Serum ghrelin response to long-term regular exercise is not related to dynamic lung volumes in mild to moderate asthma

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Abstract

Ghrelin, a 28-amino-acid peptide, is known to be associated with obesity and diabetes, although no direct evidence is currently available regarding its role in asthma. The purpose of this study was to compare serum ghrelin between sedentary adult men with mild to moderate asthma (n=28) and healthy (n=15) subjects matched for age (38 ± 6 year), height (174 ± 7 cm) and BMI (32 ± 5.2 kg/m2) that participated in this study by accessible sampling. Asthma patients were divided into experimental (exercise) and control (no training) groups by randomly. At first, fasting blood samples were collected in asthma and none-asthma participant in order to comparing serum ghrelin between them. Blood samples were repeated in experimental and control groups of asthma patients after an aerobic exercise program (60 min, 3 days/week for 3 months) to determine serum ghrelin response to exercise training. Spirometry test was performed before and after exercise program in two asthmatic groups. Statistical analysis was performed with the SPSS software version 15.0 using an independent paired t-test. At baseline, serum ghrelin levels were significantly higher in asthma patients in comparison to healthy subjects. Compared to pre-training, the ghrelin levels decreased (P<0.01) and respiratory functional increased (p<0.05) significantly after exercise program in the experimental but not in the control groups. There were no correlations between serum ghrelin concentrations and spirometry markers in
baseline or after exercise training in patients (p≥0.05). Based on this data, it was concluded that although aerobic exercise training affects bout serum ghrelin and respiratory functional in asthmatic patients, but baseline relationship between them and their responses to exercise are independent of each other.

**Key words:** Ghrelin, Asthma, Aerobic exercise, Spirometry.

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**Introduction**

Asthma is an inflammatory disease with many clinical phenotypes in both adults and children. Its major characteristics include a variable degree of airflow obstruction and chronic airway inflammation (Busse *et al.*, 2001). A growing body of literature suggests that impaired lung function as measured by FVC or FEV1 is a powerful predictor of nonfatal ischemic heart disease and of mortality due to cardiovascular disease (Sin *et al.*, 2005; Schroeder *et al.*, 2003). Increased levels of systemic markers of inflammation such C reactive protein (Aronson *et al.*, 2006), interleukine-6 (Neveu *et al.*, 2009) have been reported in patients with impaired lung function due to obstructive or restrictive lung disease. Some other studies found lower serum adiponectin in asthma patients when compared to healthy people (Sood *et al.*, 2008; Nagel *et al.*, 2008). Several studies have also reported an association between leptin and respiratory functional markers (Nagel *et al.*, 2008; Shore *et al.*, 2005).

These studies somehow suggest that these inflammatory factors affect the airway resistance and respiratory function. On the other hand, the role of these markers secreted by adipose tissue in the prevalence of other chronic diseases such as diabetes, heart and vascular diseases, metabolic syndrome, obesity and asthma has been repeatedly reported (Neveu *et al.*, 2009; Aggarwal, 2003; Gupta, 2008; Nayak *et al.*, 2010). In addition, some other studies suggest disorder in systemic ghrelin levels in the above mentioned diseases (Peng *et al.*, 2007; Luo *et al.*, 2005; Eker *et al.*, 2010). As these resources have observed that increased ghrelin levels is associated with reduced insulin secretion and increased serum glucose levels (Broglio *et al.*, 2001). However fewer studies have pointed to the circulating ghrelin role on markers determining the respiratory function in respiratory diseases, particularly asthma. It is hypothesized that adipokines such as leptin and adiponectin
affect spirometric indices determining respiratory function in obese patients by inhibiting or enhancing proliferation of smooth muscle cells of the respiratory pathways (Shin et al., 2008; Shore et al., 2006). Besides, the role of exercise as a none-pharmological factor on plasma or serum levels of these factors secreted from adipose tissue has been studied repeatedly in patients with asthma (Baek et al., 2011). However there seems to be no study conducted on effects of the short or long term exercise on plasma ghrelin levels in asthmatic patients. This study aims to compare the serum levels of ghrelin in asthmatic patients and healthy subjects, and also to determine the role of an aerobic training program on serum levels of this peptide hormone and to establish its relationship with changes in spirometric indices in response to exercise in these patients.

Subjects and Methods
The present study was carried out on adult males with moderate asthma to examine the effects of long-term aerobic exercise program on serum ghrelin and respiratory function. For this purpose, twenty eight males (Age; 38 ± 6 year, height; 174 ± 7 cm, BMI; 32 ± 5.2 kg/m2) with moderate asthma divided to experimental (exercise training) and control (no training) groups by randomly. Fifteen healthy males matched age, BMI and body weight were also participated in study merely to compare baseline serum ghrelin with asthmatic patients. All participants gave their informed written consent before participation in accordance with the ethical guidelines set by Islamic Azad University.

Asthma intensity was measured by a specialist physician through measuring spirometry indicators (using pyrometer Model Minispiire, made in Italy). Participants were included if they had not been involved in regular physical activity in the previous 6 months. Inclusion criteria to study for asthma group were as existing asthma for at least 3 years. Participants were non-athletes, non-smokers and non-alcoholics. Participants had no evidence of coronary artery disease; tobacco use; participation in exercise/diet programs; or use of systemic steroids, diabetes treatments and β-blockers.

Anthropometric measurements of height, weight and percent body fat measurements were taken pre- and post-exercise training in the physiology laboratory. Body weight
was measured in duplicate in the morning following a 12-h fast. Standing height was measured to the nearest 0.1 cm with the use of a wall-mounted stadiometer. Body mass index was measured for each individual by division of body weight (kg) by height (m²). Body composition monitor (BF508-Omron made in Finland) with a precision error of less than 100 g was used to measure weight and body fat percentage of the subjects.

**Blood Samples and spirometry:** At first, fasting blood samples were collected in asthma and none-asthma participants in order to comparing serum ghrelin between them. At baseline, spirometry test was performed for measuring FEV1, FVC, FEV1/EVC and other markers of respiratory functional asthmatic groups. Blood samples and spirometry were repeated in experimental and control groups of asthma patients after an aerobic exercise program (48 h after last exercise session) for determine serum ghrelin response to exercise training. The subjects were advised to avoid any physical activity or exercise 48 hours before the exercise test. Subjects were asked to refrain from tea, coffee, chocolates and caffeinated soft-drinks on the day of recording Spirometry. The intra-assay and inter-assay coefficient of variation of ghrelin (Biovendor, Austria) were 8.10% and 8.3% respectively.

**Exercise program:** Patients in experimental group trained under supervision (60 min, 3 days/week for 3 months) at intensity of 60-80% of HRmax. Adherence to the exercise prescription was documented through the use of Polar heart rate monitors, and subjects received feedback if training intensities were either too high or low in comparison with desirable intensities. After a warm-up, subjects trained for approximately 30 - 45 min and 5–10 min of cool down activity. Aerobic exercises in each session included walking on a treadmill and stationary cycling. Initially, subjects exercised at low intensity and the intensity of exercise was gradually increased to 80% of peak heart rate in next sessions. Attendance was taken at each exercise session to monitor compliance with the program. Subjects were contacted if an exercise session was missed. In this 12-week period, participants in the control group were barred from participating in any exercise training.

**Statistical analysis:** All values are given as mean and standard deviation. Statistical analysis was performed with the SPSS software version 15.0. Normal distribution of
data was analyzed by the Kolmogorov-Smirnov normality test. Baseline characteristics were compared by using independent t-tests. Student’s paired ‘t’ test was applied to compare the pre and post training values. Pearson correlation coefficients were used to determine the associations between serum ghrelin with spirometry markers. An alpha-error below 5% was considered as statistically significant.

Results
Table 1 shows the descriptive anthropometric, spirometric and biochemical features of the study groups. All values are represented as mean ± SD. Based on Data by independent t-tests at baseline, there were no differences in the age, body weight, BMI and other anthropometrical markers between asthma and healthy subjects (see Table 1). At baseline serum ghrelin levels in asthma patients subjects were significantly higher than those without asthma symptoms (p=0.032). Asthma patients have lower FEV1, FVC and FEV1/FVC than healthy individuals at baseline (p<0.05). Aerobic exercise training decreases serum ghrelin compared to baseline levels (p=0.028), but its level was not changed in control group (Fig 1). Exercise training resulted in significant increase in all spirometry markers in experimental group (p<0.05), but these variables remained without change in control subjects. There were no correlations between serum ghrelin concentrations and spirometry markers in baseline or after exercise training in patients.

![Fig 1](image_url) Serum ghrelin before and after aerobic exercise program in studied patients. Serum ghrelin levels exhibited a statistically significant decrease by acerbic program when compared to baseline values. Each line in the graph represents changes in serum ghrelin of one subject in response aerobic exercise training.
The major finding of this investigation was decreased serum ghrelin by aerobic exercise program in studied asthma patients. Exercise training were also increased respiratory functional in these patients. Ghrelin is one of the circulation peptides, which is involved in regulating food intake and body weight by sending signals to the hypothalamus (Kojima et al., 1999). This 28 amino acid peptide hormone is secreted primarily by the stomach and to some extent by other tissues such as the gastrointestinal tract, pancreas and saliva (Date et al., 2000; Date et al., 2002). Review of research findings show that ghrelin plays an important role in obesity and some related diseases (Tong et al., 2010).

Ghrelin role in glucose homeostasis as well as lipid and carbohydrate metabolism has also been reported in some studies (Zigman et al., 2005; Sun et al., 2008). As ghrelin administration in humans has led to decreased levels of insulin and increased glucose concentrations (Broglio et al., 2001; Broglio et al., 2004). A recent study also showed that ghrelin consumption by mice with abnormalities in lipid metabolism in adipose tissue, liver and skeletal muscle is associated with increased body weight (Barazzoni et al., 2005). Asthma is a chronic inflammatory disorder of the airways in which mast cells, eosinophils and T-lymphocytes play a major role (Sahoo et al., 2009). The current management of asthma focuses on the optimal control of symptoms and the reduction of airway inflammation as a central component of asthma control. Recent evidence has shown that aerobic physical training can

**Table 1**: Mean and standard deviation of anthropometrical, spirometric and biochemical variables of healthy and diabetic groups.

<table>
<thead>
<tr>
<th>Group Variable</th>
<th>Healthy (baseline)</th>
<th>Experimental Asthma Pretest</th>
<th>Experimental Asthma post-test</th>
<th>Control Asthma Pretest</th>
<th>Control Asthma post-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>36 ± 6</td>
<td>38 ± 5</td>
<td>38 ± 5</td>
<td>37 ± 6</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.2 ± 7.5</td>
<td>173.6 ± 6.5</td>
<td>173.6 ± 6.5</td>
<td>174.4 ± 7.1</td>
<td>174.4 ± 7.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>99.2 ± 7.6</td>
<td>97.5 ± 6.4</td>
<td>94.6 ± 9.3</td>
<td>98 ± 7.2</td>
<td>98.2 ± 6.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.4 ± 6.41</td>
<td>32.1 ± 5.16</td>
<td>31.2 ± 5.16</td>
<td>32.34 ± 5.25</td>
<td>32.40 ± 6.3</td>
</tr>
<tr>
<td>FVC</td>
<td>97.3 ± 11</td>
<td>86.1 ± 6.3</td>
<td>96.3 ± 8.1</td>
<td>85.6 ± 6.4</td>
<td>86 ± 6.3</td>
</tr>
<tr>
<td>FEV1</td>
<td>97.8 ± 9.6</td>
<td>76.2 ± 5.6</td>
<td>85.2 ± 6.5</td>
<td>75.8 ± 6.5</td>
<td>76.1 ± 5.2</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>83.1 ± 7.6</td>
<td>69.8 ± 4.8</td>
<td>76.2 ± 4.2</td>
<td>70.2 ± 4.4</td>
<td>69.4 ± 5.3</td>
</tr>
<tr>
<td>Serum Ghrelin (Pg/ml)</td>
<td>58 ± 9</td>
<td>64 ± 7</td>
<td>57 ± 8</td>
<td>66 ± 7</td>
<td>64 ± 9</td>
</tr>
</tbody>
</table>

*FVC*: forced vital capacity, *FEV1*: forced expiratory volume in 1 s, *FEV1/FVC*: forced expiratory volume in 1 s / forced vital capacity
modulate inflammation responses in healthy or diseases individuals (Pedersen et al., 2009; Woods et al., 2000). It was repeatedly reported that serum ghrelin affect by exercise training in differ population. In this area, 4 weeks of exercise brought about a significant reduction in circulation ghrelin (Vestergaard et al., 2007). But despite these findings, long-term exercise program on obese subjects in a recent study was associated with weight loss led to a significant increase in plasma ghrelin concentration (Kelishadi et al., 2008). But in another study, 60 minutes of exercise on the treadmill did not lead to changes in obestatin and ghrelin levels (Wang et al., 2008).

Despite these finding regarding ghrelin responses to exercise training, no direct evidence is currently available regarding the role of aerobic exercise program on serum ghrelin in asthma patients. In the present study, the ghrelin levels decreased significantly after aerobic exercise training in exercise group but not in the control subjects. On the other hand, exercise training was associated with increased respiratory functional in these patients. In other words, with aerobic exercise training, the spirometry parameters such as FVC, FEV1 and FEVI/FVC showed a significant improvement when compared to baseline levels. In fact, our study finding showed that aerobic exercise for long time decreases serum ghrelin and decreases respiratory functional.

In the face of the said findings, the question is raised whether the reduction in serum ghrelin levels due to exercise is related to increased respiratory function in these patients. Although some previous studies have pointed to the fact that disorder in some inflammatory or anti-inflammatory cytokines such as leptin or adiponectin or other peptides are associated with changes in respiratory function factors such as FVC and FEV1 and FEVI/FVC particularly in asthmatic patients (Shin et al., 2008; Shore et al., 2006). However, merely based on the findings of our study, it can not be concluded that serum ghrelin levels are associated with spirometric indices or respiratory functional. Because, although it was found in this study that asthmatic patients have higher levels of serum ghrelin than in healthy individuals, but no study has so far pointed to ghrelin's role in the airway resistance in asthma patients or other respirator diseases. On the other hand, in the present study, no significant relationship was observed between baseline levels of serum ghrelin with any of
spirometric indices. These findings indicate that the increase in serum ghrelin levels in asthmatic patients compared with healthy subjects with decreased respiratory function, are completely independent of each other. On the other hand, in the present study, although exercise led to reduction of ghrelin and increase of spirometric indices, the findings resulting from Pearson test showed that there was no significant correlation between these variables after exercise. These findings support the hypothesis that changes in serum ghrelin are independent of decreased respiratory function in these patients. But it is possible ghrelin indirectly affects respiratory function in patients with asthma or other respiratory diseases by affecting the levels of other peptide hormones and this signifies the need for further studies in this field.

Additionally, it is also possible that ghrelin affects respiratory functional indirectly by stimulating the secretion of counter-regulatory hormones that affect respiratory functional. As for possible indirect mechanisms of ghrelin action on respiratory function, previous studies have shown that serum ghrelin is related with cortisol (Tong et al., 2010). In this area, data of a study revealed a significant relationship between the plasma cortisol concentration and the rate of decline of FEV1 after adjustment for age, height, and smoking status (Sparrow et al., 1993).

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**References**


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