Study of serum leptin level in obese and nonobese asthmatic patients
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\textbf{Aim} The aim of the study was to investigate serum leptin levels in obese and nonobese asthmatic patients and its change during acute attack and in remission, as well as its relation to the changes in pulmonary functions.

\textbf{Methods} The study was carried out on 55 participants (40 asthmatic patients and 15 controls) who were divided according to BMI into obese (BMI >30 kg/m\textsuperscript{2}), 20 asthmatic patients and eight controls) and nonobese (BMI <25 kg/m\textsuperscript{2}), 20 asthmatic patients and seven controls). All participants were subjected to calculation of BMI, pulmonary function tests, and morning serum leptin level estimation (after at least 8 h of fasting).

\textbf{Results} Serum leptin levels (mean in ng/ml) in obese controls (64 ng/ml) and obese asthmatic patients (80.4 ng/ml during remission and 92.9 during exacerbation) were significantly higher than that in nonobese controls (6.3 ng/ml) and nonobese asthmatic patients (33.8 ng/ml during remission and 48.8 during exacerbation). There was a significant ($r = -0.456$ and $P \leq 0.05$) negative correlation between the change in serum leptin (ng/ml) and the change in forced vital capacity (FVC) (% Predicted) and forced expiratory volume in first second (FEV\textsubscript{1}) (% Predicted) in obese asthmatic patients, but not in nonobese asthmatic patients. There was a significant positive correlation between BMI (kg/m\textsuperscript{2}) and serum leptin levels (ng/ml) in obese ($r = 0.712$ and $P \leq 0.05$) and nonobese ($r = 0.747$ and $P \leq 0.05$) controls and a higher significant positive correlation in obese ($r = 0.94$ during exacerbation and $r = 0.833$ during remission, $P \leq 0.001$) and nonobese ($r = 0.687$ during exacerbation, $P \leq 0.001$ and $r = 0.488$ during remission, $P \leq 0.05$) asthmatic patients.

\textbf{Conclusion} Serum leptin levels were higher in all asthmatic patients (more during exacerbation) compared with controls and the values were higher in obese than in nonobese asthmatic patients with a significant negative correlation between the change in serum leptin and the change in FEV\textsubscript{1} and FVC in obese asthmatic patients. These findings indicate that leptin is involved in asthma inflammation. 

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Keywords: asthma, BMI, leptin, obese, pulmonary function tests

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\section*{Introduction}
Asthma is ‘a chronic inflammatory disorder of the airways associated with airway hyper-responsiveness that leads to recurrent episodes of widespread, and often reversible, airflow obstruction within the lung’ [1].

Obesity has been significantly associated with nonatopic asthma rather than with atopic asthma in women and children [2]. Some studies indicate that obesity may increase asthma severity and may reduce the efficacy of standard asthma medications [3,4].

Growing evidence suggests that the proinflammatory effects of leptin may contribute to the higher incidence of asthma in the obese population [5,6].

\section*{Aim of the study}
The aim was to study serum leptin levels in obese and nonobese asthmatic patients and its change during acute attack and in remission as well as its relation to the changes in pulmonary functions.

\section*{Methods}
This study was carried out on 55 participants (40 asthmatic patients and 15 controls) who were divided according to BMI into obese (BMI >30 kg/m\textsuperscript{2}), 20 asthmatic patients and eight controls) and nonobese (BMI <25 kg/m\textsuperscript{2}), 20 asthmatic patients and seven controls). Patients with any comorbidity that may affect the serum leptin level [7] (cardiovascular disease, cerebral vascular diseases, diabetes mellitus, liver cirrhosis, end-stage renal disease, tuberculosis, bronchiectasis, malignancy, and connective tissue disorders) and individuals with BMI 25–30 kg/m\textsuperscript{2} were excluded from the study.

All participants were subjected to full history taking, thorough clinical examination, plain chest radiography, laboratory investigations (complete blood count,
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erythrocyte sedimentation rate, liver function tests, fasting and postprandial blood sugar), and pulmonary function tests (FEV₁%, FVC%, FEF₂₅–₇₅%, and FEV₁/FVC were measured for each patient before and 10 min after inhalation of 200–400 μg salbutamol). Body weight (kg) and height (meters) were measured for each patient for calculation of BMI. Serum leptin levels were determined (morning sample after at least 8 h of fasting) during acute exacerbation and after control of the attack and also in the control group by taking blood samples, subjecting them to centrifugation, and then measuring using an ELISA kit (DRG Diagnostics, Marburg, Germany).

**Statistical analysis**

Results are given as mean ± SD. Differences between groups were statistically analyzed using an unpaired Student t-test. For patients with leptin values below the detection limit (0.25 ng/ml) the value 0.25 ng/ml was used in the analysis. After curve estimation, linear, exponential, or logarithmic Pearson product moment correlation was calculated. After the simple correlations, a regression model was fitted to the data to select the variables that contributed to the explained variation in plasma leptin concentration. Significance was determined at the 5% level. Data were analyzed using statistical package for the social sciences, version 14.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

**Results**

This study included 38 female (95%) and two male (5%) patients.

Table 1 shows the age and BMI of obese (mean age ± SD = 34.5 ± 4.44 and mean BMI ± SD = 34.1 ± 1.2) and nonobese (mean age ± SD = 42.4 ± 7.35 and mean BMI ± SD = 23.7 ± 1) controls and obese (mean age ± SD = 42.65 ± 8.98 and mean BMI ± SD = 35.15 ± 3.32) and nonobese (mean age ± SD = 42.5 ± 8.88 and mean BMI ± SD = 23.15 ± 1.81) asthmatic patients.

**Table 1 Comparison of age (years) among the studied groups**

| Parameters | Control (N = 15) | Asthmatic patients (N = 40) |
|------------|-----------------|----------------------------|
|            | Obese | Nonobese | Obese | Nonobese |
| Age (years) |       |          |       |          |
| Range      | 29–39 | 23–58    | 26–55 | 23–58    |
| Mean       | 34.5  | 42.4     | 42.65 | 42.5     |
| SD         | 4.44  | 7.35     | 8.98  | 8.88     |
| F-test     | 2.16  |          |       |          |
| P-value    | 0.104 |          |       |          |
| Significance | Nonsignificant |          |       |          |
| BMI        |       |          |       |          |
| Range      | 32.7–35.8 | 22.6–24.9 | 31.2–45 | 19.1–24.9 |
| Mean       | 34.1  | 23.7     | 35.15 | 23.15    |
| SD         | 1.2   | 1        | 3.32  | 1.81     |
| F-test     | 109.4 |          |       |          |
| P-value    | 0.001 |          |       |          |
| Significance | Highly significant |          |       |          |

**Table 2 Statistical comparison of the pulmonary function tests among the studied groups**

| Patient group | Control | Obese asthma | Nonobese asthma |
|---------------|---------|--------------|-----------------|
|               | Obese control | Obese | Nonobese | Obese control | Attack | Remission | Attack | Remission |
| FEV₁ (% predicted) | 94.4 ± 3.2 | 22.3 ± 3.3 | 74 ± 5.9 | 23.0 ± 3.2 | 77.3 ± 4.9 |
| P-value        | 0.16 | 0.001 |       | 0.001 |       |
| Significance   | Nonsignificant | Highly significant | Highly significant |
| FVC (% predicted) | 86.6 ± 5.5 | 54.8 ± 6.0 | 75.8 ± 6.1 | 53.4 ± 5.0 | 76.4 ± 4.1 |
| P-value        | 0.81 | 0.001 |       | 0.001 |       |
| Significance   | Nonsignificant | Highly significant | Highly significant |
| FEV₁/FVC | 89.75 ± 7.29 | 30.95 ± 4.98 | 76.6 ± 7.34 | 33.25 ± 3.88 | 78.05 ± 9.28 |
| P-value        | 0.734 | 0.001 |       | 0.001 |       |
| Significance   | Nonsignificant | Highly significant | Highly significant |
| FEF₂₅–₇₅ (% predicted) | 3.85 ± 0.304 | 8.73 ± 12.92 | 71.65 ± 8.65 | 30.65 ± 6.62 | 68.8 ± 8.12 |
| P-value        | 0.89 | 0.001 |       | 0.001 |       |
| Significance   | Nonsignificant | Highly significant | Highly significant |
Table 2 shows the statistical comparison of the pulmonary function tests between obese and nonobese controls with nonsignificant differences between all parameters.

Table 3 shows that serum leptin levels (ng/ml) in obese controls were significantly higher than that in nonobese controls with a mean of 64 ng/ml in obese controls and 6.3 ng/ml in nonobese controls.

Table 4 shows that serum leptin (ng/ml) was significantly higher in obese asthmatic patients during an attack than in obese asthmatic patients during remission and in obese controls.

Table 5 shows that serum leptin (ng/ml) was significantly higher in nonobese asthmatic patients during an attack than in nonobese asthmatic patients during remission and in nonobese controls.

Table 6 shows that serum leptin (ng/ml) was significantly higher in obese than in nonobese asthmatic patients both during an attack and during remission.

Table 7 shows that serum leptin (ng/ml) was significantly increased in both obese and nonobese asthmatic patients during an attack than during remission.

Table 8 shows the nonsignificant negative correlation between serum leptin (ng/ml), FVC (% Predicted), and FEF 25–75 (% Predicted) in obese controls, nonsignificant positive correlation between serum leptin (ng/ml), FEV₁ (% Predicted), and FEV₁/FVC in obese controls, and nonsignificant positive correlation between serum leptin (ng/ml), FEV₁ (% Predicted), FVC (% Predicted), FEV₁/FVC, and FEF25–75 (% Predicted) in nonobese controls.

Table 9 shows the significant negative correlation between change in serum leptin (ng/ml) and change in FVC (% Predicted) and FEV₁ (% Predicted) in obese asthmatic patients, the nonsignificant positive correlation between change in serum leptin (ng/ml) and change in FEV₁/FVC and FEF25–75 (% Predicted) in obese asthmatic patients, the nonsignificant negative correlation between the change in serum leptin (ng/ml) and the change in FVC (% Predicted) and FEV₁ (% Predicted) in nonobese asthmatic patients, and the nonsignificant positive correlation between change in serum leptin (ng/ml) and change in FEV₁/FVC and FEF25–75 (% Predicted) in nonobese asthmatic patients.

Table 10 shows that there was a nonsignificant negative correlation between age (years) and serum leptin (ng/ml) in obese and a significant negative correlation between age (years) and serum leptin (ng/ml) in nonobese controls.

There was a nonsignificant positive correlation between age (years) and serum leptin (ng/ml) in obese asthmatic patients during an attack and during remission.

### Table 3 Comparison of serum leptin (ng/ml) in obese and nonobese controls

| Leptin | Obese control | Nonobese control |
|--------|---------------|------------------|
| Mean   | 64.0          | 6.3              |
| SD     | 30.3          | 3.7              |
| T-test | 4.98          |                  |
| P-value| >0.001        |                  |
| Significance | Highly significant |                |

### Table 4 Comparison of serum leptin (ng/ml) in obese controls and obese asthmatic patients during attack and remission

| Leptin | Obese control | Obese asthmatic patients |
|--------|---------------|--------------------------|
|        | During attack | During remission          |
| N      | 8             | 20                        |
| Mean   | 64.0          | 92.9                      |
| SD     | 30.3          | 8.0                       |
| T-test | 12.09         | <0.001                    |
| P-value| <0.001        |                           |
| Significance | Highly significant |                |

### Table 5 Comparison of serum leptin (ng/ml) in nonobese controls and nonobese asthmatic patients during attack and remission

| Leptin | Nonobese controls | Nonobese asthmatic patients |
|--------|-------------------|-----------------------------|
|        | During attack     | During remission             |
| N      | 7                 | 20                          |
| Mean   | 6.3               | 48.8                        |
| SD     | 3.7               | 10.3                        |
| T-test | 58.8              | <0.05                       |
| P-value| <0.05             |                             |
| Significance | Significant       |                             |

### Table 6 Comparison of serum leptin (ng/ml) in obese and nonobese asthmatic patients during an attack

| Leptin | Obese asthmatic patients | Nonobese asthmatic patients |
|--------|--------------------------|-----------------------------|
|        | During attack             | During remission             |
| N      | 20                        | 20                          |
| Mean   | 92.9                      | 48.8                        |
| SD     | 8.0                       | 9.2                         |
| T-test | 4.59                      | 4.95                        |
| P-value| <0.001                    | <0.001                      |
| Significance | Highly significant | Highly significant |

(ng/ml) in obese and a significant negative correlation between age (years) and serum leptin (ng/ml) in nonobese controls.

There was a nonsignificant positive correlation between age (years) and serum leptin (ng/ml) in obese asthmatic patients during an attack and during remission.
Table 12 shows the significant positive correlation between BMI (kg/m²) and serum leptin levels (ng/ml) in obese and nonobese controls.

Table 13 shows the highly significant positive correlation between BMI (kg/m²) and serum leptin (ng/ml) in obese asthmatic patients during an attack and during remission. There was a highly significant positive correlation between BMI (kg/m²) and serum leptin levels (ng/ml) in nonobese asthmatic patients during an attack and a significant positive correlation during remission.

**Discussion**

Obesity and bronchial asthma are both chronic, prevalent conditions that pose a significant challenge to the clinician as well as to public health worldwide [8].

The aim of our study was to investigate serum leptin levels in obese and nonobese asthmatic patients and its change during acute attack and during remission as well as its relation to the changes in pulmonary functions.

This study included 38 female (95%) and two male (5%) patients, indicating a higher frequency and morbidity of bronchial asthma in women compared with men. In our study all asthmatic patients were admitted as inpatients in the chest department, Benha University Hospitals. Other studies showed much higher frequency of asthma and associated morbidity in women (regardless of their BMI) compared with men [9–12].

In our study serum leptin levels in all asthmatic patients were much higher than that in controls and this was statistically significant and increased sharply during acute exacerbation and decreased after control of the attack; however, it was still higher than in the control group, and the level in obese asthmatic patients was higher than the level in nonobese asthmatic patients, which may indicate a role for leptin in asthma pathogenesis.

Our results agreed with data from the Nurses’ Health Study [13], which evaluated the relationship between

### Table 7 Comparison of serum leptin (ng/ml) in obese and nonobese asthmatic patients during attack and remission

| Leptin | Obese asthmatic patients | Nonobese asthmatic patients |
|--------|--------------------------|-----------------------------|
|        | During attack | During remission | During attack | During remission |
| N      | 20 | 20 | 20 | 20 |
| Mean   | 92.9 | 80.4 | 48.8 | 33.8 |
| SD     | 8.0 | 9.2 | 10.33 | 8.8 |
| t-test | 12.05 | 13.1 | <0.001 | <0.001 |
| P-value| <0.001 | <0.001 | Non-significant | Non-significant |

### Table 8 Correlations between serum leptin (ng/ml) and pulmonary function tests in obese and nonobese controls

| Correlation between leptin and PFT | Data | FVC% predicted | FEV% predicted | FEV/FVC | FEF25–75% predicted |
|-----------------------------------|------|----------------|----------------|---------|---------------------|
| Obese control                     | N    | 8              | 8              | 8       | 8                   |
| r-value                           | −0.122 | 0.416 | 0.491 | −0.38 |
| P-value                           | >0.05 | >0.05 | >0.05 | >0.05 |
| Significance                      | NS   | NS             | NS             | NS      |
| Nonobese control                  | N    | 7              | 7              | 7       | 7                   |
| r-value                           | 0.22 | 0.252 | 0.16 | 0.29 |
| P-value                           | >0.05 | >0.05 | >0.05 | >0.05 |
| Significance                      | Nonsignificant | Nonsignificant | Nonsignificant | Nonsignificant |

NS, nonsignificant; PFT, pulmonary function test.

### Table 9 Correlations between changes in serum leptin (ng/ml) and changes in pulmonary function test scores in obese and nonobese asthmatic patients during attack and remission

| Correlation between leptin and PFT | Data | FVC% change | FEV% change | FEV/FVC% change | FEF25–75% change |
|-----------------------------------|------|-------------|-------------|-----------------|-----------------|
| Obese asthmatics                  | N    | 20          | 20          | 20              | 20              |
| r-value                           | −0.456 | −0.471 | 0.2 | 0.372 |
| P-value                           | <0.05 | <0.05 | >0.05 | >0.05 |
| Significance                      | Significant | Significant | Non-significant | Non-significant |
| Nonobese asthmatic patients       | N    | 20          | 20          | 20              | 20              |
| r-value                           | −0.043 | −0.015 | 0.164 | 0.045 |
| P-value                           | >0.05 | >0.05 | >0.05 | >0.05 |
| Significance                      | Nonsignificant | Nonsignificant | Nonsignificant | Nonsignificant |

PFT, pulmonary function test.
body weight and the incidence of self-reported physician-diagnosed asthma in women. That study included 85,911 patients and was conducted over 4 years. As in the case–control studies, those investigators found a significant relationship between BMI and the incidence of asthma, with obesity increasing the asthma risk by 2.7–3.8-fold and overweight increasing the risk by 50–70%.

Haynes et al. [14] concluded that leptin could predispose to asthma through its effect on immune function [tumor necrosis factor-a (TNF-α) and interleukin-6 (IL-6)] and its effect on the sympathetic nervous system; in addition, Guler et al. [15] found that the median serum leptin concentrations of children (especially boys) were significantly higher in those with asthma than in healthy controls (3.53 vs. 2.26 ng/ml, \( P = 0.01 \)), even though there was no difference in BMI levels.

Our study also agreed with that by Mai et al. [16] involving children born with very low birth weight who subsequently became overweight. The study showed that current asthmatic patients had median leptin concentrations twice as high as that in children without current asthma (30.8 vs. 14.3 ng/ml, \( P = 0.14 \)), but this was not the case in nonoverweight children. Taken together, our study and prior studies suggest that leptin may potentially play an important role in the pathophysiology of asthma.

In a study [17] conducted on 5876 individuals after exclusion of those who were either pregnant or had missing values for covariates it was found that adults with the highest quartile of leptin concentrations had an odds ratio (OR) of 1.56 (95% confidence interval 0.96–2.53) for current asthma after adjustment in a multivariable logistic regression analysis for age, sex, race/ethnicity, educational status, smoking status, concentration of cotinine, physical activity, and atopy. This association was stronger in women (OR 1.85) than in men (OR 1.27). In women, adjustment for triceps skin fold thickness strengthened the association between serum leptin concentrations and asthma, whereas adjustment for BMI weakened this association.

Kilic et al. [18] found that the median leptin level was higher in patients with uncontrolled asthma than in those with controlled asthma, but the difference was not significant. In the obese group, a nonsignificant negative correlation (\( r = -0.138, P = 0.390 \)) was found between leptin levels and asthma control test scores. In the nonobese group, mean unadjusted leptin concentrations were higher in participants who had current asthma than in those who had never had asthma.

Shore et al. [5] found that leptin concentrations are increased acutely during inflammation and, in turn, promote inflammation. Other experiments showed a prompt dose-dependent increase in serum leptin levels and leptin mRNA expression in the adipose tissue of mice following administration of proinflammatory cytokines such as TNF-α and IL-1 \[19,20\] as well as demonstration of increased serum TNF-α, IL-6, and IL-12 levels and increased phagocytosis by macrophages on exogenous administration of leptin \[21\]. Inflammatory mediators such as TNF-α also promote the expression and release of leptin from the adipose tissue, formulating a positive feedback mechanism \[22\].

Vernooy et al. also reported that leptin had an effect on inflammation through enhancement of production of TNF-α and IL-6 from endotoxin-treated macrophages and lymphocytes \[23\].

In our study there was a significant negative correlation between serum leptin and both FVC and FEV\(_1\) in obese asthmatic patients but not in nonobese asthmatic patients.

Our findings agreed with a population-based study \[24\] in which individuals with impaired lung function had raised serum leptin levels; King et al. \[25\] also reported declines in airway conductance in obese compared with nonobese individuals, which could reflect the proinflammatory role of leptin.

### Table 10 Correlation between serum leptin and age in obese and nonobese controls

| Correlation between leptin and age | Obese controls | Nonobese controls |
|-----------------------------------|----------------|------------------|
| \( N \)                           | 8              | 7                |
| \( r \)-value                      | -0.351         | -0.663           |
| \( P \)-value                      | >0.05          | <0.05            |
| Significance                       | Nonsignificant | Significant      |

### Table 11 Correlation between serum leptin (ng/ml) and age (years) in obese and nonobese asthmatic patients during attack and remission

| Correlation between leptin and age | Obese asthmatic patients | Nonobese asthmatic patients |
|-----------------------------------|--------------------------|----------------------------|
|                                   | During attack | During remission | During attack | During remission |
| \( r \)-value                     | 0.034        | 0.133           | 0.45          | 0.46            |
| \( P \)-value                     | >0.05        | >0.05           | <0.05         | <0.05           |
| Significance                      | Nonsignificant | Nonsignificant | Significant   | Significant      |
Leptin release from adipose tissue or the lung may be induced by disease-related inflammation, which further increases the airway inflammation and hyper-reactivity [17,29,30]. Leptin has been identified to have proinflammatory properties through the stimulation of TNF-α and IL-6 from the adipose tissue [31], and through the modulation of immunity to promote Th1 immune responses with increased production of interferon-γ (IFN-γ) [32]. In asthmatic children, IFN-γ-producing CD4+ T cells are inversely correlated with blood eosinophilia but positively correlated with airway hyper-responsiveness, suggesting a possible involvement of IFN-γ in nonatopic asthma [33].

In our study there was a significant negative correlation between change in serum leptin (ng/ml) and change in both FVC (% Predicted) and FEV₁ (% Predicted) in obese asthmatic patients but not in nonobese asthmatic patients. This finding may indicate that leptin has an effect on airway response in obese asthmatic patients during exacerbation.

### Conclusion

Serum leptin levels were higher in all asthmatic patients (more during exacerbation) than in controls and the values were higher in obese than in nonobese asthmatic patients with a significant negative correlation between the change in serum leptin and the change in FEV₁ and FVC in obese asthmatic patients. These findings indicate that leptin is involved in asthma inflammation.

### Acknowledgements

**Conflicts of interest**

There are no conflicts of interest.

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### Table 12 Correlation between serum leptin and BMI in obese and nonobese controls

| Correlation between leptin and BMI | Obese controls | Nonobese controls |
|-----------------------------------|----------------|-------------------|
| r-value                           | 0.712          | 0.757             |
| P-value                           | <0.05          | <0.05             |
| Significance                       | Significant    | Significant        |

### Table 13 Correlation between serum leptin (μg/ml) and BMI (kg/m²) in obese and nonobese asthmatic patients during attack and remission

| Correlation between leptin and BMI | Obese asthmatic patients | Nonobese asthmatic patients |
|-----------------------------------|---------------------------|----------------------------|
|                                  | During attack             | During remission           |
|                                  |                            |                            |
| r-value                           | 0.94                      | 0.833                     |
| P-value                           | <0.001                    | <0.001                     |
| Significance                       | Significant               | Significant                |

In our study there was a significant positive correlation between BMI (kg/m²) and serum leptin levels (ng/ml) in obese and nonobese control and asthmatic individuals.

Several studies have identified an association between asthma and obesity in women [9,13,18]. BMI was positively associated with asthma, wheezing, asthma treatment, atopy, and immunoglobulin E, and inversely with the FEV₁/FVC ratio in women. One would expect that most obese individuals would become short of breath much more quickly, especially if some of them had exercise-induced asthma. It remains unclear whether this association is due to asthma itself or due to symptoms caused by overweight or adipokines such as leptin.

Hancox et al. [26] reported that a raised BMI was associated with asthma and atopy in women than in men, and population attributable fraction calculations estimated that 28% (95% confidence interval 7–45) of asthma cases in women after age 9 are due to overweight.

Guler et al. [15] noted that, even after controlling the BMI, serum leptin is higher in male asthmatic patients compared with nonasthmatic individuals.

Some studies have suggested that leptin may play an important role in asthma pathophysiology through its ability to activate the sympathetic nerves. Leptin was found to increase the activity of sympathetic nerves in various organs, but its effects on the lung sympathetic nerves are unknown [14,27,28]. In animal studies, leptin-treated mice were found to exhibit augmented responses to metacholine and increased levels of IgE, following ovalbumin challenge, when compared with saline-infused mice.

## Table 12 Correlation between serum leptin and BMI in obese and nonobese controls

| Correlation between leptin and BMI | Obese controls | Nonobese controls |
|-----------------------------------|----------------|-------------------|
| r-value                           | 0.712          | 0.757             |
| P-value                           | <0.05          | <0.05             |
| Significance                       | Significant    | Significant        |

## Table 13 Correlation between serum leptin (μg/ml) and BMI (kg/m²) in obese and nonobese asthmatic patients during attack and remission

| Correlation between leptin and BMI | Obese asthmatic patients | Nonobese asthmatic patients |
|-----------------------------------|---------------------------|----------------------------|
|                                  | During attack             | During remission           |
|                                  |                            |                            |
| r-value                           | 0.94                      | 0.833                     |
| P-value                           | <0.001                    | <0.001                     |
| Significance                       | Significant               | Significant                |

There are no conflicts of interest.
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