

Asthma in Obese Women: Outcomes and Factors Involved

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■ Abstract

Objective: It has been shown that the prevalence of asthma in obese people has increased in recent years. The aim of this study was to evaluate factors involved in the relationship between asthma and obesity in women.

Methods: We evaluated serum leptin levels, fractional exhaled nitric oxide (FE_{NO}), asthma control (using the Asthma Control Test [ACT]), and presence of atopy in 41 obese women with asthma and 40 non-obese women with asthma. We also compared the relationship between body mass index (BMI) and these parameters between the 2 groups.

Results: Serum leptin levels were significantly higher in obese asthmatics than in nonobese asthmatics ($P < .05$). In the obese group, leptin levels were positively correlated with FE_{NO} levels ($r = 0.439$, $P = .004$). Uncontrolled asthma (ACT score < 20) was detected in 61% of women in the obese group compared to just 38% of those in the nonobese group ($P = .035$). In atopic patients, total immunoglobulin E levels were positively correlated with leptin levels ($r = 0.329$, $P = .038$). When the 81 women were classified according to asthma control, high BMI was found to be the only significant factor that contributed to poor asthma control.

Conclusion: We have shown that serum leptin levels might have a role in poor asthma control in obese patients, and can conclude that obesity is an important factor in uncontrolled asthma.

Key words: Asthma. Asthma control. Exhaled nitric oxide. Leptin. Obesity

■ Resumen

Objetivo: Se ha demostrado que la prevalencia del asma en personas obesas ha aumentado en los últimos años. El objetivo de este estudio fue evaluar los factores implicados en la relación entre el asma y la obesidad en mujeres.

Métodos: Se evaluaron los niveles séricos de leptina, el óxido nítrico exhalado (NOe), el control del asma (con el uso de la prueba de control del asma [ACT]) y la presencia de atopia en 41 mujeres obesas con asma y 40 mujeres no obesas con asma. También se comparó la relación entre el índice de masa corporal (IMC) y estos parámetros entre los 2 grupos.

Resultados: Los niveles séricos de leptina fueron significativamente mayores en las mujeres asmáticas obesas en comparación con las asmáticas no obesas ($p < 0,05$). En el grupo de mujeres obesas, los niveles de leptina presentaron una correlación positiva con los niveles de NOe ($r = 0,439$; $p = 0,004$). Se detectó asma no controlada (puntuación de la ACT < 20) en el 61% de las mujeres del grupo con obesidad y solo en el 38% de las mujeres del grupo sin obesidad ($p = 0,035$). En las pacientes atópicas, los niveles totales de inmunoglobulina E presentaron una correlación positiva con los niveles de leptina ($r = 0,329$; $p = 0,038$). Al clasificar a las 81 mujeres en función del control del asma, se observó que el IMC elevado era el único factor significativo que contribuía a un mal control del asma.

Conclusión: Se ha mostrado que los niveles séricos de leptina pueden estar implicados en el mal control del asma en pacientes obesas, y se puede concluir que la obesidad es un factor importante en el asma no controlada.

Palabras clave: Asma. Control del asma. Óxido nítrico exhalado. Leptina. Obesidad.

Introduction

Obesity and asthma are chronic diseases that affect millions of people all over the world. There has been a considerable increase in the frequency of both diseases over the last 2 decades [1,2]. A systematic review published in 2008, for example, reported that the frequency of asthma and obesity in the United States increased by 50% and 73%, respectively, between 1980 and 2000 [3]; this simultaneous rise may not be coincidental.

Moreover, recent data emphasize that obesity is an important risk factor for asthma [4-6]. It has been shown that the increased deposition of adipose tissue in obesity may play a critical role in the development of airway inflammation and bronchial hyperreactivity [7]. Leptin, a 16-kD adipocyte-derived cytokine that is essential for body homeostasis, is synthesized and released from fat cells in response to changes in body fat. It inhibits lipogenesis, stimulates lipolysis, improves insulin sensitivity, and has angiogenic activity [8]. It is also elevated in obesity, correlates positively with body mass index (BMI), and induces satiety. There is also evidence that it upregulates various cytokines, promoting a state of chronic inflammation [9]. Furthermore, in the lung, leptin (or rather the leptin receptor pathway) has been shown to be involved in normal lung development and surfactant production [10]. Leptin is believed to regulate T-cell proliferation or activation and may provide a link between obesity and asthmatic inflammation [11,12].

Asthma control, which is defined as the extent to which the various manifestations of asthma are reduced or removed by treatment, is increasingly receiving attention in both clinical trials and clinical practice. In recent years, validated composite measures have been designed to capture different and often independent aspects of asthma control [13].

Measurement of exhaled nitric oxide is an accepted, recommended, and standardized technique for assessing airway inflammation in asthma. Several publications have reported high fractional concentrations of orally exhaled nitric oxide (FE_{NO}) in individuals with asthma and a fall in these concentrations after appropriate treatment [14].

In this study we aimed to evaluate the effects of obesity on asthma and asthma control. A secondary aim was to evaluate the contribution of inflammatory markers such as leptin and FENO to the relationship between asthma and obesity.

Methods

Study Design and Participants

This cross-sectional study was performed at the asthma outpatient clinic of the Department of Pulmonary Medicine at the Gazi University School of Medicine in Ankara, Turkey. Female asthmatic patients who visited our outpatient clinic and who had been using at least 1 asthma control medication regularly for at least 6 months were consecutively evaluated over a year for inclusion in 4 study groups: 1) obese atopic patients, 2) obese nonatopic patients, 3) nonobese atopic patients, and 4) nonobese nonatopic patients. For each group,

the first 25 patients who met the eligibility criteria were recruited.

Asthma diagnosis was made according to the Global Initiative for Asthma (GINA) recommendations [4]. Asthma severity was also classified according to the GINA guidelines, using symptoms and pulmonary function test results from when the patients were clinically stable and had been free of acute respiratory infections for at least 2 months [4].

Patients with a BMI of over 30 kg/m² were classified as obese. Patient characteristics, comorbidities (allergic rhinitis, sinusitis, and nasal polyposis), treatment adherence, and presence of premenstrual worsening of asthma symptoms were recorded.

Patients who had had an asthma exacerbation or experienced a lower or upper respiratory tract infection in the last month were excluded, as were current or former smokers, and patients with systemic inflammatory diseases or cardiac disorders.

The study was approved by the ethics committee at Gazi University School of Medicine, and written informed consent was obtained from all individuals.

Spirometry

Spirometric parameters were measured with a Vmax 20 spirometer (Sensor Medics/ VIASYS, Conshohocken Pennsylvania, USA). The best of 3 manoeuvres was selected and expressed as a percentage of the predicted value and as an absolute value.

Atopy

Atopy was assessed by skin prick tests to 13 common allergens (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, penicillium mix, aspergillus mix, cat fur, dog hair, grass mix, *Corylus avel*, *Populus alba*, *Olea europea*, and cereal mix [Stallergenes SA, Antony, Cedex, France]). Histamine in distilled water (10 mg/mL) and a glycerol-buffered diluent of the allergen preparations were used as positive and negative controls, respectively. Skin reactions were analyzed 15 minutes after inoculation by comparing the wheal diameter produced by each allergen to those produced by the positive and negative controls. Participants were characterized as atopic if they had at least 1 skin reaction with a wheal diameter of 3 mm or greater.

Fractional Exhaled Nitric Oxide

FE_{NO} measurements were performed using a handheld FE_{NO} analyzer (NIOX MINO; Aerocrine, Solna, Sweden), which measures NO via an electrochemical sensor. The measurement range is between 0 and 300 ppb with an accuracy of ± 5 ppb or $\pm 10\%$ if FE_{NO} is >30 ppb. Deep inhalation through the mouthpiece provides NO-free air via an NO scrubber. After inhalation, the individual exhales for 10 seconds with a constant flow of 50 mL/sec. Constant flow is ensured via a visual and audible feedback system that helps to maintain pressure within preset limits. Measurements are approved if the exhaled pressure is between 10 and 20 cm H₂O with deviation allowed during the first 3 seconds of measurement [15]. The measurement method is consistent with the recommendations

of the American Thoracic Society/European Respiratory Society [14]. FE_{NO} was measured prior to spirometry.

Serum Total Immunoglobulin E Levels

Peripheral blood samples were obtained from each individual and total immunoglobulin (Ig) E levels (IU) were measured by chemiluminescence automatic immunoassay.

Serum Leptin Levels

Peripheral blood samples were obtained from each individual after overnight fasting. Serum leptin levels (pg/mL) were analyzed with a solid-phase Leptin enzyme-linked immunosorbent assay based on the sandwich principle (DRG Instruments GmbH, Marburg, Germany).

Asthma Control Test

The Asthma Control Test (ACT) [16] was used to evaluate asthma control. The ACT is a validated self-administered questionnaire consisting of 5 questions covering the previous 4 weeks. The questions are related to episodes of breathlessness, nocturnal awakenings, limitations of daily activities, need for rescue medication, and self-rating of asthma control. Each question has 5 possible answers, with scores ranging from 1 to 5. The total possible score thus ranges from 5 to 25, with higher scores indicating better control.

Well-controlled asthma is defined by a score of 20 or higher [16].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (release 13.0) (SPSS, Chicago, Illinois, USA). Normally distributed variables were expressed as means (SD) and nonnormally distributed variables as medians (range). The Mann-Whitney U test was used to compare categorical variables. Correlations between variables were assessed using Spearman correlation tests. The χ^2 test was used to compare categorical variables and discriminate analysis was used to determine significant factors. All *P* values were 2-tailed, and a *P* of .05 or less was considered statistically significant.

Results

After the exclusion of patients with missing data, 81 women with asthma (41 of whom were obese [21 atopic and 20 nonatopic] and 40 of whom were not [20 atopic and 20 nonatopic]) were included in the study.

Demographic data, comorbidities, and spirometric values for both groups (obese and nonobese) are shown in Table 1. According to the GINA guidelines [4], 3 of the women in the obese group had severe persistent disease, 5 had moderate persistent disease, and the rest (n=33) had mild persistent disease. In the nonobese group, 5 of the women had moderate persistent disease and the rest (n=35) had mild persistent disease. All the patients had been taking at least 1 asthma control medication regularly for at least 6 months.

The patients in the obese group were significantly older than those in the nonobese group (Table 1). There were no within-group differences for mean demographic data or spirometric values, or presence of asthma-related comorbidities (allergic rhinitis, sinusitis and nasal polyposis) when the patients were analyzed by atopic status.

The mean leptin level was significantly higher in obese asthmatics than in nonobese asthmatics (*P*=.50), but no significant difference was found for FE_{NO} levels (Table 2). The mean (SD) ACT scores were 20.75 (4.55) and 18.30 (5.50) for obese and nonobese patients, respectively. However, when the patients were classified as having controlled asthma (ACT score ≥ 20) or uncontrolled asthma (ACT score < 20), 61% of the patients in the obese group had uncontrolled asthma compared to just 38% of those in the nonobese group (*P*=.035).

For the group as a whole (n= 81), a significant correlation

Table 1. Demographic Features and Spirometric Values of Obese^a and Nonobese^b Asthmatic Women^c

	Obese Group (n=41)	Nonobese Group (n=40)	<i>P</i>
Age, y	53.90 (10.19)	47.30 (15.65)	.024
Duration of asthma, y	8.94 (8.79)	8.30 (8.68)	.477
BMI, kg/m ²	34.87 (4.26)	25.55 (2.84)	<.001
FEV ₁ , %	93.10 (18.83)	99.48 (17.85)	.308
PEF, %	89.63 (24.16)	95.81 (19.29)	.290
Total IgE, IU/mL	134.46 (201.8)	117.09 (218.0)	.238
Presence of allergic rhinitis, %	63.40	57.50	.207
Presence of sinusitis, %	53.70	40.00	.711
Presence of nasal polyposis, %	7.30	0	.58

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in the first second; IgE, immunoglobulin E; PEF, peak expiratory flow.

^aBMI < 20 according to Asthma Control Test (ACT) [16].

^bBMI ≥ 20 according to ACT.

^cData are shown as mean (SD) unless otherwise indicated.

Table 2. Study Parameters for Obese and Nonobese Asthmatic Women Analyzed^a

	Obese Group (n=41)	Nonobese Group (n=40)	<i>P</i>
Leptin, pg/mL	22.60 (4.80- 100.00)	16.70 (2.32- 92.11)	.050
FE _{NO} , ppb	21.00 (11.00- 52.00)	22.50 (6.00-297.00)	.532

Abbreviation: FE_{NO}, fractional exhaled nitric oxide.

^aData are shown as median (range).

was found between BMI and serum leptin levels ($r=0.394$, $P<.001$) (Figure 1). No correlation was found between BMI and FENO levels ($r= -0.025$, $P=.82$), and there was a weak but insignificant negative correlation between BMI and ACT scores ($r= -0.116$, $P=.301$).

When the women in the obese group ($n=41$) were categorized according to current asthma control (ACT score <20 or ≥ 20), no significant difference was found for median FE_{NO} levels between those with uncontrolled asthma ($n=24$; 21.00 ppb [15-51 ppb]) and those with controlled asthma ($n=17$; 20.50 ppb [11-52 ppb]) ($P=.799$). Median leptin levels were higher in patients with uncontrolled asthma (23.19 pg/mL [4.80-100 pg/mL]) than in those with controlled asthma (19.70 pg/mL [11.14-100 pg/mL]) but the difference was not significant ($P=.371$). The results for the nonobese group ($n=40$) were similar. FE_{NO} levels were 26.00 ppb (10.00-297.0 ppb) for those with uncontrolled asthma ($n=15$) and 19.50 ppb (6.0-171.0 ppb) for those with controlled asthma ($n=25$) ($P=.194$). For leptin, the levels were 20.69 pg/mL (4.03-35.10 pg/mL) and 15.90 pg/mL (2.30-92.11 pg/mL), respectively ($P=.890$).

In the obese group, a significant positive correlation was observed between serum leptin levels and FE_{NO} levels ($r=0.439$, $P=.004$) (Figure 2). There was also a positive correlation between serum leptin levels and total IgE, ($r=0.43$, $P=.789$) and a negative correlation ($r=-0.138$, $P=.390$) between leptin levels and ACT scores but these were not significant. In the nonobese group, no correlations were found for these parameters.

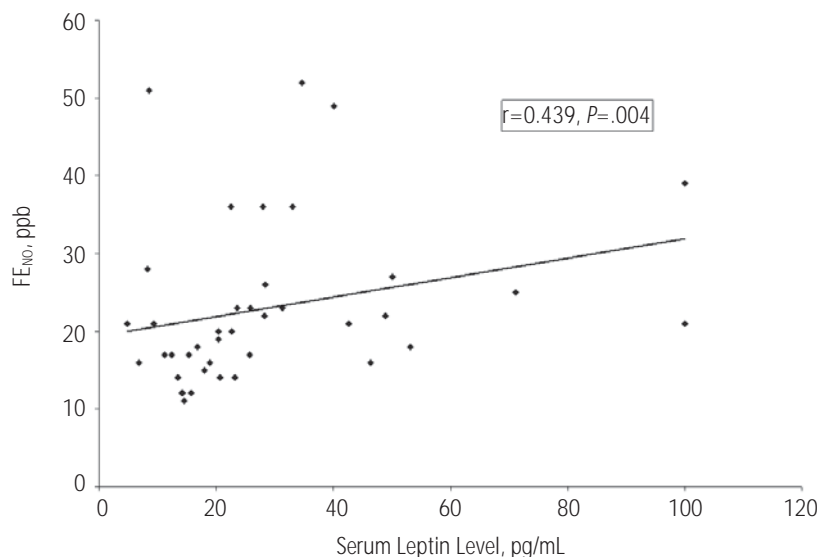


Figure 2. Relationship between serum leptin levels and fractional exhaled nitric oxide (FE_{NO}) in obese female patients.

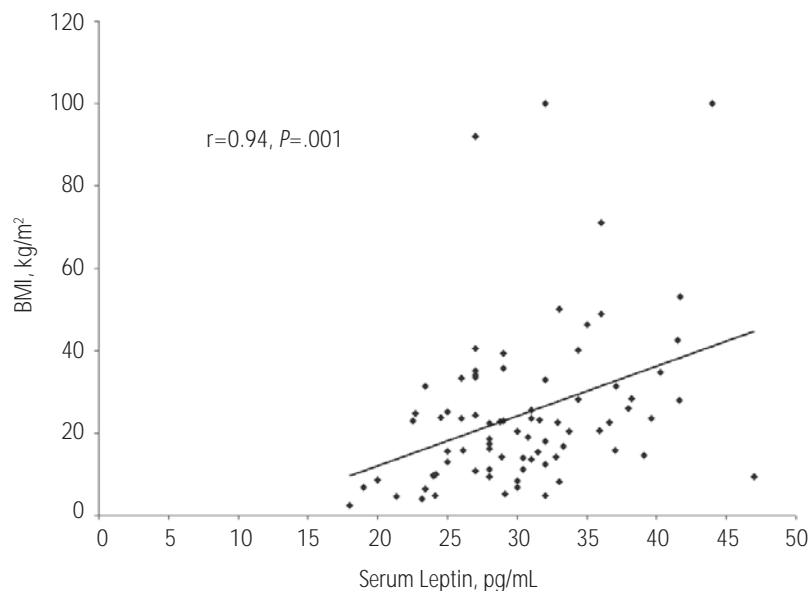


Figure 1. Relationship between body mass index (BMI) and serum leptin levels in the whole study group.

For the 41 patients with atopy, a significant correlation was found between serum leptin levels and total IgE levels ($r= 0.329$, $P=.038$).

The only asthma-related comorbidity significantly associated with increased risk for uncontrolled asthma (ACT score <20) was obesity (BMI >30), with an odds ratio of 2.6 (95% confidence interval, 1.06-6.38; $P=.036$). No significant effects were found for allergic rhinitis, sinusitis, or nasal polyposis.

Twenty-four (58%) of the women in the obese group and 16 (40%) of those in the nonobese group were premenopausal. However, only 4 of the women (all in the obese group) reported deterioration of asthma symptoms prior to menstruation. These 4 patients, classified as having premenstrual asthma, also had significantly higher leptin levels (47.61 pg/mL [27.94-53.17 pg/mL]) than those who did not complain of premenstrual asthma symptoms (20.39 pg/mL [2.32-100 pg/mL]) ($P=.005$).

Discussion

We have shown that high BMI and high leptin levels negatively influence asthma control. Furthermore, the significant positive correlation observed between serum leptin and FE_{NO} levels in the obese group suggests the presence of an increased inflammatory process, induced by leptin, in these patients. We have also shown, as expected, that serum leptin levels were significantly higher in obese asthmatics compared to nonobese asthmatics, with a positive correlation between BMI and leptin levels.

In the past decade, asthma and obesity

have been associated in different ways. Prospective studies, for example, have shown that obesity is a risk factor for the development of asthma, with a risk or odds ratio of between 1.1 and 3.0 [12,17]. In a meta-analysis of 7 studies comprising 333 102 individuals, overweight and obesity conferred an increased risk of incident asthma (odds ratio, 1.51) [18]. Recent data have shown that obesity is associated not only with a high prevalence of asthma but also with a decrease in lung function and an increase in symptoms in asthmatic patients [4,12,19,20]. Moreover, weight reduction in obese asthmatic patients has been found to improve lung function and asthma symptoms, as well as result in reduced medication use [20-22]. As can be seen thus, the relationship between obesity and asthma is not only causal as obesity also appears to have a negative impact on asthma symptoms.

The pathophysiological mechanisms underlying the association between asthma and obesity have been the subject of much recent research. While they are still unknown, one theory is that leptin might play a role in the pathogenesis of obesity-related asthma [1].

Asthma is unquestionably an inflammatory disease of the lung, but there is also an increasing body of literature indicating that obesity is also an inflammatory state. Certain inflammatory cytokines, such as tumor necrosis factor (TNF) α and interleukin (IL) 6 are elevated in both obesity and asthma [1]. Leptin—a proinflammatory cytokine—is increased in the majority of obese individuals [7], and high levels of leptin have been associated with current asthma [11,23,24]. While several studies, including ours, have found an association between high leptin levels and high BMI [7,23], others have found no differences in BMI between asthmatic and nonasthmatic individuals with high leptin levels [11,24].

Adipocytes in white adipose tissue are the main source of leptin. These fat cells also secrete cytokines and chemokines such as TNF- α , IL-6, and IL-10. TNF- α stimulates the production of TH₂ type cytokines. In summary, a common inflammatory pathway in both obesity and asthma is orchestrated by TNF- α . Expression of leptin can also be increased by TNF- α . Leptin, IL-6, and IL-10 have been shown to downregulate regulatory T cell activity, which can result in a tendency to atopy [17].

There is also limited evidence that obese asthmatics have greater systemic inflammation and airway inflammation than nonobese asthmatics [7]. There are conflicting results regarding the association between FE_{NO}, an accepted noninvasive marker of airway inflammation [25,26], and BMI in asthmatics. Komakula et al [27], for example, showed that BMI and leptin levels were negatively correlated with FE_{NO} in asthmatics. The explanation they provided for this discrepancy was the fact that the increase in oxidative stress in obese individuals changes the NO redox metabolism. This means that airway NO could be converted into reactive nitrogen species, resulting in lower measured FE_{NO} levels. We did not find a correlation between BMI and FE_{NO} in the present study but we did observe a positive correlation between leptin levels and FE_{NO}, indicating that leptin plays a significant role in airway inflammation.

One interesting finding of this study was that leptin levels were higher in the small group of women with premenstrual asthma (n=4 and all obese) than in those who did not report

worsening of asthma symptoms prior to menstruation. Premenstrual asthma has been shown to be caused by increased airway inflammation [28]. A common pathway in premenstrual asthma and leptin-induced airway inflammation is excessive nuclear factor- κ B (NF- κ B) formation. Because progesterone receptors directly interact with NF- κ B, a fall in progesterone levels in the late luteal phase of the menstrual cycle would tend to increase asthmatic inflammation via excessive NF- κ B formation [29]. It is also noteworthy that leptin can activate the transcription factors that activate NF- κ B in endothelial cells [30]. We hypothesize that leptin, using the same pathway, can enhance the effects of hormonal changes in the premenstrual period. Nonetheless, further investigation into the role of leptin in premenstrual asthma is needed.

Atopy also appears to be linked to obesity in a similar manner to asthma. In our analysis, we found a positive correlation between leptin and IgE levels in patients with atopy, and it has been suggested that obesity might be a risk factor for atopy [6,17]. In a study of 98 children, obese children had significantly higher serum IgE levels than nonobese children [31]. Leptin levels have also been found to correlate positively with IgE levels in atopic individuals [31]. Finally, in an animal model, leptin has been shown to increase IgE levels and augment airway hyperresponsiveness [32].

It has been proposed that sex might play a significant role in the association between asthma and obesity, which has been found to be stronger in women than in men [1]. Higher leptin levels have also been reported in women compared to men [33]. These differences might be associated with sex hormones, but they might also be related to differences in the percentage of body fat between women and men as serum levels of leptin are positively correlated with body fat mass [23]. A high BMI does not necessarily reflect a high percentage of body fat in men (men are more muscular than women and a high BMI might be due to increased muscle mass rather than increased adipose tissue). Indeed, an association between high BMI and asthma has mostly been detected for women [7,17]. This is why we only included women in this study. There is already sufficient evidence that leptin levels are elevated in obese patients, but we specifically wished to study obese and nonobese asthmatic women to investigate how leptin might contribute to the association between asthma and obesity.

The main finding of our study is that both obesity and high leptin levels had a negative impact on asthma control. Obesity was the only asthma-related factor analyzed that was significantly associated with poor asthma control in our series. Relatively little is known about the association between obesity and asthma control, although 2 recent studies have shown poorer asthma control and increased emergency room visits in obese patients [34,35]. Moreover, according to data from Lavoie et al [36], asthmatics with higher BMI have worse asthma control (assessed by the Asthma Control Questionnaire), regardless of disease severity [36]. Our results support this observation. In our study, the risk of having uncontrolled asthma, measured by the ACT, was 2.6 times higher in obese patients than in nonobese patients. Maniscalco et al [37], also using the ACT, found that asthma control improved significantly, and in parallel to a significant decrease in BMI, in obese patients after gastric banding surgery; they

also reported a significant improvement in asthma symptoms and rescue medication use with the reduction in BMI [37].

In a recent systemic review which showed that weight loss resulted in improved asthma status, the authors mentioned numerous factors that might contribute to the association between asthma and weight loss, including gastroesophageal reflux, inflammatory mediators, dietary intake, chest wall mechanics, and physical activity [3].

The current study is limited by its cross-sectional design. Longitudinal studies are needed to draw conclusions about the negative impact of high leptin levels on lung parameters and asthma outcomes.

In conclusion, obesity and high leptin levels might play a role in the disease process of asthma and also have a negative impact on asthma control, probably by increasing airway inflammation. The positive correlation between leptin and FE_{NO} levels would support this hypothesis. Longitudinal studies will help us to understand the pathophysiological association between asthma, obesity, and leptin and may also open new therapeutic options for asthma treatment in obese patients.

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References

1. Tantisira KG, Weiss ST. Complex interactions in complex traits: Obesity and asthma. *Thorax*. 2001; 56:ii64-74.
2. Shore SA. Obesity and Asthma: Implications for treatment. *Curr Opin Pulm Med*. 2007; 13:56-62.
3. Eneli IU, Skybo T, Camargo CA. Weight loss and asthma: a systematic review. *Thorax*. 2008; 63:671-76.
4. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. NHLBI/WHO Workshop Report. National Institute of Health. National Heart, Lung and Blood Institute. Revised 2006. Available from: www.ginasthma.com.
5. Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyper responsiveness. *J Allergy Clin Immunol*. 2005; 115:925-7.
6. Vieira V, Ronan AM, Windt MR, Tagliaferro AR. Elevated atopy in healthy obese women. *Am J Clin Nutr*. 2005; 82:504-9.
7. Shore SA, Johnston RA. Obesity and asthma. *Pharmacol Ther*. 2006; 110:83-102.
8. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. *Clin Endocrinol (Oxf)* 2006; 64: 355-65.
9. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD, Diehl AM. Leptin regulates proinflammatory immune responses. *FASEB J*. 1998; 12:57-65.
10. Torday JS, Sun H, Wang L, Torres E. Pre- and Postnatal Lung Development, Maturation, and Plasticity. Leptin mediates the parathyroid hormone-related protein paracrine stimulation of fetal lung maturation. *Am J Physiol Lung Cell Mol Physiol*. 2002; 282:405-10.
11. Guler N, Kirerleri E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol*. 2004; 114:254-9.
12. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med*. 2006; 174:112-19.
13. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations *Am J Respir Crit Care Med*. 2009;180: 59-99.
14. ATS Board of Directors, December 2004, and by the ERS Executive Committee. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. *Am J Respir Crit Care Med*. 2005; 171:912-30.
15. Pijnenburg MW, Floor SE, Hop WC, De Jongste JC. Daily ambulatory exhaled nitric oxide measurements in asthma. *Pediatr Allergy Immunol*. 2006; 17:189-93.
16. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: A survey for assessing asthma control. *J Allergy Clin Immunol*. 2004; 113: 59-65.
17. Hersoug L-G, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *J Allergy*. 2007; 62:1205-13.
18. Beuther DA, Sutherland ER. Over-weight, obesity and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007; 175: 661-6.
19. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Association of body mass with pulmonary function in the Childhood Asthma Management Programme (CAMP). *Thorax*. 2003; 58:1036-41.
20. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Yikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ*. 2000; 320:827-32.
21. Dhabuwala A, Cannan RJ, Stubbs RS. Improvement in comorbidities following weight loss from gastric bypass surgery. *Obes Surg*. 2000; 10:428-35.
22. Murr MM, Siadati MM, Sarr MG. Results of bariatric surgery for morbid obesity in patients older than 50 years. *Obes Surg*. 1995; 5:399-402.
23. Mai X-M, Böttcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. *Pediatr Allergy Immunol*. 2004; 15:523-30.
24. Sood A, Ford ES, Camargo CA. Association between leptin and asthma in adults. *Thorax*. 2006; 61:300-5.
25. Zeidler MR, Kleerup EC and Tashkin DP. Exhaled nitric oxide in the assessment of asthma. *Curr Opin Pulm Med*. 2004; 10:31-6.
26. Turktas H, Oguzulgen IK, Kokturk N, Memis L, Erbas D. Correlation of exhaled nitric oxide levels and airway inflammation markers in stable asthmatic patients. *J Asthma*. 2003; 40:425-30.
27. Komakula S, Khatri S, Mermis J, Savill S, Haque S, Rojas M, Brown L, Teague GW, Holguin F. Body mass index is associated with reduced exhaled nitric oxide and exhaled 8 isoprostanes in asthmatics. *Respir Res*. 2007; 8:32-44.
28. Oguzulgen IK, Turktas H, Erbas D. Airway inflammation in premenstrual asthma. *J Asthma*. 2002; 39:517-22.
29. Barnes PJ, Woolcock AJ. Difficult asthma. *Eur Respir J*. 1998; 12:1209-18.
30. Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. *FASEB J*. 1999; 13:1231-8.

31. Matsuda K, Nishi M, Okamatsu M, Kojima M, Matsuishi T. Ghrelin and leptin: a link between obesity and allergy? *J Allergy Clin Immunol*. 2006; 117: 705-6.
32. Shore SA, Schwartzmann IN, Mellema MS, Flynt L, Imrich A, Johnston RA. Effect of leptin on allergic airway responses in mice. *J Allergy Clin Immunol*. 2005; 115:103-9.
33. Hickey MS, Israel RG, Gardiner SN, Considine RV, McCammon MR, Tyndall GL, Houmard JA, Marks RH, Caro JF. Gender differences in serum leptin levels in humans. *Biochem Mol Med*. 1996; 59:1-6.
34. Akerman MJ, Calacanis CM, Madsen MK. Relation between asthma severity and obesity. *J Asthma*. 2004; 41:521-6.
35. Thomson CC, Clark S, Camargo JA Jr. Body mass index and asthma severity among adults presenting to the emergency department. *Chest*. 2003; 124:795-802.
36. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated worse asthma control and quality of life but not asthma severity. *Respir Med*. 2006; 100:648-57.
37. Maniscalco M, Zedda A, Faraone S, Cerbone MR, Cristiano S, Giardiello S. Weight loss and asthma control in severely obese asthmatic females. *Respir Med*. 2008; 102:102-8.

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