Plasma inflammatory biomarkers response to aerobic versus resisted exercise training for chronic obstructive pulmonary disease patients.

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a main risk for morbidity, associated with alterations in systemic inflammation. Recent studies proved that morbidity and mortality of COPD is related to systemic inflammation as it contributes to the pathogenesis of atherosclerosis and cardiovascular disease. However, increase of inflammatory cytokines adversely affects quality of life, alteration in ventilatory and skeletal muscles functions. Moreover, exercise training has many beneficial effects in correction of the adverse effects of COPD.

Objective: This study aimed to compare the response of inflammatory cytokines of COPD to aerobic versus resisted exercises.

Materials and methods: One hundred COPD diseased patients participated in this study and were randomly included in two groups; the first group received aerobic exercise, whereas the second group received resisted exercise training for 12 weeks.

Results: The mean values of TNF-α, Il-2, IL-4, IL-6 and CRP were significantly decreased in both groups. Also, there was a significant difference between both groups at the end of the study with more reduction in patients who received aerobic exercise training.

Conclusion: Aerobic exercise is more appropriate than resisted exercise training in modulating inflammatory cytokines level in patients with chronic obstructive pulmonary disease.

Keywords: Aerobic exercise, chronic obstructive pulmonary disease, inflammatory cytokines, resisted exercises.

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Introduction

Globally, chronic obstructive pulmonary disease (COPD) becomes more prevalent and becomes the third cause of death¹². However, by 2030 it is expected to have about 9 million patients to die due to COPD every year³. Moreover, the economic and health related burdens of COPD are enormous⁴.

Recently, studies proved that morbidity and mortality of COPD is related to systemic inflammation⁵ as it contributes to the pathogenesis of atherosclerosis and cardiovascular disease⁶. Moreover, increase of inflammatory cytokines adversely affects quality of life, alteration in ventilator and skeletal muscles functions⁷⁻¹².

The adverse effects of COPD are not limited to the respiratory system, but have many systemic adverse effects. Pulmonary rehabilitation has a vital role for management of the de-conditioning effects of systemic inflammation and other pathological features of COPD as exercise intolerance and poor quality of life¹³,¹⁴.

Exercise training has many beneficial effects in correction of the adverse effects COPD¹⁵,¹⁶. In healthy subjects, exercises were proved to improve immune system response¹⁷. Even low intensity exercise training was found to modulate the elevated level of systemic inflammation in patients with systemic inflammation¹⁸. However, poor quality of life and exercise intolerance can be modulated by exercise training in chronic obstructive pulmonary disease patients¹⁶.

As the ideal exercise intensity that efficiently modulates the elevated inflammatory cytokines is inconclusive, this

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study was designed to compare the impact of aerobic versus resisted exercises on inflammatory cytokines in chronic obstructive pulmonary disease patients.

Patients and methods

Subjects

One hundred chronic obstructive pulmonary disease patients participated in this study; their age ranged from 35 to 55 years and was selected from the Internal Medicine Department at King Abdul Aziz University hospital and other hospitals at Jeddah area. Exclusion criteria included smokers, cardiovascular disorders, alcohol abuse problems, hepatitis and renal diseases. Participants were randomly assigned into 2 groups; group (A) received aerobic exercise training for 3 months and group (B) received resisted exercise training. The original sample consisted of 178 participants who underwent the eligibility assessment. In the enrollment phase, 50 of them were excluded as they didn’t meet inclusion criteria and 13 refused to participate, then the randomization was done.

This substudy thus included 115 subjects (58 patients in group (A) received aerobic exercise training and 57 patients in group (B) received resisted exercise training). During the follow up, in group (A) 5 patients discontinued intervention (2 patients disliked the diet regimen, 2 patients had work related schedule problems and 1 patient discontinued due to unknown reasons) and in the group (B) 4 patients discontinued intervention (3 patients had work related schedule problems and 1 patient discontinued due to unknown reasons). In addition, 3 patients in group (A) and 3 patients in group (B) were excluded from the analysis due to insufficient blood samples. The Scientific Research Ethical Committee, Faculty of Applied Medical Sciences at King Abdulaziz University, approved this study. All participants signed the consent form before enrollment in the study.

Measurements

Blood samples were drained from the antecubital vein after a 12-h fasting, the blood samples were centrifuged at 4°C (1000 = g for 10 min). Interleukin-2 (IL-2), Interleukin-4 (IL-4), Interleukin-6 (IL-6) levels were analyzed by “Immulite 2000” immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). However, tumor necrosis factor- alpha (TNF-α) and C-reactive protein (CRP) levels were measured by ELISA kits (ELX 50) in addition to ELISA microplate reader (ELX 808; BioTek Instruments, USA). Measurements of TNF-α, IL-2, IL-4, IL-6 and CRP were taken before starting of the study (pre-test) and after 12 weeks (post-test).

Procedures

Following the previous evaluation, all participants were randomly assigned into two groups:

1. **Group (A)** participated in a treadmill aerobic exercise (Enraf Nonium, Model display panel Standard, NR 1475.801, Holand) which was conducted according to recommendation of aerobic exercise application approved by the American College of Sports Medicine. Training program included five minutes for warming up in the form of range motion and stretching exercises, thirty minutes of aerobic exercise training (60-70% of maximum heart rate) and five minutes of cooling down (on treadmill with low speed and without inclination). Participants had three sessions /week for 3 months with close supervision of a physical therapist.

2. **Group (B)** participated in the resistance exercises on some resistance gym machines (Nautilus Sports/Medical Industries, Independence, VA). The work load was approximately 70% to 85% of one resistance maximum (1-RM), as suggested by the recommendations of the American College of Sports Medicine (ACSM, 2002), with weekly load adjustments. The execution of physical exercises prioritized the major muscle groups followed by the smaller ones in terms of leg extension, hamstring curl, bench press with free weights, pulldown, pronation grip, arm curl with free weights, triceps extension with curl bar in the pulley, horizontal leg press, sit-ups, side elevation and calf. For abdominal exercises and calf three sets of 15 repetitions were prescribed during the entire experimental period. Resistance training (RT) was conducted in three weekly sessions, on alternating days and with the duration of approximately 60 min/session for 3 months. The volunteers were supervised by a physical therapist during the entire experimental period, on a maximum of 3 volunteers per physical therapist.

Statistical analysis

The mean values of the investigated parameters obtained before and after three months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups (P<0.05).
Results

The baseline characteristics of all participants are shown in Table (1). Most participants (61%) were men. Forty participants were assigned to the aerobic exercise group (n = 40; 25 males and 15 females), while the resistance exercise group (n = 40; 24 males and 16 females). None of the baseline characteristics differed significantly between the two groups is listed in table (1).

Table (1): Mean value of baseline and demographic data for participants in both groups:

<table>
<thead>
<tr>
<th></th>
<th>Mean ±SD</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Aerobic exercise group</td>
<td>Resistance exercise group</td>
</tr>
<tr>
<td>Age (year)</td>
<td>34.17± 6.25</td>
<td>36.14± 4.79</td>
</tr>
<tr>
<td>Gender ratio(male/female)</td>
<td>25/15</td>
<td>24/16</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.31 ± 5.42</td>
<td>58.92 ±7.53</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.27 ± 9.35</td>
<td>159.14 ± 8.63</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.53 ±1.81</td>
<td>20.93 ± 1.72</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>6.13 ± 1.52</td>
<td>5.84 ± 1.71</td>
</tr>
<tr>
<td>IL-2 (pg/ml)</td>
<td>8.10 ± 2.34</td>
<td>7.91 ± 2.48</td>
</tr>
<tr>
<td>IL-4(pg/ml)</td>
<td>5.83 ± 1.57</td>
<td>5.72± 1.65</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>8.32 ± 2.36</td>
<td>8.16 ± 2.21</td>
</tr>
<tr>
<td>CRP(mg/dl)</td>
<td>15.12 ± 3.48</td>
<td>14.95 ± 3.36</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.41 ± 0.76</td>
<td>2.29 ± 0.65</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.38 ± 0.57</td>
<td>1.14 ± 0.48</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>47.15 ± 8.14</td>
<td>45.82 ± 9.12</td>
</tr>
<tr>
<td>MVV (L/minute)</td>
<td>46.34 ± 10.18</td>
<td>43.25 ±11.23</td>
</tr>
</tbody>
</table>

BMI = Body mass index; TNF-α: tumor necrosis factor – alpha; IL-2: Interleukin-2; IL-4: Interleukin-4; IL-6: Interleukin-6; CRP: C-reactive protein; FVC = forced vital capacity; FEV₁= forced expiratory volume in the first second; FEV₁/FVC = Ratio between forced expiratory volume in the first second and forced vital capacity; FEF25-75= forced expiratory flow during the middle half of the FVC maneuver; MVV = Maximum voluntary ventilation.

The mean value of TNF-α, IL-2, IL-4, IL-6 and CRP were significantly lower in both groups after treatments (Table 2 & 3). There were significant differences between mean levels of the investigated parameters in group (A) and group (B) after treatment (Table 3) with more reduction in patients received aerobic exercise training. These results confirm that aerobic exercise is more appropriate than resisted exercise training in modulating inflammatory cytokines level of chronic obstructive pulmonary disease patients.
Table (2): Mean value and significance of TNF-α, IL-2, IL-4, IL-6 and CRP in group (A) before and after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Mean +SD</th>
<th>T- value</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>6.13 ± 1.52*</td>
<td>4.25 ± 1.43</td>
<td>6.83</td>
</tr>
<tr>
<td>IL-2 (pg/ml)</td>
<td>8.10 ± 2.34*</td>
<td>4.61 ± 1.92</td>
<td>7.64</td>
</tr>
<tr>
<td>IL-4 (pg/ml)</td>
<td>5.83 ± 1.57*</td>
<td>3.57 ± 1.41</td>
<td>6.91</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>8.32 ± 2.36*</td>
<td>5.16 ± 1.97</td>
<td>7.32</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>15.12 ± 3.48*</td>
<td>8.93 ± 3.16</td>
<td>8.21</td>
</tr>
</tbody>
</table>

TNF-α: tumor necrosis factor – alpha; IL-2: Interleukin-2; IL-4: Interleukin-4; IL-6: Interleukin-6; CRP: C-reactive protein; (*) indicates a significant difference between the two groups, P < 0.05.

Table (3): Mean value and significance of TNF-α, IL-6, IL-8 and CRP in group (B) before and after treatment.

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<th>Mean +SD</th>
<th>T- value</th>
<th>Significance</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>5.84 ± 1.71*</td>
<td>5.03 ± 1.52</td>
<td>3.41</td>
</tr>
<tr>
<td>IL-2 (pg/ml)</td>
<td>7.91 ± 2.48*</td>
<td>6.53 ± 2.15</td>
<td>3.27</td>
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<tr>
<td>IL-4 (pg/ml)</td>
<td>5.72 ± 1.65*</td>
<td>4.61 ± 1.38</td>
<td>3.48</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>8.16 ± 2.21*</td>
<td>6.74 ± 2.15</td>
<td>3.56</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>14.95 ± 3.36*</td>
<td>11.52 ± 3.16</td>
<td>4.13</td>
</tr>
</tbody>
</table>

TNF-α: tumor necrosis factor – alpha; IL-2: Interleukin-2; IL-4: Interleukin-4; IL-6: Interleukin-6; CRP: C-reactive protein, (*) indicates a significant difference between the two groups, P < 0.05.

Table (3): Mean value and significance of TNF-α, IL-6, IL-8 and CRP in group (A) and group (B) after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Mean +SD</th>
<th>T- value</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group (A)</td>
<td>Group (B)</td>
<td></td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>4.25 ± 1.43*</td>
<td>5.03 ± 1.52</td>
<td>3.46</td>
</tr>
<tr>
<td>IL-2 (pg/ml)</td>
<td>4.61 ± 1.92*</td>
<td>6.53 ± 2.15</td>
<td>3.72</td>
</tr>
<tr>
<td>IL-4 (pg/ml)</td>
<td>3.57 ± 1.41*</td>
<td>4.61 ± 1.38</td>
<td>3.41</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>5.16 ± 1.97*</td>
<td>6.74 ± 2.15</td>
<td>3.52</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>8.93 ± 3.16*</td>
<td>11.52 ± 3.16</td>
<td>4.05</td>
</tr>
</tbody>
</table>

TNF-α: tumor necrosis factor – alpha; IL-2: Interleukin-2; IL-4: Interleukin-4; IL-6: Interleukin-6; CRP: C-reactive protein, (*) indicates a significant difference between the two groups, P < 0.05.
**Discussion**

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality; it is currently the fourth highest cause of death in the world, and is predicted to be the third leading cause of mortality worldwide by the year 2020\(^{21,22}\). Inflammation is one of key processes in the pathogenesis of COPD\(^{23,24}\). Chronic obstructive pulmonary disease (COPD) is understood as a systemic inflammation mediated by cigarette smoking and air pollution, and subsequently induced inflammatory cytokines, such as tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-6, and IL-8\(^{25}\). To date, there are relatively few adequately-powered, trials of an exercise intervention on inflammatory biomarkers in individuals with COPD, to the best of our knowledge, this is the first study to compare the response of inflammatory cytokines of COPD to aerobic versus resisted exercises. In our study, the mean values of TNF-\(\alpha\), IL-2, IL-4, IL-6 and CRP were significantly decreased in both groups. Also; there was a significant difference between both groups at the end of the study with more reduction in group (A) who received aerobic exercise training. This means that in chronic obstructive pulmonary disease patients aerobic exercise is more appropriate for modulating inflammatory cytokine levels than is resisted exercise training. These results are in line with many previous studies.

Dekker et al. stated that a 12-week exercise intervention resulted in a significant decrease in circulating IL-6 in subjects with type 2 diabetes mellitus who underwent an exercise program without weight loss\(^{26}\). Also, Mikkelsen et al. proved that life-long endurance exercise was associated with a lower level of the inflammatory markers CRP and IL-6 in elderly subjects\(^{27}\). While, Sugawara et al. concluded that the levels of elevated inflammatory cytokines decreased significantly after intervention with an anti-inflammatory nutrition combined with the low-intensity exercise in stable elderly COPD patients\(^{28}\). In addition, there is evidence of lowered IL-6 and TNF-\(\alpha\) after prolonged exercise in obese women\(^{29}\) and decreased TNF-\(\alpha\) after 12 weeks of aerobic exercise in patients with heart disease\(^{30}\). Moreover, in obese postmenopausal women with type 2 diabetes, 14 weeks of aerobic exercise decreased CRP by 15% and marginally decreased IL-6 (\(p=0.07\))\(^{31}\). Likewise, 12 weeks of exercise reduced IL-18 levels by 17.5% in patients with metabolic syndrome\(^{32}\). In one of the largest, yet non-randomized, exercise studies conducted to date (HERITAGE Family Study), plasma CRP was significantly reduced with 20 weeks of aerobic training only in the sub-group of persons with a high baseline CRP. The approximate 29% CRP decrease in this study was not mediated by changes in body weight\(^{33}\).

Neto et al. proved that high-intensity exercise training program induced an improvement of biomarkers of inflammation (a reduction of IL-6, TNF-\(\alpha\) & leptin and an increase of interleukin-4 (IL-4) & interleukin-10 (IL-10) thus indicating that exercise has a full anti-inflammatory effect\(^{34}\). While, Balducci et al. applied their study on eighty-two patients were randomized into 4 groups: sedentary control (A) received low-intensity aerobic exercise, group (B) performed high-intensity aerobic, group (C) performed aerobic and resistance exercises and group (D) performed exercise (with the same caloric expenditure) for 12 months. Physical exercise in type 2 diabetic patients with metabolic syndrome was associated with a significant reduction of inflammatory biomarkers\(^{35}\). Moreover, Brooks et al. stated that a 16-week resistance training intervention reduced CRP and increased adiponectin levels in older adults with type 2 diabetes\(^{36}\).

In contrast to the previous studies Rall et al., reported that 12 week of high-intensity progressive resistance strength training does not affect TNF\(\alpha\), IL-6, or interleukin-2 (IL-2) production\(^{37}\). Also, Rodrigo and colleagues founded that weight-lifting exercises for 6 muscle groups in the upper and lower limbs (2 sets of 8 repetitions each), and the initial load was set at 80% of the 1-repetition maximum load for one month led to improvement in the six minute walking test, health related quality of life (HRQOL) and lower-limb muscle strength, without altering the levels of systemic inflammation\(^{38}\). Similarly, McFarlin et al. did not observe an improvement in inflammatory cytokine expression (IL-6 and TNF\(\alpha\)) in resistance-trained older women (65–80 years), compared to untrained controls after an acute bout of resistance exercise\(^{39}\). The small sample sizes in both of these studies (\(n=6–10\) per treatment group) may have contributed to this null effect. Moreover, van Helvoort et al. conducted a study on sixteen COPD patients who performed a maximal incremental bicycle test and proved that COPD patients are exposed to systemic inflammation that is intensified by exhaustive exercise\(^{40}\).
On the other side, Rosety-Rodriguez and colleagues in their study on young male adults with Down Syndrome for twenty-four years who were assigned to perform resistance circuit training with 6 stations, 3 days per week for 12 weeks. Exercise intensity was based on function of the 8 resistance maximum (RM) assessments proved that resistance circuit training improved low-grade systemic inflammation in male sedentary adults with Down syndrome. Also, Nikseresht et al. conducted a 12 week study on middle-aged obese men and proved that aerobic interval training which consisted of running on a treadmill (4 sets of 4 minutes at 80-90% of maximal heart rate, with 3-minute recovery intervals) had better anti-inflammatory effects (as indicated by the IL-10: TNF-α ratio) than nonlinear resistance training which consisted of 40-65 minutes of weight training at different intensities with flexible periodization. While, Kohut et al. proved that aerobic exercise intervention, but not flexibility/resistance exercise, reduces serum inflammatory cytokines including interleukin-18 (IL-18), CRP and IL-6 among older adults; this reduction would be mediated, in part, by improvements in psychosocial factors and/or by β-adrenergic receptor mechanisms.

The exact mechanisms by which physical activity may reduce inflammation are not entirely understood, there are some data pointing to factors that may contribute to an effect of repeated bouts of muscle contraction leading to improvements in inflammatory status over time. Exercise training-induced improvements in inflammatory status may also result from the modulation of intracellular signaling pathways and cellular function that are mediated by nitric oxide (NO) and ROS. Also, exercise training decreases mononuclear cell production of atherogenic cytokines (TNFα and IL-1α), while the production of atheroprotective cytokines (IL-10, IL-4, and transforming growth factor beta-1 (TGFβ1) is increased. Exercise training also reduces CD14+CD16+ monocyte number, as well as TNF-α production by monocytes and reduces monocyte cell-surface expression of toll-like receptor-4 (TLR4), a lipopolysaccharide (LPS) signaling receptor that likely contributes to attenuation of acute immune responses to infection or trauma. Similarly, higher-intensity aerobic exercise training reduces stimulated production of TNF-α by monocytes. Thus, this data points to an adaptive down-regulation of cytokine release from innate immune cells in response to regularly performed muscular contraction. Moreover, the potential mechanisms for the anti-inflammatory effect of exercise may include reduced percentage of body fat and macrophage accumulation in adipose tissue, muscle-released interleukin-6 inhibition of tumor necrosis factor-a, and the cholinergic anti-inflammatory pathway. Finally, within the limit of this study, aerobic exercise is more appropriate for modulating inflammatory cytokine levels than resisted exercise training in patients with chronic obstructive pulmonary disease.

The current study has important strengths and limitations, the major strength is the supervised nature of the study in addition to the number of subjects in our study was relatively larger than those of previous studies in COPD. However, one of the limitations of this study is that the results were based on selection of participants with moderate degree COPD severity.

Conclusion
The current study provides evidence that aerobic exercise is more appropriate for modulating inflammatory cytokine levels than resisted exercise training in patients with chronic obstructive pulmonary disease.

Acknowledgment
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