Exercise and Asthma: What patients and doctors can do to improve outcomes

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Conflicts of Interest

Research
• Novartis
• GSK
• Forest
• Genentech
• Merck
• Astra Zeneca
• Teva

Objectives

• 1. To understand the physiology of EIB
• 2. To be able to diagnose EIB
• 3. To successfully treat EIB
• 4. To understand that patients with asthma avoid exercise
• 5. Demonstrate the importance of exercise in mice and humans with asthma
What causes EIB?

- A. Hot humid air
- B. Cold air
- C. Dry air
- D. Ozone
- E. Both cold and dry air

Ans: C


RHE = Respiratory Heat Exchange


Hyperpnea with Dry Air Reduces Mucociliary Clearance

Inflammatory Cells in sputum with EIB

Hallstrand et al, JACI 2005;116:586-593

Inflammatory mediators in EIB

Curr Opin Allergy Clin Immunol 2006;6:37-42

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DIFFERENTIAL DIAGNOSIS FOR EIB

• Asthma
• Pulmonary diseases other than asthma: bronchitis, pneumonia, emphysema, pulmonary embolism, CF, croup, bronchiolitis
• GE reflux
• Anaphylaxis
• Severe nasal congestion
• Laryngeal dysfunction, VCD
• Carcinoid tumor
• Cardiac
• Poor conditioning

Ans: B

What percent of children with dyspnea will have EIB on exercise challenge test?

• A. 1
• B. 11
• C. 55
• D. 85
• E. 95

Ans: B
Percent diagnosis of 117 children with exercised induced dyspnea diagnosed by treadmill

- Physiologic: 74%
- VCD: 13%
- EIB: 11%
- Restrictive: 7%
- Other: 5%

Weinberger et al 2008

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Is the history of EIB reliable in athletes?

- A. No
- B. Yes

Answer: no
Evaluation:

- Detailed history and exam
- Prevented by albuterol before exercise.
- PFT pre and post beta-agonists
- Challenge test, but what type?
  - free run
  - controlled exercise challenge
  - surrogate challenge

Exercise Challenge: external source dry air

<table>
<thead>
<tr>
<th>Step</th>
<th>Duration</th>
<th>Target HR</th>
<th>Treadmill Rate</th>
<th>Treadmill Incline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 minutes</td>
<td>50% MHR</td>
<td>2.5 mph</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>2 minutes</td>
<td>70% MHR</td>
<td>increase</td>
<td>increase</td>
</tr>
<tr>
<td>3</td>
<td>6 minutes</td>
<td>&gt;80% MHR</td>
<td>increase</td>
<td>increase</td>
</tr>
</tbody>
</table>
Positive test

- Adequate test is 8 minutes with >80% MHR achieved in 2 minutes, with 6 minutes at MHR
- Ventilation should be 40-60% MVV
- Positive EST: symptoms with 10% or more drop in FEV-1
- If negative on treadmill do a "in venue challenge" in children or surrogate test for adults

% fall in FEV1 after exercise in relation to PD15 to mannitol

![Graph showing the relationship between PD15 Mannitol (mg) and % fall in FEV1 to Exercise.](image)

Brannan et al, AJRCCM 1998; 158:1120-6

Relationship of sensitivity to EVH & sensitivity to 4.5% saline

![Graph showing the relationship between rank order of sensitivity to EVH and rank order of sensitivity to 4.5% hypertonic saline.](image)

Smith CM & Anderson SD Eur Respir J 1989; 2: 36-43
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The effect of inhaled corticosteroids on EIB is?

- 1. not effective to eliminate EIB
- 2. reduces EIB by 10%
- 3. reduces EIB by 25%
- 4. reduces EIB by 50%
- 5. reduces EIB by greater than 75%

Ans: 5

The effect of inhaled corticosteroids on EIB is?

- 1. not effective to eliminate EIB
- 2. reduces EIB by 10%
- 3. reduces EIB by 25%
- 4. reduces EIB by 50%
- 5. reduces EIB by greater than 75%

Ans: 5
Effect of progressive doses of ICS on EIA
Average attenuation of EIA was 30% for all doses, but with 25% in low
doses and 50% in higher doses of qd ciclesonide, compared to up to 65
to 80% in other bid studies.

Subbarao. JACI 2006; 117: 1008

Regular Use of Beta-agonists May Lead to Increased EIB

Comparing salmeterol, formoterol and terbutaline for EIA by change in % FEV-1 over time

Placebo's effect on % of patients responding post albuterol in minutes at week 0, 1 and week 4

Montelukast's effect on % of patients responding post albuterol in minutes at week 0, 1 and week 4

Salmeterol's effect on % of patients responding post albuterol in minutes at week 0, 1 and week 4

Effect of ipratropium bromide on EIA

All three arms had a 16% drop in FEV1 with exercise

Assessing effect of Nedocromil (NCS) and Cromolyn (SCG) on EIB

No significant difference in post exercise FEV1, complete protection or clinical protection between NCS and SCG.
Comparing salmeterol, montelukast, zileutin and placebo in change of FEV1 over hours after exercise

No difference between montelukast, zafirlukast or salmeterol, but zileutin at 8 and 12 hours was less effective

Coreno et al. JACI. 2000: 106; 500-6

Research Design

Do children with stable asthma benefit from addition of montelukast to inhaled corticosteroids: Randomized, placebo-controlled trial

Jacek Styrczak 1 , Agata Giersz-Hac 1 , Magdalena Zaczek 1 , Wiesława Jerzyńska 1 , Katarzyna Smejda 2 , Paweł Majak 2 , Joanna Jerzyńska 2 , Jacek Zabczyk 2 , Jacek Szarny 2

Research Design
exacerbations

3.7. EB and bronchial provocation tests

We found a higher frequency of positive exercise treadmill challenge test results in the placebo group (17.6%) compared to the montelukast group (0%) at the completion of the study.
Summary

Conclusion: It is reasonable to add montelukast to ICS therapy in asthmatic children during the school year, to lower cumulative ICS dose in children with well controlled asthma symptoms, as well as to reduce number of exacerbations, and to achieve better control of EIB.

Other Therapies

- Warming up
- Salt restriction
- Hydration
- Fish oil
- Magnesium
- Anti-oxidants vitamins

Alternative therapies should not replace traditional therapies since data supporting their use are limited.

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What % of Children with asthma admitted that asthma interfered with participation in school sports?

- A. 10
- B. 26
- C. 50
- D. 76
- E. 90

Answer: B
Avoid Activities Because of Symptoms

Q22a. Are there any activities that you would like to do but avoid doing because of coughing, wheezing, shortness of breath after exercise, play or exertion?
Base: Asthma patients that experience symptoms DURING OR SHORTLY AFTER exercise

Health Limits Activities: A Lot or Some

Q49. How much do you feel that your health limits what you can do in each of the following areas. Do you feel your health would limit you - a lot, some, only a little or not at all?
Base: Adult cross-section

Emotional Burden of Asthma by Symptoms

Q55. As a result of your asthma, how often do you feel …?
Base: All Asthma Patients, Unweighted
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What is the importance of exercise in the mouse model with asthma

Effect of exercise on inflammatory mediators of asthma

Pastva. J Immunol 2004;172;4520-4526
Exercise decreased VCAM-1 surface expression in the lungs of OVA-sensitized mice
The number of total cells, eosinophils and epithelial cells in the bronchoalveolar lavage.

R.P. Vieira et al. / Respiratory Physiology & Neurobiology 175 (2011) 383–389

Mice study design

Airway remodeling is reversed by aerobic training in a murine model of chronic asthma

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Summary

The effects were maintained until the 30th day. AT reverses AR after 15 days and this effect is preceded by the inhibition of leukocyte migration and occurs simultaneously with the reduction in the expression of inflammatory mediators and AR inducers.
RESULTS: In a total of 17 studies including 599 subjects, meta-analyses

- CONCLUSION: EXT was shown to improve asthma symptoms, QoL, exercise capacity, BHR, EIB, and FEV1 in asthmatics and improvements in BHR explained part of the improvement in QoL and exercise capacity. Thus, physical activity should be recommended as a supplementary therapy to medication. However, more well controlled studies should be performed assessing the relationship of physical activity, QoL, airway hyperreactivity, lung function and especially airway inflammation as well as medication intake.

Main results
Twenty-one studies (377 participants) were included in the review with two additional, 2012 studies identified in meeting classification. Physical training was well-tolerated with no adverse effects reported. None of the studies mentioned worsening of cardiac symptoms following physical training. Physical training showed marked improvement in cardiorespiratory fitness as measured by a statistically and clinically significant increase in maximum oxygen uptake (mean difference: 1.4 ± 0.7 mL/kg/min; 95% confidence interval: 0.3).

Physical training for cardiac (Review)

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What is the bottom line?

Improvements in aerobic fitness reduced bronchial hyperresponsiveness in one doubling dose of histamine and reduced systemic inflammation in patients with moderate or severe asthma under optimal medical treatment, suggesting that this therapy is an important adjuvant in asthma treatment.


Exercise Improves Asthma Outcomes
“Quality of Life”

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Exercise Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
</tr>
<tr>
<td></td>
<td>(n=12)</td>
<td>(n=11)*</td>
</tr>
<tr>
<td>AQQL Questionnaire</td>
<td>4.10 (1.65)</td>
<td>3.58 (1.35)</td>
</tr>
<tr>
<td>AQQL with Symptommetry</td>
<td>0.86 (1.10)</td>
<td>0.82 (0.79)</td>
</tr>
<tr>
<td>Percental Asthma Control</td>
<td>2.5% (0.7%)</td>
<td>2.3% (0.7%)</td>
</tr>
<tr>
<td>MIP-2500</td>
<td>5.36 (0.79)</td>
<td>5.10 (0.79)</td>
</tr>
<tr>
<td>Maximal V̇O₃</td>
<td>2.61 (0.27)</td>
<td>2.73 (0.29)</td>
</tr>
<tr>
<td>Submaximal V̇O₂/V̇V̇E</td>
<td>25.21 (0.72)</td>
<td>23.61 (0.80)</td>
</tr>
<tr>
<td>Maximal V̇E/V̇V̇E</td>
<td>19.65 (0.72)</td>
<td>19.65 (0.72)</td>
</tr>
<tr>
<td>Submaximal DI</td>
<td>0.02 (0.01)</td>
<td>0.02 (0.01)</td>
</tr>
<tr>
<td>Maximal DI</td>
<td>0.03 (0.01)</td>
<td>0.03 (0.01)</td>
</tr>
</tbody>
</table>

Exercise Improves Asthma Outcomes
“Symptom Free Days”

Mendes. CHEST / 138 / 2 / AUGUST, 2010
Exercise Improves Asthma Outcomes

**“Oxygen consumption”**

![Graph showing before and after effects of exercise on VO2max (% predicted) for trained and control groups.]

Mendes. CHEST / 138 / 2 / AUGUST, 2010

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### Exercise in children: all compared to open label conventional treated group

<table>
<thead>
<tr>
<th>Author</th>
<th>Duration</th>
<th>Frequency</th>
<th>Type</th>
<th>P value</th>
<th>Subject #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basaran 2006</td>
<td>2 months</td>
<td>1 hour, 3X a week</td>
<td>Aerobic, moderate</td>
<td>0.001</td>
<td>62</td>
</tr>
<tr>
<td>Fanelli 2007</td>
<td>4 months</td>
<td>1.5 hours, 2X a week</td>
<td>Aerobic to 70%</td>
<td>0.03</td>
<td>38</td>
</tr>
<tr>
<td>Flapper 2008</td>
<td>3 months</td>
<td>2.5 hours, 1 time a week</td>
<td>Aerobic</td>
<td>0.02</td>
<td>36</td>
</tr>
<tr>
<td>Moreira 2008</td>
<td>3 months</td>
<td>50 minutes, 2X weekly</td>
<td>Aerobic</td>
<td>0.004</td>
<td>34</td>
</tr>
</tbody>
</table>

D. Pacheco, J of Asthma, 2012

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### Exercise in adults: all compared to open label conventional treated group

<table>
<thead>
<tr>
<th>Author</th>
<th>Duration</th>
<th>Frequency</th>
<th>Type</th>
<th>P value</th>
<th>Subject #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner 2010</td>
<td>6 weeks</td>
<td>1.5 hour, 3X a week</td>
<td>Aerobic, moderate</td>
<td>0.04</td>
<td>34</td>
</tr>
<tr>
<td>Goncalves 2008</td>
<td>3 months</td>
<td>0.5 hours, 2X a week</td>
<td>Aerobic to 70%</td>
<td>0.001</td>
<td>20</td>
</tr>
<tr>
<td>Mendes 2010</td>
<td>3 months</td>
<td>0.5 hours, 2X a week</td>
<td>Aerobic to 70%</td>
<td>0.001</td>
<td>101</td>
</tr>
</tbody>
</table>

D. Pacheco, J of Asthma, 2012
Exercise in Adults, non aerobic: all compared to open label conventional treated group

<table>
<thead>
<tr>
<th>Author</th>
<th>duration</th>
<th>frequency</th>
<th>type</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabina 2005</td>
<td>1 month</td>
<td>1.5 hour, 2X a week</td>
<td>Yoga</td>
<td>NS 62</td>
</tr>
<tr>
<td>Thomas 2009</td>
<td>1 and 6 months</td>
<td>3 sessions Breathing exercises</td>
<td>NS 183</td>
<td></td>
</tr>
<tr>
<td>Vempati 2009</td>
<td>2 months</td>
<td>1.5 hours, daily</td>
<td>Yoga</td>
<td>0.013 57</td>
</tr>
</tbody>
</table>

D. Pacheco, J of Asthma, 2012

Intervention

The training program was standardized across all groups. A 15-min. warm-up period of walking at different speeds accompanied by light exercises of different muscle groups was followed by endurance and circuit training including upper and lower extremities for 30 minutes. Participants were encouraged to exercise at a cardiac frequency of 60% of the maximum heart rate reached during the initial cardiopulmonary exercise test. Such training intensity is generally rated as moderate.
Table 2: Peak exercise tolerance of training and control group before (T1) and after (T2) one year

<table>
<thead>
<tr>
<th></th>
<th>Training group</th>
<th>Control group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 15)</td>
<td>(n = 15)</td>
<td>(n = 14)</td>
<td>(n = 15)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td>HRrest (bpm)</td>
<td>78 ± 12</td>
<td>77 ± 11</td>
<td>76 ± 10</td>
<td>75 ± 9</td>
<td>76 ± 10</td>
</tr>
<tr>
<td>VO2peak (mL/kg/min)</td>
<td>50 ± 6</td>
<td>52 ± 5</td>
<td>49 ± 5</td>
<td>51 ± 4</td>
<td>49 ± 5</td>
</tr>
</tbody>
</table>

There were no significant differences between the two groups (p > 0.05).

Summary

**Conclusion:** A physiotherapy-led, long-term, moderate-intensity exercise program of one year duration can induce clinically relevant improvements in exercise capabilities and health-related quality of life in well-motivated adults with asthma.
The efficacy of aerobic training in improving the inflammatory component of asthmatic children. Randomized trial
Livio Barboza de Andrade*, Murilo C.A. Britto, Norma Lucena-Silva, Renan Garcia Gomes, José N. Figueroa

Intervention

The intervention consisted of supervised aerobic training performed three times a week for six weeks on an electric treadmill (Pro-Form®, model 329i, São Paulo, Brazil) in an appropriate environment at a temperature of 22–25 °C, with the participants dressed in sports shorts and wearing running shoes. The exercise consisted of a 5-min stretching period focused on the major muscle groups of the lower limbs, followed by 10-min of warm-up, 20-min of training in the first and second weeks and 30-min in the third to sixth weeks, followed by a 5-min cooling down period. The

| Table 3: inter- and intra-group comparisons of the variables related to pulmonary function and the distance covered in the 6 min walk test between the exercise and the control groups prior to commencement of the study, in the middle and at the end of the program in asthmatic children. |
|---|---|---|---|---|
| | Group | Variable | Baseline | Final | p-Value |
| | | | average (SD) | average (SD) | |
| BFV | Control | Exercise (E) | 17 | 2.34 (0.5) | 2.21 (0.1) | 0.198 |
| BFV | Control | Exercise (E) | 16 | 2.39 (0.7) | 2.28 (0.1) | 0.185 |
| BFV | Control | Exercise (C) | 17 | 2.36 (0.2) | 2.50 (0.1) | 0.007 |
| BFV | Control | Exercise (C) | 10 | 2.30 (0.2) | 2.38 (0.1) | 0.005 |
| BFV | Exercise (E) vs. Control (C) | Exercise (E) vs. Control (C) | 17 | 2.36 (0.2) | 2.50 (0.1) | 0.007 |
| BFV | Exercise (E) vs. Control (C) | Exercise (E) vs. Control (C) | 10 | 2.30 (0.2) | 2.38 (0.1) | 0.005 |
| BFV | Exercise (E) | Exercise (E) | 10 | 1.94 (0.2) | 1.85 (0.4) | 0.005 |
| BFV | Exercise (E) | Exercise (E) | 10 | 2.30 (0.2) | 2.38 (0.1) | 0.005 |
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| BFV | Exercise (E) | Exercise (E) | 10 | 2.30 (0.2) | 2.38 (0.1) | 0.005 |
### Table 4: Inter- and intra-group comparison of the variables for the quality of life questionnaire (PAQOL) prior to commencement of the aerobic training program and after the end of the program in asthmatic children.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>n</th>
<th>Baseline Mean (SD)</th>
<th>Final Mean (SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity</td>
<td>Control (C)</td>
<td>13</td>
<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
<td>0.933</td>
</tr>
<tr>
<td></td>
<td>Exercise (E)</td>
<td>9</td>
<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C vs. E: p-value</td>
<td></td>
<td>0.380</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Emotional function</td>
<td>Control (C)</td>
<td>13</td>
<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
<td>0.848</td>
</tr>
<tr>
<td></td>
<td>Exercise (E)</td>
<td>9</td>
<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C vs. E: p-value</td>
<td></td>
<td>0.293</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Control (C)</td>
<td>13</td>
<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
<td>0.377</td>
</tr>
<tr>
<td></td>
<td>Exercise (E)</td>
<td>9</td>
<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C vs. E: p-value</td>
<td></td>
<td>0.932</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>Control (C)</td>
<td>13</td>
<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
<td>0.642</td>
</tr>
<tr>
<td></td>
<td>Exercise (E)</td>
<td>9</td>
<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C vs. E: p-value</td>
<td></td>
<td>0.528</td>
<td>0.033</td>
<td></td>
</tr>
</tbody>
</table>

t-test, p < 0.05.

### Table 5: Comparison of intergroup and inter-group mean plasma cytokine measurements prior to commencement of the aerobic training program and after the end of the program in asthmatic children.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>n</th>
<th>Baseline Mean (SD)</th>
<th>Final Mean (SD)</th>
<th>p-Value</th>
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<td>IL-17</td>
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<td>13</td>
<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
<td>0.933</td>
</tr>
<tr>
<td></td>
<td>Exercise (E)</td>
<td>9</td>
<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C vs. E: p-value</td>
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<td>0.380</td>
<td>0.033</td>
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<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
<td>0.933</td>
</tr>
<tr>
<td></td>
<td>Exercise (E)</td>
<td>9</td>
<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C vs. E: p-value</td>
<td></td>
<td>0.380</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Control (C)</td>
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<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
<td>0.933</td>
</tr>
<tr>
<td></td>
<td>Exercise (E)</td>
<td>9</td>
<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>C vs. E: p-value</td>
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<td>0.033</td>
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<td>15.7 (0.3)</td>
<td>5.2 (0.3)</td>
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<tr>
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<td>Exercise (E)</td>
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<td>4.6 (0.4)</td>
<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
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<tr>
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<td>C vs. E: p-value</td>
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<tr>
<td>IL-2</td>
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<td>15.7 (0.3)</td>
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<tr>
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<td>Exercise (E)</td>
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<td>6.1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
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<td>C vs. E: p-value</td>
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<td>0.380</td>
<td>0.033</td>
<td></td>
</tr>
</tbody>
</table>

(1) Interleukin, (IFN Interferon, (TNF) tumor necrosis factor, Mann–Whitney test for independent samples (inter-groups), p < 0.05.

### Summary

In conclusion, six weeks of aerobic exercise no changes in plasma cytokine patterns in asthmatic children and adolescents; however, an improvement was found in functional capacity, maximal respiratory pressure, quality of life and asthma-related symptoms.
Summary:

Patients can improve their asthma by:

• 1. Using maintenance medications regularly can decrease EIB
• 2. Pre-medicating before exercise with albuterol can eliminate EIB in some
• 3. Warming up, hydrating and cooling down is important to decrease EIB
• 4. Exercising regularly can improve quality of life, improve asthma control and reduce T-helper cell induced inflammation

Please contact me at
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Have a great day