lenner RA, Taskinen MR, Smith U. Lipid intolerance in smokers. *J Intern Med.* 1995;237(5):449-55. [PubMed: [7738484](https://pubmed.ncbi.nlm.nih.gov/7738484/)].
- Moodie FM, Marwick JA, Anderson CS, Szulakowski P, Biswas SK, Bouter MR, et al. Oxidative stress and cigarette smoke alter chromatin remodeling but differentially regulate NF-kappaB activation and proinflammatory cytokine release in alveolar epithelial cells. *FASEB J.* 2004;18(15):1897-9. doi: [10.1096/fj.04-1506fje](https://doi.org/10.1096/fj.04-1506fje). [PubMed: [15456740](https://pubmed.ncbi.nlm.nih.gov/15456740/)].
- Holt EM, Steffen LM, Moran A, Basu S, Steinberger J, Ross JA, et al. Fruit and vegetable consumption and its relation to markers of inflammation and oxidative stress in adolescents. *J Am Diet Assoc.* 2009;109(3):414-21. doi: [10.1016/j.jada.2008.11.036](https://doi.org/10.1016/j.jada.2008.11.036). [PubMed: [19248856](https://pubmed.ncbi.nlm.nih.gov/19248856/)].
- Kirkham P, Rahman I. Oxidative stress in asthma and COPD: antioxidants as a therapeutic strategy. *Pharmacol Ther.* 2006;111(2):476-94. doi: [10.1016/j.pharmthera.2005.10.015](https://doi.org/10.1016/j.pharmthera.2005.10.015). [PubMed: [16458359](https://pubmed.ncbi.nlm.nih.gov/16458359/)].
- Vlahos R, Bozinovski S, Jones JE, Powell J, Gras J, Lilja A, et al. Differential protease, innate immunity, and NF-kappaB induction profiles during lung inflammation induced by subchronic cigarette smoke exposure in mice. *Am J Physiol Lung Cell Mol Physiol.* 2006;290(5):L931-45. doi: [10.1152/ajplung.00201.2005](https://doi.org/10.1152/ajplung.00201.2005). [PubMed: [16361358](https://pubmed.ncbi.nlm.nih.gov/16361358/)].

24. Wang J, Wilcken DE, Wang XL. Cigarette smoke activates caspase-3 to induce apoptosis of human umbilical venous endothelial cells. *Mol Genet Metab.* 2001;**72**(1):82-8. doi: [10.1006/mgme.2000.3115](https://doi.org/10.1006/mgme.2000.3115). [PubMed: [11161833](https://pubmed.ncbi.nlm.nih.gov/11161833/)].
25. Kehrler JP, Biswal SS. The molecular effects of acrolein. *Toxicol Sci.* 2000;**57**(1):6-15. [PubMed: [10966506](https://pubmed.ncbi.nlm.nih.gov/10966506/)].
26. Ficicilar H, Zergeroglu AM, Ersoz G, Erdogan A, Ozdemir S, Tekin D. The effects of short-term training on platelet functions and total antioxidant capacity in rats. *Physiol Res.* 2006;**55**(2):151-6. [PubMed: [15910176](https://pubmed.ncbi.nlm.nih.gov/15910176/)].
27. Azizbeigi K, Azarbayjani MA, Peeri M, Agha-alinejad H, Stannard S. The effect of progressive resistance training on oxidative stress and antioxidant enzyme activity in erythrocytes in untrained men. *Int J Sport Nutr Exerc Metab.* 2013;**23**(3):230-8. [PubMed: [23239675](https://pubmed.ncbi.nlm.nih.gov/23239675/)].
28. Ackerman J, Clifford T, McNaughton LR, Bentley DJ. The effect of an acute antioxidant supplementation compared with placebo on performance and hormonal response during a high volume resistance training session. *J Int Soc Sports Nutr.* 2014;**11**(1):10. doi: [10.1186/1550-2783-11-10](https://doi.org/10.1186/1550-2783-11-10). [PubMed: [24650275](https://pubmed.ncbi.nlm.nih.gov/24650275/)].
29. Cavagnoli DA, Esteves AM, Ackel-D'Elia C, Maeda MY, de Faria AP, Tufik S, et al. Aerobic exercise does not change C-reactive protein levels in non-obese patients with obstructive sleep apnoea. *Eur J Sport Sci.* 2014;**14 Suppl 1**:S142-7. doi: [10.1080/17461391.2012.663412](https://doi.org/10.1080/17461391.2012.663412). [PubMed: [24444198](https://pubmed.ncbi.nlm.nih.gov/24444198/)].
30. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2013;**72**(11):1819-25. doi: [10.1136/annrheumdis-2012-202075](https://doi.org/10.1136/annrheumdis-2012-202075). [PubMed: [23155222](https://pubmed.ncbi.nlm.nih.gov/23155222/)].
31. Samjoo IA, Safdar A, Hamadeh MJ, Raha S, Tarnopolsky MA. The effect of endurance exercise on both skeletal muscle and systemic oxidative stress in previously sedentary obese men. *Nutr Diabetes.* 2013;**3**:e88. doi: [10.1038/nutd.2013.30](https://doi.org/10.1038/nutd.2013.30). [PubMed: [24042701](https://pubmed.ncbi.nlm.nih.gov/24042701/)].
32. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J.* 2005;**26**(17):1765-73. doi: [10.1093/eurheartj/ehi183](https://doi.org/10.1093/eurheartj/ehi183). [PubMed: [15817606](https://pubmed.ncbi.nlm.nih.gov/15817606/)].