# Immunomodulatory Effect of Exercise in Patients with Asthma

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## Abstract

**Objective:** Immune responses can change with exercise. We aimed to show the changes in cytokine levels pre- and post-exercise in patients with asthma.

**Methods:** In this prospective control trial, data of 32 patients with asthma that was under control were classified into two groups, pre- and post-exercise. Serum IL-1β and monocyte IL-1β, IL-2, and IL-10 expressions were evaluated using enzyme-linked immunosorbent assay. The patients were advised to walk for at least 30 min for 4 days/week for 12 weeks.

**Results:** There was no significant difference in demographic properties of the participants. Monocyte IL-1β levels in the pre- and post-exercise groups were 1.99±0.35 and 1.01±0.22 pg/mL, respectively (p=0.003). IL-10 levels in the pre- and post-exercise groups were 1.64±0.02 and 1.21±0.03 pg/mL, respectively (p=0.04). IL-2 levels in the pre- and post-exercise groups were 0.64±0.045 and 0.32±0.09 pg/mL, respectively (p=0.001). However, there was a significant difference in serum IL-1β and monocyte IL-1β, IL-2, and IL-10 levels between the groups (p=0.02, p=0.003, p=0.04, and p=0.001, respectively).

**Conclusion:** Systemic inflammatory parameters that are commonly elevated in asthma may improve by exercise. The elucidation of the mechanism of immune control in patients with asthma is useful for the future treatment of asthma.

**Keywords:** Asthma, exercise, interleukin 1β, interleukin 2, interleukin 10

## INTRODUCTION

Asthma, a complex disease, increases allergen-specific IgE production and eosinophilic infiltration, which arise from the contribution of multiple genetic and environmental factors (1). The prevalence and severity of allergic asthma have markedly increased in the last several decades. Dysregulated expression patterns of pro- and anti-inflammatory mechanisms are considered to be responsible for the development of chronic inflammation. The sequence of immunopathogenesis is unclear, but there is clearly a genetic predisposition. Asthma occurs because of multiple interacting genes; some genes have a protective effect, whereas others contribute to the disease pathogenesis. Each gene has its own tendency to be influenced by the environment. Immune parameters may vary depending on the age, physical activity, and emerging diseases (2). Some parameters can change in healthy populations, whereas others remain constant with age (3). Although previous studies in healthy populations have shown changes in CD40 and CD45 levels, interleukin 1β (IL-1 β), interleukin 2 (IL-2), interleukin 6 (IL-6), interleukin 10 (IL-10), Tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) levels remain constant (3).

It has been shown that regular exercise could lead to improvements in lung function and management of asthma symptoms (4). Researchers concluded that aerobic exercise induced various improvements such as improved lung function assessed by pulmonary function tests, decreased airway inflammation (low total and eosinophil counts in induced sputum), reduced asthma exacerbations, good asthma control, few visits to hospitals (emergency departments), and decreased anxiety and depression (5-7).

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Clinical studies have demonstrated that the treatment of asthma with anti-IgE improved clinical outcomes and reduced common cytokine release (8). The change in serum levels of these markers with anti-IgE treatment shows the importance of cytokine regulation with the IgE pathway.

Although it is known that exercise can induce improvements in asthma, it is not an appreciated therapy because of insufficient data. This study aimed to evaluate systemic inflammatory parameters in asthma and how they were affected during exercise and to contribute to the literature regarding its clinical implications.

## METHODS

Consecutive patients with asthma (n=32) who had no other chronic and/or autoimmune disorders, were aged >18 years, and were undergoing treatment at the Clinical Immunology and Allergy Unit were recruited. The patients were being followed up in our clinic after being diagnosed as having controlled asthma based on the Global Initiative for Asthma guidelines (9). Serum biomarker levels pre- and post-exercise were compared.

The study was approved by the local Ethics Committee. All studies conformed to the ethical guidelines of the 2000 Helsinki declaration. All participants provided witnessed written informed consent prior to the study.

The patients were advised to walk for least 30 min for 4 days/week for 12 weeks. First serum samples were obtained between 08:00 and 09:00 AM from all patients following a 12-h fasting period and after 30 min of rest on the first day of their study participation. The second serum samples were obtained between 08:00 and 09:00 AM from all patients following a 12-h fasting period and after 30 min of rest on the first day after the completion of the 12-week exercise program.

Samples were centrifuged (Shimadzu UV160A, S. No: 28006648, Japan) at 3000 rpm for 10 min, and the serum was stored at –80°C until analysis. Hemoglobin level and leukocyte counts were determined using an Advia 2120i Hematology System (Siemens Healthcare Diagnostics, Tarrytown NY, USA).

IL-1β levels were measured using an enzyme-linked immunosorbent assay kit (Diaclone, Catalog No: 851.610.005, San Diego, CA, USA). All assays were conducted according to the manufacturer's instructions. Samples that revealed higher levels were diluted and measured in duplicate. The calculated effector: target ratio was 50:1. Pulmonary function tests and evaluation of fractional exhaled nitric oxide (FeNO) levels were assessed on the same clinical visit day. Clinical assessment and adverse effects, serum IgE and ECP levels with pulmonary function tests (Quality Metric Incorp.), asthma control test (ACT), and FeNO concentrations were assessed during each outpatient visit. FeNO was assessed according to the American Thoracic Society/ European Respiratory Society guidelines. Patients' daily medications, asthma severity, and control test scores were recorded (9).

### Statistical Analyses

Results are presented as mean±standard error of the mean and mean±standard deviation. Comparison of parameters between the two groups was performed using paired samples t-test. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using Statistical Package for the Social Sciences 18.0 (SPSS IBM Corporation, New York, USA).

**Table 1.** Clinical findings of patients. Data are expressed as mean ± standard deviation (SD)

| Parameters | Pre-exercise | Post-exercise | p |
|---|---|---|---|
| Age (years) | 39.47±6.3 | 39.69±4.8 | p=0.4 |
| Weight (kg) | 81.3±6.9 | 80.5±3.3 | p=0.3 |
| Smoker | 25% | 25% | p=0.4 |
| BMI (kg/m$^2$) | 33.9±5.9 | 32.59±4.0 | p=0.2 |
| Sex (Male/Female) | 12/20 | 12/20 | |
| FeNO (ppb) | 40.81±5.23 | 38.24±5.25 | p=0.2 |
| $FEV_1$ % | 89.25±9.26 | 93.64±6.25 | p=0.1 |
| FVC% | 88.65±4.42 | 89.46±5.08 | p=0.3 |
| ACT score | 22.32±3.16 | 22.47±3.94 | p=0.4 |

ACT: Asthma control test (Quality Metric Incorp.); BMI: body mass index; FeNO: fractional exhaled nitric oxide; $FEV_1$%: forced expiratory volume in 1 s; FVC%: forced vital capacity

**Table 2.** Laboratory findings of patients. Data are expressed as mean ± standard error mean (SEM)

| Markers | Pre-exercise | Post-exercise | p |
|---|---|---|---|
| Fasting glucose (mmol l$^{-1}$) | 4.5±0.6 | 4.5±0.2 | p=0.33 |
| Fasting serum free fatty acids (mmol l$^{-1}$) | 0.45±0.16 | 0.43±0.12 | p=0.01 |
| Fasting triglycerides (mmol l$^{-1}$) | 1.49±0.98 | 1.38±0.66 | p=0.002 |
| Hemoglobin (g/dL) | 13.2±0.5 | 13.48±0.4 | p=0.43 |
| White Blood Cell (mm$^3$) | 5456.256±159.13 | 5290.64±146.68 | p=0.39 |
| Eosinophil (mm$^3$) | 468.3±15. 3 | 464.5±12. 8 | p=0.16 |
| Total IgE (U/L) | 425.56±15.6 | 420.95±16.64 | p=0.3 |
| IL-1β (pg/mL) Serum | 29.69±1.25 | 23.32±1.62 | p=0.02 |
| IL-1β (pg/mL) Monocyte | 1.99±0.35 | 1.01±0.22 | p=0.003 |
| IL-10 (pg/mL) Monocyte | 1.64±0.02 | 1.21±0.03 | p=0.04 |
| IL-2 (pg/mL) Monocyte | 0.64±0.045 | 0.32±0.09 | p=0.001 |

## RESULTS

The patient population comprised 32 participants, of which 20 were women (62.5%) and 12 were men (37.5%). The patients' data were classified into two groups, pre- and post-exercise. There was no significant difference between participants regarding weight, body mass index, dyspnea scoring, and smoking after 12 weeks ($p>0.05$). Patients were followed up in unscheduled healthcare visits. The patients' ACT score (including subgroups of the test), FeNO levels, $FEV_1$%, and FVC% status were insignificant between the pre- and post-exercise groups ($p>0.05$). The main demographic and clinical findings of the participants are summarized in Table 1. The comparison of laboratory findings of the pre- and post-exercise groups is shown in Table 2. There was no significant difference between the pre- and post-exercise

groups for glucose metabolism (fasting glucose) and serum hemoglobin level, white blood cell count, and eosinophil and total IgE levels ($p>0.05$). There was a significant difference between the groups with respect to serum and monocyte IL-1β levels and monocyte IL-2 and IL-10 levels ($p=0.02$, $p=0.003$, $p=0.04$, $p=0.001$, respectively). There was also a significant difference between the pre- and post-exercise groups for fasting triglyceride and fasting serum free fatty acid levels ($p=0.002$ and $p=0.01$, respectively).

**DISCUSSION**

Cytokines play a dominant role in the pathophysiology of airway disease. Systemic interleukin levels are elevated in patients with asthma and airway hyperreactivity (10). In our study, regular exercise reduced anti-inflammatory cytokine levels, thereby decreasing dyspnea symptoms of the patients.

As exercise modulates immune responses in healthy people, exercise should be considered in the management of a disease in which the immune system has a vital role (11, 12).

Improvements in overall physical fitness with increased ventilatory capacity and reduced asthma-related symptoms because of aerobic exercise have been documented in several studies (5, 13). Even the American Thoracic Society guidelines for pulmonary rehabilitation program recommends low- to moderate-intensity aerobic exercise for patients with chronic respiratory disease (14).

Exercise-induced endogenous neuroendocrine factors, such as corticosterone and catecholamines, may explain mechanisms that underlie the effect of exercise (15). These neuroendocrine factors regulate immune-related events such as cytokine production, surface molecule expression, lymphocyte proliferation, and NF-κB activation (11, 15).

The effect of exercise on the lungs of patients with asthma has been previously examined. Emtner et al. (5) reported that adults with mild to moderate asthma who engaged in a 10-week physical training program demonstrated increased ventilatory capacity and reduced exercise-induced bronchospasm and asthma-related symptoms. During the long-term follow-up, it was observed that patients who performed moderate exercise for 3 years had reduced asthma-related emergency room visits during this time (16).

Evaristo et al. (17) performed a prospective, comparative, blinded, and randomized clinical trial with 48 patients with asthma who were grouped as aerobic and breathing exercises. The authors demonstrated that inflammation was reduced with exercise. Our findings support the findings of their study. Rearrangement of monocyte cytokine regulation is an important new mechanism in the pathogenesis of asthma.

Del Giacco et al. (18) evaluated the association among lymphocyte subtypes, cytokines, and long-term effects of exercise in professional soccer players. They showed that regular exercise reduced IL-4 levels, decreasing symptoms in the population with allergies and asthma. In addition, aerobic exercise was beneficial for preventing inflammation in allergic diseases, and treatment strategies were identified (18).

Vieira et al. (19) were the first to demonstrate a reduction or an improvement in each of the following after aerobic exercise in patients with asthma: airway epithelial oxidative and nitrosative stress, Th2 cytokines, chemokines, adhesion molecules, anti-inflammatory effects, growth factors, and matrix metalloproteases. These anti-inflammatory effects of NF-kB and the reduction of purinergic receptor P2X7 are related to the increased epithelial secretion of IL-10. Patients with severe asthma had regulatory T cell, which releases known anti-inflammatory cytokine IL-10 and is increased by anti-Ig E treatment (20). Compared with sedentary controls, in vitro exercise enhanced the suppression function of CD4(+), CD25(+), and Foxp3(+) Treg cells derived from OVA-treated mice. According to these data, exercise-induced Treg cell function can play a role in airway inflammation attenuation. These results also demonstrated that moderate intensity aerobic exercise training could change Treg cell function in the airway of a patient with asthma (21). In our study, there was a statistically significant decrease in the anti-inflammatory cytokine IL-10.

Although we found significant results in inflammatory marker levels, we were unable to clinically observe significant results reflected from spirometry values and in the ACT score because the study period was not long enough. The limitations of our study were small-sized study population, and we had no control group. Furthermore, these results should be verified with long-term training programs.

Future studies will shed light on the underlying mechanisms of the effect of exercise training. Exercise-induced endogenous glucocorticoids can explain some of the mechanisms. The hypothalamic–pituitary–adrenal axis is modulated with exercise by increasing the amount of endogenous glucocorticosteroids in the circulation. It is strongly suggested that endogenous glucocorticosteroids are a vital modulator of the course of an allergic disease. The circulating inflammatory cell count and lung function both vary with the diurnal production of endogenous glucocorticosteroids (22).

These findings demonstrated for the first time that aerobic exercise training significantly decreased the level amount and function of IL-10, monocyte and serum IL-1β, and monocyte IL-2 in the post-exercise group. In our study, regular exercise is related to reducing anti-inflammatory cytokine levels and is also related to reduction in free fatty acids and triglycerides.

**CONCLUSION**

In our study, there was a significant reduction in the anti-inflammatory cytokine IL-10 with exercise, and a decrease of dyspnea was observed. In addition, monocyte and serum IL-1β levels and monocyte IL-2 levels were significantly decreased in the inflammatory process. The significant reduction in free fatty acids and triglycerides of patients with asthma may decrease the risk for cardiac pathologies. Exercises that people can perform in their daily lives regulate asthma by affecting many cytokines.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Antalya University.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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## REFERENCES

1. Su MW, Tung KY, Liang PH, Tsai CH, Kuo NW, Lee YL. Gene-gene and gene-environmental interactions of childhood asthma: a multifactor dimension reduction approach. PLoS One 2012; 7: e30694. [CrossRef]
2. Miller RA. The aging immune system: Primer and prospectus. Science 1996; 273: 70-4. [CrossRef]
3. Yalcin AD, Gorczynski RM, Kahraman MS, Demirel MU, Terzioğlu E. CD40, CD45, CTLA-4 levels are eleveted in healthy older adults. Clin Lab 2012; 58: 449-56.
4. Ritz T, Rosenfield D, Steptoe A. Physical activity, lung function, and shortness of breath in the daily life of individuals with asthma. Chest 2010; 138: 913-8. [CrossRef]
5. Emtner M, Herala M, Stalenheim G. High-intensity physical training in adults with asthma. A 10-week rehabilitation program. Chest 1996; 109: 323-30. [CrossRef]
6. Mendes FA, Goncalves RC, Nunes MP, Saraiva-Romanholo BM, Cukier A, Stelmach R, et al. Effects of aerobic training on psychosocial morbidity and symptoms in patients with asthma: A randomized clinical trial. Chest 2010; 138: 331-7. [CrossRef]
7. Mendes FA, Almeida FM, Cukier A, Stelmach R, Jacob-Filho W, Martins MA, et al. Effects of aerobic training on airway inflammation in asthmatic patients. Med Sci Sports Exerc 2011; 43: 197-203. [CrossRef]
8. Yalcin AD, Gumuslu S, Parlak GE, Bisgin A, Yildiz M, Kargi A, et al. Systemic Levels Of Ceruloplasmin Oxidase Activity In Allergic Asthma And Allergic Rhinitis. Immunopharmacol Immunotoxicol 2012; 34: 1047-53. [CrossRef]
9. Global Initiative for Asthma: GINA Report, Global Strategy for Asthma Management and Prevention - updated 2012. Available at: www.ginasthma.org.
10. Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. Front Microbiol 2013; 10: 263. [CrossRef]
11. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev 2000; 80: 1055.
12. Ceddia MA, Voss EW, Woods JA. Intracellular mechanisms are responsible for the exhaustive exercise-induced suppression of macrophage antigen presentation. J Appl Physiol 2000; 88: 804.
13. Hallstrand TS, Bates PW, Schoene RB. Aerobic conditioning in mild asthma decreases the hyperpnea of exercise and improves exercise and ventilatory capacity. Chest 2000; 118: 1460. [CrossRef]
14. American Thoracic Society. Pulmonary rehabilitation-1999. Am J Respir Crit Care Med 1999; 159: 1666-82.
15. Nagatomi R, Kaifu T, Okutsu M, Zhang X, Kanemi O, Ohmori H. Modulation of the immune system by the autonomic nervous system and its implication in immunological changes after training. Exerc Immunol Rev 2000; 6: 54.
16. Emtner M, Finne M, Stalenheim G. A three year follow-up of asthmatic patients participating in a ten week rehabilitation program with emphasis on physical training. Arch Phys Med Rehabil 1998; 79: 539.[CrossRef]
17. Evaristo KB, Saccomani MG, Martins MA, Cukier A, Stelmach R, Rodrigues MR, et al. Comparison between breathing and aerobic exercise on clinical control in patients with moderate-to-severe asthma: protocol of a randomized trial. BMC Pulmonary Medicine 2014; 14: 160. [CrossRef]
18. Del Giacco SR, Scorcu M, Argiolas F, Firinu D, Del Giacco GS. Exercise training, lymphocyte subsets and their cytokines production: experience of an Italian professional football team and their impact on allergy. Biomed Res Int 2014;2014:429248. [CrossRef]
19. Vieira RP, Toledo AC, Ferreira SC, Santos AB, Medeiros MC, Hage M, et al. Airway epithelium mediates the anti-inflammatory effects of exercise on asthma. Respir Physiol Neurobiol 2011; 15: 383-9. [CrossRef]
20. Yalcin AD, Bisgin A, Gorczynski RM. IL-8, IL10, TGF-β and GCSF levels were increased in severe persistent allergic asthma patients with the anti-IgE treatment. Mediators Inflamm 2012; 2012: 720976. [CrossRef]
21. Lowder T, Dugger K, Deshane J, Estell K, Schwiebert LM. Repeated bouts of aerobic exercise enhance regulatory T cell responses in a murine asthma model. Brain Behav Immun 2010; 24: 153-9. [CrossRef]
22. Schleimer RP. Interactions between the hypothalamic-pituitary-adrenal axis and allergic inflammation. J All Clin Immunol 2000; 106: S270–4. [CrossRef]