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# Weight Reduction Modulates Ventilatory Functions, Inflammatory and Adipocytokines in Obese Asthmatic Children

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**Abstract:** Pediatric asthma and obesity are two of the most prevalent and problematic public health challenges. Obesity is proposed to represent an important predisposing condition to serious respiratory disturbances including asthma. The effects of consistent weight loss on asthma control and inflammatory and adipocytokines cytokines are not well known. This study was an attempt to measure the effects of weight reduction on cytokines and ventilatory functions in obese children with bronchial asthma. Forty obese children with bronchial asthma (21 boys and 19 girls) with mean age 12.51±4.86 years divided into two equal groups. The training group received diet regimen, exercise training in addition to the medical treatment for two months, whereas the control group received the medical treatment only. Results revealed that the mean values of C- reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL-6), Leptin and body mass index (BMI), were significantly decreased with significant improvement of ventilatory function test of forced vital capacity (FVC) and forced expiratory volume in the first second ($FEV_1$) of the training group. Also, there was a significant difference between the groups after treatment on all measured variables. In conclusion, weight reduction improves ventilatory functions and modulates adipocytokines and inflammatory cytokine levels in obese children with bronchial asthma.

**Key words:** Obesity · Asthma · Weight reduction · Cytokines and ventilatory function tests

## INTRODUCTION

The prevalence of childhood obesity has more than tripled over the past five decades. Obesity results in low lung volumes, likely through increased loading of the chest wall and abdomen. The prevalence of asthma in children has paralleled the rise in obesity; obesity may increase the severity of asthma [1]. Asthma and obesity have serious health consequences and significant financial costs. The burden of obesity on pulmonary function in children is highlighted by the increased frequency of bronchial hyper-responsiveness, increased number of prescribed medications and inhaled corticosteroid use and reduced peak expiratory flow rate in overweight / obese asthmatic children as compared to non-overweight asthmatic children Excess body weight is also associated with an increase in the number of school days missed by asthmatic children and significantly reduced quality of life [2].

Obesity creates a proinflammatory environment via an increase in adipocyte volume and number and production of inflammatory mediators produced by tissue-resident macrophages and adipocytes, including tumour necrosis factor-α (TNF-α), interleukins, leptin and adiponectin. The presence of excess adiposity therefore provides a consistent stimulus for chronic, low grade systemic inflammation [3]. There is also evidence of systemic inflammation in children with asthma which may be exacerbated by the systemic inflammatory process caused by obesity [4].

Leptin typically stimulates a Th1 cytokine response that leads to the production of additional pro-inflammatory cytokines. The amount of leptin secreted by adipose tissue is in direct proportion to the

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level of adiposity. Leptin may contribute to asthma pathogenesis via vascular endothelial growth factor (VEGF)-induced airway remodelling and angiogenesis, as VEGF release from human airway smooth muscle cells is enhanced following leptin stimulation [5].Cross-sectional studies have found significantly higher leptin levels in healthy weight asthmatic children versus healthy controls [6].

Interleukin-6 IL-6 contributes to inflammation by raising CRP levels and suppressing adiponectin production. Multiple cross-sectional studies have identified significantly elevated levels of IL-6 in obese compared to non-obese children and adolescents [7, 8]. Cell studies obtained from children with and without asthma have found a significantly increased release of IL-6 from the epithelial cells of children with asthma. Increased levels associated with obesity therefore have the potential to contribute to increased pulmonary inflammation and asthma symptoms [9].

Tumour Necrosis Factor-alpha (TNF-α) contributes to a proinflammatory environment by stimulating NF-kB signalling and increasing production of acute phase proteins and cytokines [10]. Levels of TNF-α have been found to be significantly higher in obese compared to non-obese children [11]. TNF-α receptors are located on ASM cells and human *in vivo* studies have demonstrated airway hyper-responsiveness to TNF-α stimulation. TNF-α levels are reported to be 5.6 times higher in the alveolar macrophages of infants with wheeze compared to infants without wheeze [12].

C-reactive protein (CRP) activates NF-kB signalling, complement & tissue factor and the production of cytokines and chemokines which subsequently produce more CRP, creating a positive feedback loop [13]. Studies have identified a positive relationship between BMI and CRP with significantly higher CRP levels consistently documented in obese children and adolescents compared to non-obese controls [14]. CRP was shown to be elevated in asthmatic children during periods of exacerbation, with CRP levels negatively correlating with $FEV_1$ [15].

The aim of this study was to measure the effects of weight reduction on cytokines and ventilatory functions in obese children with bronchial asthma.

## MATERIAL AND METHODS

**Subjects:** Forty obese children with mild bronchial asthma (21 boys and 19 girls), their age ranged 12 -16 years, their body mass index (BMI) ranged 30-35 kg/m$^2$. Children participated in this study were divided into two equal groups (The training and the control groups). The training group received diet regimen, exercise training and medical treatment whereas the control group received only medical treatment. Cardiac, diabetic and patients with chest disease rather than bronchial asthma were excluded from the study.

### Methods

### Evaluated Parameters

**Chemical Analysis:** A blood sample after fasting for 12 h was taken from each patient in clean tubes containing 10 mg of K2EDTA and centrifuged; plasma was separated and stored frozen at -20°C; and plasma TNF-α, leptin, CRP and interleukin-6 (IL-6) were estimated using a colorimetric method.

**Ventilatory Function Test:** Spirometer (Schiler- Spirovit SP-10) was used to measure forced vital capacity (FVC) and forced expiratory volume in the first second ($FEV_1$).

**Body Mass Index (BMI):** Weight and height scale (Metrotype –England) was used to measure weight and height to calculate the body mass index (BMI). Body mass index was calculated by dividing the weight in kilograms by the square of the height in meters (Kg/m$^2$). According to the WHO classification, a BMI of <18.5 kg/m$^2$ is under weight, 18.5-24.9 kg/m$^2$ is normal 25-29.9 kg/m2 is overweight. A BMI of > 30 kg/m$^2$ is classified as obese and this group was further divided into moderate obesity (30-34.9 kg/m$^2$), sever obesity (35-39.9 kg/m$^2$) and very sever obesity (≤40 kg /m$^2$) [16].

Measurements of C- reactive protein ( CRP), tumor necrosis factor-α (TNF-α), interleukin (IL-6), Leptin, body mass index (BMI), forced vital capacity (FVC) and forced expiratory volume in the first second ($FEV_1$) were taken before starting of the study and repeated after two months at the end of the study.

**The Prescribed Low Calorie Diet:** The interview-based food survey was performed for all patients by dieticians to specify previous food habits and possible anomalies in dietary behavior. The prescribed low calorie diet was balanced, with 15% as protein, 30 to 35% as fat and 50 to 55% as carbohydrate, on average, in order to provide about 1000 calories daily for two months for whole participants in this study.

The prescribed diet included the breakfast consisted of 2 boiled eggs (80.calorie), 50 gm cheese (100 calorie) and one bread (105 calorie), where the lunch consisted of

2 pieces of boiled meat 100g (240 calorie) or chicken (300), 500 gram salad (105 calorie), 300 gram boiled vegetables (110 calorie) 100 gram and banana (100 calorie), However, the dinner consisted of 200 gram light milk (120 calorie).

**The Physical Training Program:** The aerobic treadmill-based training program (PRECOR 9.1/ 9.2, China) was set to 60% of the maximum heart rate ($HR_{max}$) achieved according to a modified Bruce protocol. This rate was defined as the training heart rate (THR).After an initial, 5-minute warm-up phase performed on the treadmill at a low load, each endurance training session lasted 30 minutes and ended with 5-minute recovery and relaxation phase. All patients performed three weekly sessions for 2 months.

**Statistical Analysis:** The mean values of FVC, $FEV_1$, CRP, TNF-α, IL-6, Leptin were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups ($P<0.05$).

## RESULTS

The mean values of C- reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL-6), Leptin and body mass index (BMI), were significantly decreased with significant improvement of ventilatory function test of forced vital capacity (FVC) and forced expiratory volume in the first second ($FEV_1$) of the training group (Table 1 & Figure 1). Results of the control group were not significant (Table 2 & Figure 2). Also, there was a significant difference between the groups after treatment on all measured variables (Table 3 & Figure 3).

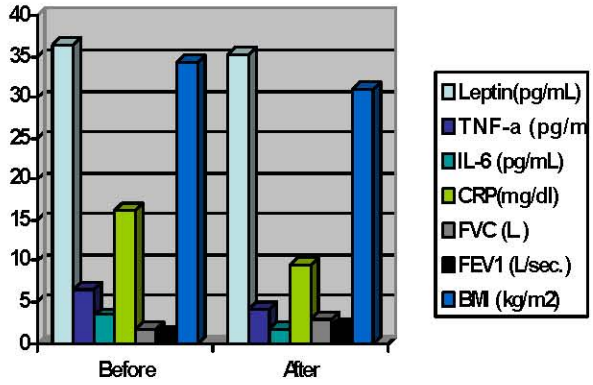


Fig. 1: Mean value and significance of leptin, TNF- α, IL-6, CRP, FVC, $FEV_1$ and BMI in the training group before and after treatment.

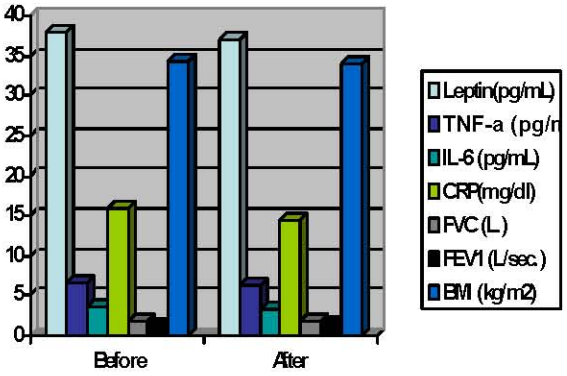


Fig. 2: Mean value and significance of leptin, TNF- α, IL-6, CRP, FVC, $FEV_1$ and BMI in the control group before and after treatment.

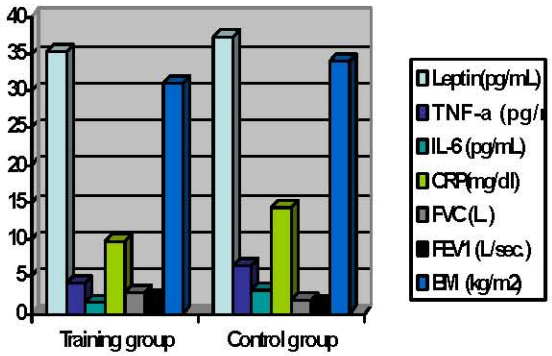


Fig. 3: Mean value and significance of leptin, TNF- α, IL-6, CRP, FVC, $FEV_1$ and BMI in the training group and the control group after treatment.

## DISCUSSION

There is evidence that the proinflammatory environment created by excess adiposity may provide a mechanism leading to obese asthma in children. Obese individuals demonstrate elevated circulating systemic inflammatory mediators, including the adipokines (proteins produced by the adipocyte) leptin and ghrelin, TNF-α, interleukin-6 (IL-6), interleukin-18 (IL-18), transforming growth factor-β1 and C-reactive protein [17]. Weight loss studies conducted in children without asthma have demonstrated a reduction in systemic inflammation. However, the impact of weight loss in the obese paediatric population with asthma has not been investigated. So, the paucity of information highlights the need for high quality randomized controlled trials of weight loss in this population that include assessment of systemic and airway inflammation and clinical asthma outcomes.

Table 1: Mean value and significance of leptin, TNF- α, IL-6, CRP, FVC, $FEV_1$ and BMI in the training group before and after treatment

| | Mean±SD | | | |
|---|---|---|---|---|
| | Pre | Post | t- value | Significant |
| Leptin(pg/mL) | 38.62±5.32 | 35.24±5.18 | 5.78 | P<0.05 |
| TNF-α (pg/mL) | 6.47±1.95 | 4.11±1.56 | 4.23 | P<0.05 |
| IL-6 (pg/mL) | 3.38±1.17 | 1.62±1.22 | 4.21 | P<0.05 |
| CRP(mg/dl) | 16.23±2.75 | 9.56±2.48 | 4.19 | P<0.05 |
| FVC (L.) | 1.67+0.64 | 2.86+0.51 | 4.20 | P<0.05 |
| $FEV_1$ (L/sec.) | 1.12+0.42 | 2.15+0.52 | 4.85 | P<0.05 |
| BMI ($kg/m^2$) | 34.25+3.41 | 31.13+2.88 | 3.86 | P<0.05 |

Table 2: Mean value and significance of leptin, TNF- α, IL-6, CRP, FVC, $FEV_1$ and BMI in the control group before and after treatment.

| | Mean±SD | | | |
|---|---|---|---|---|
| | Pre | Post | t- value | Significant |
| Leptin | 37.87±5.91 | 37.13±4.86 | 1.11 | P>0.05 |
| TNF-α (pg/mL) | 6.73±2.01 | 6.25±1.79 | 0.98 | P>0.05 |
| IL-6 (pg/mL) | 3.64±1.35 | 3.20±1.14 | 0.87 | P>0.05 |
| CRP(mg/dl) | 15.96±2.89 | 14.37±2.06 | 1.32 | P>0.05 |
| FVC (L.) | 1.72+0.71 | 1.88 + 0.85 | 0.66 | P>0.05 |
| $FEV_1$ (L/sec.) | 1.22+0.48 | 1.35+0.50 | 0.75 | P>0.05 |
| BMI ($kg/m^2$) | 34.43+3.66 | 33.98+3.11 | 1.14 | P>0.05 |

Table 3: Mean value and significance of leptin, TNF- α, IL-6, CRP, FVC, $FEV_1$ and BMI in the training group and the control group after treatment.

| | Mean±SD | | | |
|---|---|---|---|---|
| | Training group | Control group | t- value | Significant |
| Leptin | 35.24±5.18 | 37.13±4.86 | | P<0.05 |
| TNF-α (pg/mL) | 4.11±1.56 | 6.25±1.79 | | P<0.05 |
| IL-6 (pg/mL) | 1.62±1.22 | 3.20±1.14 | | P<0.05 |
| CRP(mg/dl) | 9.56±2.48 | 14.37±2.06 | 3.82 | P<0.05 |
| FVC (L.) | 2.86+0.51 | 1.88 + 0.85 | 3.13 | P<0.05 |
| $FEV_1$ (L/sec.) | 2.15+0.52 | 1.35+0.50 | 3.06 | P<0.05 |
| BMI ($kg/m^2$) | 31.13+2.88 | 33.98+3.11 | 3.65 | P<0.05 |

The results of this study proved that weight reduction could modulate adipocytokines and inflammatory cytokine levels in obese children with bronchial asthma; these findings are agreed and supported with many previous studies as Esposito and colleagues [18] who reported that medical weight loss in obese women resulted in significant decreases in previously elevated IL-6, IL-18, C-reactive protein and insulin resistance and a significant increase in the anti-inflammatory adipokine, adiponectin.

Reinher *et al.* [19], proved that weight loss was accompanied by a 15% increase in adiponectin and 19% reduction in leptin. Similarly, substantial weight loss following a combined diet, activity and behavioural intervention produced a significant decrease in CRP levels but no effect upon TNF-α level [20]. The same intervention period also achieved a 34% increase in adiponectin levels following positive body composition changes in obese adolescents [21].

Kelishadi *et al.* [22], stated that diet and exercise combination in obese children has effectively reduced CRP levels after 6wks following weight and percentage body fat reduction. Also, significant reductions in BMI, fat mass, IL-6 and leptin concentrations was achieved after only 3wks following a diet and physical activity intervention [23].

Epidemiologic data indicated that obesity increases the prevalence and incidence of asthma and reduces asthma control. In obesity, lung volume and tidal volume are reduced, events that promote airway narrowing. Obesity also leads to a state of low-grade systemic inflammation that may act on the lung to exacerbate asthma. Obesity-related changes in adipose-derived hormones, including leptin and adiponectin, may participate in these events [24].

The results of this study indicated that weight reduction improves ventilatory functions in obese children with bronchial asthma; these findings are agreed and supported with many previous studies as.

Hakala *et al.* [25], reported reductions in airway obstruction in obese asthmatics who underwent an 8-week very low calorie diet that resulted in about 14% reduction in body and was associated with increases in peak expiratory flow (PEF), $FEV_1$ and FVC and reductions in dyspnea score and use of rescue medications. Aaron *et al.* [26], also reported increases in $FEV_1$ and FVC. They suggested that benefits of weight loss were due to reductions in mass loading of the respiratory system rather than improvements in asthma per se. However, Johnson *et al.* [27], used an alternate day calorie restriction and *ad libitum* diet in 9 obese asthmatic adults for 8wks and reported a significant improvement in post-salbutamol $FEV_1$ following an mean 8% weight loss.

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