

# Acute and Recovery Changes of TNF- $\alpha$ and IL-1 $\beta$ in Response to Aerobic Exercise in Smokers and Non-smokers

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## Abstract

**Introduction:** Recent evidence has shown that acute exercise affects the immune response in healthy individuals. However, the effect of aerobic exercise on inflammatory markers in smokers has not been well studied. This study evaluated acute and recovery responses of inflammatory cytokines to moderate aerobic exercise in male smokers.

**Methods:** For this purpose, 15 sedentary male smokers and 15 male non-smokers matched for age and body mass index (BMI) performed aerobic exercise involving 40-minute running at 70% of maximum heart rate (HRmax). Blood samples were obtained pre-exercise (baseline), immediately post exercise (zero), as well as 60 minutes and 24 hours after exercise for analysis of interleukin-1 beta (IL-1 $\beta$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ) levels. The data were analyzed using SPSS 16.0 and one-way analysis variance (ANOVA) with repeated measures.

**Results:** No differences were observed for baseline IL-1 $\beta$  between smokers and non-smokers. However, serum TNF- $\alpha$  level was significantly higher in smokers ( $75.1 \pm 14.3$ ) than in non-smokers ( $37.2 \pm 9.11$ ) at baseline ( $P=0.01$ ). Aerobic exercise significantly reduced TNF- $\alpha$  level immediately after exercise ( $58.9 \pm 11.6$ ), and at 60 minutes ( $50.1 \pm 14.8$ ), and 24 hours ( $53.44 \pm 12.3$ ) post exercise in comparison with baseline ( $P=0.02$ ) in smokers. TNF- $\alpha$  levels remained significantly higher in smokers compared to non-smokers immediately, 60 minutes, and 24 hours post exercise. IL-1 $\beta$  levels revealed no significant differences between smokers and non-smokers at baseline, immediately, 60 minutes, and 24 hours post exercise. Furthermore, exercise did not significantly affect acute or recovery changes of TNF- $\alpha$  and IL-1 $\beta$  in non-smokers.

**Conclusion:** In conclusion, based on acute and recovery responses of serum TNF- $\alpha$  to exercise, it seems that a moderate aerobic exercise may reveal beneficial effects on inflammatory profile in smokers.

**Keywords:** Inflammation, Smoking, Aerobic exercise, Recovery



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## Introduction

Regular consumption of tobacco has been known as the second leading cause of death. It is predicted that more than 9 million people will lose their lives each year due to its consumption until 2030.<sup>1</sup> Heart diseases and some lung conditions such as lung cancer and chronic obstructive pulmonary disease (COPD) and skeletal muscle inflammation are the major consequences of tobacco consumption.<sup>2,3</sup> Pro-inflammatory cytokines have been suggested to be secreted from immune cells as a result of smoking. Recent studies have reported changes in inflammatory

cytokines in healthy smokers, not only in the lungs but also in blood circulation. Some studies have reported high levels of these inflammatory cytokines even 10 to 20 years after quitting.<sup>4</sup>

Recent studies have revealed that inflammatory reactions (i.e. elevation in cytokines such as interleukin-1 beta [IL-1 $\beta$ ] and tumor necrosis factor-alpha [TNF- $\alpha$ ]) are increased particularly in response to cigarette smoking predisposing to chronic disorders such as diabetes.<sup>5,6</sup> On the one hand, the role of smoking in increasing the inflammatory cytokines was observed in some other studies.<sup>7</sup>



Meanwhile, some studies have confirmed the additive effect of smoking on serum TNF- $\alpha$  as one of the pro-inflammatory cytokines in blood circulation.<sup>8,9</sup> Increased IL-1 $\beta$  leads to respiratory inflammation, destruction of elastic fibers in pulmonary alveolar walls, obstruction of the airway wall, and accumulation of lymphocytes in the respiratory airways.<sup>10</sup> Scientific references have reported higher levels of IL-1 $\beta$  in smokers compared to non-smokers.<sup>11</sup> Therefore, implementing strategies for reducing the effects of smoking has always been health science researchers' top priority.

The role of exercise and physical activity is of great importance in regulating inflammation. In this context, although the inflammatory response to various exercise training has been less frequently studied in smokers, scientific findings in other healthy and sick populations have shown the anti-inflammatory impacts of exercise with a reduction in the levels of inflammatory mediators such as IL-1 $\beta$ .<sup>12</sup> In addition, TNF- $\alpha$  level was reduced in skeletal muscle of thin older people in response to exercise.<sup>13</sup> Despite the evidences, there are few studies regarding acute or recovery responses of cytokines such as TNF- $\alpha$  and IL-1 $\beta$  to exercise in smokers. Therefore, this study aimed to measure and compare acute and recovery responses of these inflammatory cytokines following an exercise session in smokers and non-smokers.

## Materials and Methods

### Human Subjects and Study Inclusion

This semi-experimental study examined acute and post exercise responses of serum TNF- $\alpha$  and IL-1 $\beta$  in smoker and nonsmokers. Participants including 15 non-trained healthy male smokers and 15 nonsmokers matched for sex, age, height and body mass index (BMI) were recruited by convenience sampling. The sample size was determined according to equation 1.

$$n = \frac{(\sigma_1^2 + \sigma_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{d^2}$$

with  $\alpha = 0.05$ ,  $1-\beta = 0.8$ , and  $\Delta$  (effect size) = 0.36.

### Inclusion and Exclusion Criteria

To understand medical history, subjects were asked to complete questionnaires on present medications, general health, alcohol consumption and smoking. The inclusion criterion for the smoker group was smoking history of at least 10 cigarettes a day for 3 years (current smokers).<sup>14</sup> All subjects of the two groups were inactive and non-alcoholics. None of the subjects used therapies or drugs for obesity, and none had a past history of injury or disease that would prevent daily exercise. All subjects of two groups had not participated in regular diet programs/exercise for the preceding six months. Patients with a known history of neuromuscular disease, acute or chronic respiratory infections and cardiopulmonary disease

were excluded from the study. Any subject who did not complete the exercise program was also excluded from the final analysis.

### Anthropometric Measurements

Body weight was measured to the nearest 10 g using digital scales (OMRON, BF: 508, Finland). The height of barefoot participants was measured to the nearest 0.1 cm. Body fat percentage was measured using body composition monitor (OMRON, BF: 508, Finland). BMI was measured for each subject by the division of weight (kg) by height (m<sup>2</sup>).

### Acute Exercise and Blood Analysis

Aerobic exercise test lasted 40 minutes at 70% of maximum heart rate (HRmax) involved running on a flat surface with no slope. Target HR was controlled using polar telemetry system. Venous blood samples were obtained before, immediately, 60 minutes and 24 hours after exercise test in the 2 groups. Blood samples were dispensed into EDTA-coated tubes and then centrifuged for 10 minutes in order to separate serum. Serum was used to measure TNF- $\alpha$  and IL-1 $\beta$  by ELISA.

Serum TNF- $\alpha$  concentration was determined using ELISA for quantitative detection of human TNF- $\alpha$  (Human TNF- $\alpha$  total Platinum ELISA BMS2034/BMS2034TEN, Biovendor, Vienna, Austria). The intra-assay CV for TNF- $\alpha$  was 6.0% and inter-assay variability ranged from 23 to 1500 pg/mL. Serum IL-1 $\beta$  was determined using ELISA for quantitative detection of human IL-1 $\beta$  (Human IL-1 $\beta$  Platinum ELISA BMS224/2/BMS224/2TEN, Biovendor, Vienna, Austria). The intra-assay CV for IL-1 $\beta$  was 5.1%, and inter-assay variability ranged from 3.9 to 250 pg/mL.

### Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, version 16.0. Normal distribution of the data was determined by the Kolmogorov-Smirnov normality test. One-way analysis of variance (ANOVA) was used to effectively assess the changes in serum TNF- $\alpha$  and IL-1 $\beta$  by exercise test in the 2 groups. A *P* value of less than 0.05 was considered statistically significant.

### Results

Values of anthropometric characteristics have been reported as means and standard deviations (Table 1). Based on independent sample student *t* test, no statistically significant differences were found between smokers and non-smokers with regard to anthropometric characteristics (*P* > 0.05).

TNF- $\alpha$  serum levels were significantly higher in smokers than in non-smoker subjects at baseline (*P* = 0.01). In contrast, smokers and non-smokers did not reveal any significant difference regarding serum IL-1 $\beta$  at

**Table 1.** Anthropometric Indexes in Our Sample Population

Variables	Smokers n=15	Non-smokers n=15	P Value
Age (y)	35 ± 5	36 ± 5.8	0.452
Height (cm)	176 ± 6.8	177 ± 5.3	0.652
Weight (kg)	97 ± 9.8	98 ± 5.8	0.865
AC (cm)	101 ± 8.8	100 ± 9.7	0.536
BMI (kg/m <sup>2</sup> )	31.31 ± 4.3	31.28 ± 3.3	0.756
BF (%)	29.3 ± 3.5	29.8 ± 4.1	0.695

AC, abdominal circumference; BF, body fat percentage; BMI, body mass index

baseline ( $P = 0.31$ ).

As mentioned above, the main objective of the present study was to determine the acute and recovery response of IL-1 $\beta$  and TNF- $\alpha$  to aerobic exercise in the two groups. Based on repeated measure data, although acute and recovery response (1 and 24 hours) of serum TNF- $\alpha$  to exercise test was not significantly different compared with pre-exercise (baseline) in non-smokers ( $P > 0.05$ ), its levels were significantly decreased after exercise (0, 1 and 24 hours) compared to pre-exercise in smoker subjects (Table 2).

Regarding serum IL-1 $\beta$  response to aerobic exercise test, no differences were observed immediately and recovery post-exercise compared to pre-exercise in this cytokine concentration in smoker and non-smokers ( $P > 0.05$ , Table 3).

## Discussion

Although previous studies have confirmed higher levels of inflammatory cytokines in smokers than non-smokers, in the current study, no significant differences were observed between smokers and non-smokers in terms of serum IL-1 $\beta$  levels at baseline. Furthermore, no significant changes

were detected at acute (1 hour) and recovery (24 hours) phases post exercise in smoker and non-smoker groups. This is despite the fact that smokers had significantly higher serum TNF- $\alpha$  levels compared to non-smokers at baseline and recovery phases. In this regard, a study reported increased IL-1 $\beta$ , not only in smokers but also in people indirectly exposed to smoking.<sup>14</sup>

The fact that no difference was observed in IL-1 $\beta$  in smokers and non-smokers can be attributed to our small sample size. However, levels of inflammatory profile in smokers do not follow a regular pattern. Nevertheless, smokers showed higher serum TNF- $\alpha$  compared to non-smokers. In addition to smoking, inflammatory cytokines levels seem to fluctuate in response to exercise and physical activity as well. In the present study, the reduction of TNF- $\alpha$  at acute or recovery phases (1 and 24 hours respectively) in response to exercise was observed in male smokers. In general, both acute and long-term exercises seem to affect inflammatory cytokines. In this regard, low-intensity aerobic exercise and combined aerobic-resistance training program decreased levels of IL-1 $\beta$  in people suffering from obesity and diabetes.<sup>15</sup>

Similar to our findings, no significant change occurred in the levels of IL-1 $\beta$  as a result of long-term exercise training in another study.<sup>16</sup> In addition, short-term exercise training did not lead to any change in the plasma levels of IL-1 $\beta$ .<sup>17</sup> In some studies, despite the increase of physical fitness levels in female smokers in response to exercise training for 12 weeks, inflammatory cytokines did not significantly change in response to exercise.<sup>12</sup> In another study, aerobic training for 12 weeks significantly decreased serum CRP levels, but no changes were observed in TNF- $\alpha$  level.<sup>18</sup>

In the current study, despite the lack of change in IL-1 $\beta$  in response to aerobic exercise in the smokers, serum levels of TNF- $\alpha$  showed a decreasing trend immediately

**Table 2.** Acute and Recovery Response of Serum TNF- $\alpha$  to Aerobic Exercise of 2 Groups

Group	TNF- $\alpha$ Level (ng/mL)		P Value (Between Groups)
	Smoker (n = 15)	Non-smoker (n = 15)	
Pre-exercise	75.1 ± 14.3	37.2 ± 9.11	0.01
Acute response	58.9 ± 11.6*	36.3 ± 10.7	0.009
60 min recovery	50.1 ± 14.8*	36.9 ± 9.47	0.013
24 h recovery	53.44 ± 12.3*	38.1 ± 13.2	0.019
P value (within groups)	0.023	0.325	-

\* represent significant difference compared to pre-exercise ( $P < 0.05$ )

**Table 3.** Acute and Recovery Response of Serum IL-1 $\beta$  to Aerobic Exercise of 2 Groups

Group	IL-1 $\beta$ Level (ng/mL)		P Value (Between Groups)
	Smoker (n = 15)	Non-smoker (n = 15)	
Pre-exercise	6.24 ± 1.23	2.11 ± 6.41	0.310
Acute response	5.85 ± 1.14	1.12 ± 5.14	0.265
60 min recovery	6.51 ± 1.33	2.11 ± 6.13	0.562
24 h recovery	5.87 ± 1.02	0.98 ± 5.76	0.436
P value (within groups)	0.524	0.621	-

and 24 hours following exercise. Nevertheless, TNF- $\alpha$  levels demonstrated no such changes in non-smokers compared to baseline levels. These indicated no acute and recovery responses of IL-1 $\beta$  to exercise in smokers and non-smokers. Regarding the acute response of IL-1 $\beta$  to exercise, Martin et al showed that a single session of exercise increased IL-1 $\beta$  in obese mice.<sup>19</sup> Moreover, in the study of Duran et al, despite the acute and recovery increase in IL-6 in response to a high-intensity interval training session (10 sets of 2-minute cycling followed by one-minute rest intervals), the levels of TNF- $\alpha$  and IL-10 showed no significant changes.<sup>20</sup>

In another study, significant differences were not observed in the levels of IL-6 at 40 minutes post moderate-intensity cycling exercise between smokers and non-smokers.<sup>21</sup> It has been noted that systemic inflammation in response to smoking results from stimulation of various types of inflammatory cells.<sup>11,22</sup> The results of a recent study showed that serum TNF- $\alpha$  and IL-1 $\beta$  levels in smokers were significantly higher compared to non-smokers and simultaneous inhibition of TNF- $\alpha$  and IL-1 $\beta$  signaling pathways prevented endothelial disruption caused by smoking.<sup>23</sup>

#### Limitation

We did not measure other inflammatory cytokines which is the main limitation of the current study.

#### Conclusion

Acute or recovery response of the two inflammatory cytokines IL-1 $\beta$  and TNF- $\alpha$  to an aerobic exercise session with moderate-intensity are different in male smokers. In this regard, despite the absence of change in IL-1 $\beta$ , serum levels of TNF- $\alpha$  immediately decreased significantly compared to baseline levels, within 1 and 24 hours after the exercise. In this regard, it can be stated that a relatively long-term aerobic exercise session with moderate intensity is, to some degree, associated with improvement of the inflammatory profile with emphasis on TNF- $\alpha$  in a recovery period of up to 24 hours after the test in non-active male smokers, while these changes are not observed in male non-smokers.

#### Ethical Approval

The study was approved by the Ethics Committee of Islamic Azad University, Iran (73/454791). Informed consent was obtained from all participants before recruitment to the project.

#### Competing Interests

Authors declare that they have no competing interests.

#### Acknowledgments

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