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Leptin, Adiponectin, and Ghrelin Levels in Female Patients with Asthma during Stable and Exacerbation Periods

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Objective. The mechanisms underlying the relationship between obesity and asthma have not been fully established. Data in the literature suggest that adipose tissue-derived hormones may be implicated. However, no definite conclusion regarding the role of leptin and adiponectin with asthma are available. No studies have examined the role of ghrelin in asthma. *Methods.* We assessed the circulating concentrations of leptin, adiponectin, and ghrelin in 32 postmenopausal stable asthma patients, 37 female asthmatics during exacerbations and 8 weeks later, and 22 controls. We examined the relationship between the three peptides and indexes of pulmonary function, airway inflammation, and atopy. *Results.* Stable asthma patients exhibited higher leptin and lower ghrelin concentrations compared with controls. Patients with severe asthma had higher leptin and lower adiponectin levels versus patients with mild to moderate asthma. Both leptin concentrations and leptin/adiponectin ratio served as markers for discriminating asthma patients from controls on the one hand, and severe from mild to moderate asthmatics on the other. Leptin levels were inversely correlated with both FEV_1/FVC and $FEF_{25–75}$ in patients with mild to moderate asthma. Atopic asthma patients had higher leptin concentrations than nonatopic asthma patients. There was a positive correlation between serum leptin and total IgE levels in atopic asthmatics. Finally, serum leptin levels and leptin/adiponectin ratio were significantly increased during asthma exacerbations, while adiponectin and ghrelin levels were significantly decreased. *Conclusion.* Our findings suggest that leptin, adiponectin, and ghrelin may play a significant role in the pathogenesis of asthma during both stable state and asthma exacerbation, independent of obesity.

Keywords adiponectin, airway inflammation, asthma, exacerbation, ghrelin, leptin

INTRODUCTION

Several studies have shown that obesity increases the risk of incident asthma (1) and asthma severity (2). The mechanisms underlying these relationships are not fully established. However, evidence suggests that adipose tissue-derived immunomodulatory changes are possibly implicated. Obesity represents a state of low-grade systemic inflammation affecting lung microenvironment (3). Imbalance in hormones that are secreted by the adipose tissue, such as leptin and adiponectin, may contribute to airway hyperresponsiveness, even though it does not affect airway eosinophilia or Th_2-cytokine expression (4).

Leptin was originally described as a satiety hormone produced by adipocytes (5). Its circulating levels increase in obesity to inform the host about the excess of peripheral lipid energy storage. Leptin is a pleiotropic hormone implicated in the immune response and considered to be proinflammatory (6). It has been shown to prime leukocytes for increased cytokine synthesis (7), enhanced oxidative burst (8) and nitric oxide (NO) production (9). Previous reports demonstrating that leptin up-regulates leukotriene (LT) biosynthesis in murine alveolar macrophages may provide a link between obesity and airway inflammation in the setting of asthma (10). Further, activation of leptin receptors in airway smooth muscle (ASM) has been shown to increase the release of vascular endothelial growth factor (VEGF), which is implicated in asthma severity (11–13). Cross sectional studies in adults and children have shown that asthmatics have higher plasma leptin levels (14, 15). Leptin has been associated with asthma in females and this association seems stronger in premenopausal women. However, other studies have failed to document any direct association between leptin and the presence of asthma (16). While recent data indicate that hormonal factors may play a role in the severity of asthma (17), only few studies examining the relationship between leptin and asthma have excluded the potential sex-related bias. Finally, leptin administration increases airway hyperresponsiveness (AHR) caused by allergens in animals (4). In this respect, one could argue that leptin may worsen asthma control.

Adiponectin is the most abundant gene product of adipose tissue and, unlike leptin, its levels decline in obesity (18). Adiponectin demonstrates anti-inflammatory effects; it increases interleukin-10 (IL-10) mRNA expression and

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IL-10 production in human macrophages (19). IL-10 is a major anti-inflammatory cytokine and plays a crucial role in the regulation of the immune system (20–23). Thus, decreased adiponectin levels associated with obesity may result in decreased immune tolerance (24). High adiponectin concentrations have been associated with lower asthma prevalence rates in women (25), while exogenous administration of adiponectin has been shown to suppress allergen-induced AHR and airway inflammation in a murine model (26). Interestingly, the lungs of adiponectin-deficient mice exhibit an emphysema-like phenotype that is associated with activated alveolar macrophages spontaneously elaborating TNF-α and matrix metalloproteinase-12 (27). In a later study of allergen-induced asthma model, Medoff et al. have reported that adiponectin-deficient mice exhibit increased pulmonary inflammation, severe pulmonary arterial muscularization, and pulmonary arterial hypertension (28). Since adiponectin exerts anti-inflammatory properties and may have antimitogenic effects on airway smooth muscle cells (13), one could argue that the decreased serum concentrations of adiponectin observed in the obese may contribute to the propensity toward AHR in this population (2). Additionally, reduced adiponectin levels, induced by allergic reactions, may aggravate allergic asthma (26).

Ghrelin is a peptide hormone released from neuroendocrine cells in the stomach. The functions of ghrelin are closely related to those of adipokines, that is, it is important in body weight regulation. In particular, ghrelin levels rise during fasting and just before a meal and decrease after food intake (29). Negative correlations between circulating ghrelin concentrations and body mass index have been found in human (30). Moreover, ghrelin demonstrates immunomodulatory properties. It plays a crucial role in maintaining immune tolerance through two distinct mechanisms: by regulating the balance between proinflammatory and anti-inflammatory factors, and by inducing the emergence of regulatory T cells with suppressive activity (31). Indeed, alterations in serum ghrelin levels and/or its receptors' affinity may lead to changes in susceptibility to inflammatory and autoimmune diseases. Additionally, ghrelin exhibits antimicrobial actions, suggesting that it may act as a primary mediator of innate defense. Studies have shown an inverse correlation between plasma ghrelin and serum IgE levels in obese children (32). However, the role which ghrelin plays in adult asthma has not been studied.

In this study, we attempt to elucidate the role of leptin, adiponectin, and ghrelin in asthma severity and atopy. We hypothesized that leptin, adiponectin, and ghrelin are important contributors to the airway inflammation in asthmatic women, especially during acute attacks. In order to exclude the effect of reproductive hormones, only postmenopausal women were included in the study.

Materials and Methods

Additional details on the methods are available in the online depository (http://informahealthcare.com/doi/suppl/[10.3109/02770903.2012.747101]).

Study Subjects

The study included 32 female postmenopausal asthma patients who were consecutively evaluated in the outpatient asthma clinic of Respiratory Medicine Department at the University Hospital of Larissa from February 2007 until April 2009. Female postmenopausal asthma patients were eligible for inclusion in the study if (1) they had not been having a menstrual period for at least 1 year; (2) they had a diagnosis of persistent asthma confirmed by chest physician; (3) diagnosis had occurred at least 6 months before the beginning of the study; (4) they had stable asthma, defined as no history of exacerbation at the time of presentation or in the past 12 months and no change of controller medication within the last 4 weeks prior to the start of the study; and (5) they had not received oral corticosteroids in the past 8 weeks and had never been treated with other immunosuppressive agents.

Exclusion criteria included: (1) chronic respiratory disease other than asthma; (2) recent lower or upper respiratory tract infection; (3) systemic inflammatory disease or cardiac disorders; (4) use of nonsteroid anti-inflammatory drugs or antihistamines; (5) hormonal replacement therapy; (6) comorbidities (e.g., diabetes mellitus, food intake disorders); and (7) smoking history or habit (only never or ex-smokers with a smoking history of less than 10 pack-years were eligible for inclusion in the study).

Asthma control was assessed by clinical features of disease and lung function abnormalities on the basis of the 2006 GINA report. Only patients with controlled asthma were included. Because patients were already receiving treatment, some considerations were made. Asthma severity was described not only in relation to the level of asthma control but also in terms of the intensity of treatment required to achieve asthma control. Asthma that was well controlled with low intensity treatment, such as low-dose inhaled corticosteroids either alone or in combination with a long-acting β-agonist was characterized as mild to moderate. Severe asthma was asthma that required high intensity treatment, for example, GINA step 4, to maintain good control (33).

Twenty two healthy postmenopausal women, matched for age and body mass index (BMI) with the patient group served as controls. The subjects included had neither known medical history nor acute respiratory disease and performed normal pulmonary function tests .

A parallel study was performed in the Emergency Department (ED) including 37 women admitted with acute exacerbation of asthma. Acute exacerbation of asthma was defined according to standard criteria as following: episodes of rapidly progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms necessitating a nonscheduled visit, and associated to a decrease of respiratory airflow quantified by measurements of peak expiratory flow or forced expiratory volume in the 1st second ($FEV_{1)}$. Exclusion criteria included: pneumonia, impaired consciousness on admission, requirement of assistant ventilation, recent use of systemic corticosteroids, and pregnancy.

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The study protocol was approved by the Ethics Committee and all participants provided written informed consent.

First Part

A detailed clinical history was obtained and a complete physical examination was performed. BMI was calculated as kg/m^2. Bioelectrical impendance analysis of fat mass (FM) and fat-free mass (FFM) was assessed by a commercially available body analyzer (BIA 101 System Analyser, Akern, Florence, Italy), according to current recommendations. Fat mass index (FMI) and fat-free mass index (FFMI) were calculated as FM/height^2 and FFM/height^2, respectively. Spirometry was performed by the same technician (A.T.) (Viasys, USA), according to American Thoracic Society (ATS) recommendations. Blood was collected after a 12-hour overnight fast, centrifuged at 1500 g for 15 min at 4°C and supernatants were stored at −80°C until measurements. Total serum leptin, ghrelin and adiponectin levels were measured using human radioimmunoassay kits, with a sensitivity of 0.1 ng/ml for leptin (Active Human Leptin IRMA DSL-23100; Diagnostic Systems Laboratories, Inc., USA), 40 pg/ml for ghrelin (Phoenix Pharmaceuticals Inc., Belmont, CA, USA), and 1 ng/ml for adiponectin (Active Human Adiponectin CYT-024, Diagnostic Systems Laboratories, Inc.).

Skin prick tests and specific IgE assays were performed. Total IgE was assessed with particle-enhanced immunonephelometry (Dade Behring, Marburg GmbH, USA). Subjects were classified as atopic if they had at least one positive skin prick response or IgE over 100 IU/ml.

Fraction of exhaled Nitric Oxide (NO) (FeNO) was measured using a commercial portable NO analyzer (NIOX MINO®, Aerocrine, Solna, Sweden). Exhaled breath condensate (EBC) was collected using a commercially available condenser (EcoScreen, Viasys, Hoechberg, Germany) under standard recommendations. Stable pH was achieved after deaeration with inert gas and was measured with commercially available pH meter.

Second Part

Thirty-seven women with acute exacerbation of asthma were submitted to measurements of FeNO, spirometry, and arterial blood gases, while blood was obtained before they received any medication at the ED, based on a self-reported fasting state for at least 10 hours for the measurement of serum leptin, adiponectin, and ghrelin levels. Weight and height were recorded. Subjects were followed up after 8 weeks of discharge and underwent the same measurements. Blood samples were collected between 6:00 a.m. and 6:00 p.m., at a given time for each pair of variables.

Statistical Analysis

Normally distributed data are presented as mean (SD: standard deviation), whereas skewed data are reported as median (IQR: interquartile range). Normality of distribution for numerical variables was assessed by the Shapiro–Wilk normality test, which is more appropriate for small sample sizes. The values were statistically analyzed with independent Student's *t*-test or one-way ANOVA (for inter-group comparisons) and paired *t*-test (for intra-group comparisons). Once multiple comparisons had been made, a commonly used post hoc test, the Bonferroni test, was performed to adjust the observed significance level among the means. Categorical variables are expressed as a percentage; comparisons between the groups were performed using Fisher's exact test.

The values of serum leptin, adiponectin, and ghrelin concentrations and leptin-to-adiponectin (L/A) ratios were natural-logarithmically (ln) transformed to obtain a near-normality distribution before analysis. A general linear model (GLM) procedure was used to perform comparisons between groups. The differences between asthmatics and controls were further adjusted for possible effect modifiers (age, BMI, and atopic status) using the GLM and employing separately each of leptin, adiponectin, and ghrelin concentrations and L/A ratio as dependent variable. In comparing severe versus mild to moderate asthma, the differences were also adjusted for possible effect modifiers (age, BMI, FM, atopic status, and inhaled corticosteroid [ICS] use) using again the GLM; but, the later model included each effect modifier in turn due to the limited number of patients.

Receiver operating characteristic (ROC) curve analyses were performed in order to obtain the area under the ROC curve (AUC) and estimate the efficacy of serum leptin, adiponectin, and ghrelin concentrations and L/A ratios in discriminating patients with asthma from controls and severe from mild to moderate asthmatics. No threshold values were defined. AUCs more than 0.5 were considered statistically significant. Pearson and Spearman's rank correlation coefficients were used for simple correlation analysis between normally distributed and skewed variables, respectively. Analyses were performed using GraphPad Prism 5 (GraphPad Software Inc, La Jolla, CA, USA) and SPSS 18 (SPSS, Chicago, IL, USA). All tests were two-sided and a *p*-value less than .05 was considered statistically significant.

RESULTS

Clinical characteristics of participants in the first part of the study are summarized in Table 1. Thirty-two female postmenopausal asthma patients (17 with mild to moderate asthma and 15 with severe asthma, according to the criteria described previously) and 22 controls were included.

Severe asthmatics were more obese ($n = 15$, BMI: 36.5 ± 5.4 kg/m^2) than patients with mild to moderate asthma ($n = 17$, BMI: 32.3 ± 6.0 kg/m^2) ($p = .046$). However, the two groups were not different in terms of body composition (FM, FMI, FFM, and FFMI) ($p > .05$) (not all data shown).

As expected, asthma patients exhibited higher FeNO ($p = .001$) compared with controls, while severe asthma

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TABLE 1.—Clinical characteristics of study participants.

Variables	Asthma: Severe mean ± SD median (IQR)	Asthma: Mild to moderate mean ± SD median (IQR)	Controls mean ± SD median (IQR)	*P* value
N	15	17	22	–
Age (years)	55.3 ± 9.9	59.6 ± 7.8	57.6 ± 10.9	.473
BMI (kg/m^2)	36.5 ± 5.4*·**	32.3 ± 6.0	31.2 ± 6.1	.030
FM (kg)	44.6 ± 14.1	33.1 ± 14.8	–	.059
FEV_1 (%pred)	79.4 ± 12.3*·**	92.9 ± 9.2*	99.9 ± 11.2	.014
FEV_1/FVC (%)	71.3 ± 10.4*·**	79.4 ± 5.9*	82.9 ± 3.0	.002
EBC-pH	6.7 (6.1–7.1)*·**	7.3 (6.5–7.5)	7.3 ± 0.2	.001
FeNO (ppb)	9.0 (8.0–11.0)*	15.0 (7.5–16.5)*	6.0 (5.0–10.0)	.001
Atopic status *n* (%)	8 (53.3)	8 (47.1)	4 (18.2)	.055
IgE_{total} (U/ml)	32.1 (25.7–77.0)	43.1 (29.0–75.3)*	31.0 (17.3–44.3)	.042

Note: BMI, body mass index; FM, fat mass; FEV_1, forced expiratory volume in the 1st second (%pred: percentage of the reference value for someone of that ethnic group, gender, age and height); FVC, forced vital capacity; EBC, exhaled breath condensate; FeNO, fraction of exhaled nitric oxide; ppb, parts per billion; IgE, immunoglobulin E.
*$P < .05$ compared with controls, **$P < .05$ compared with mild to moderate asthmatics.

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was characterized by lower values of pH in EBC compared with both mild to moderate asthmatics ($p = .031$) and controls ($p = .000$).

Leptin, Adiponectin, and Ghrelin Association with Asthma

In comparing the asthma group with controls for each of leptin, adiponectin, and ghrelin concentrations and L/A ratio, significant differences were derived for leptin and ghrelin levels and L/A ratio ($p = .003$, $p = .001$, and $p = .002$, respectively) (Table 2). In particular, leptin concentrations and L/A ratio were higher in the asthma group; on the contrary, asthmatics exhibited lower ghrelin levels (Table 2). In adjusting the differences between the two groups for possible effect modifiers, such as age, BMI, and atopic status, the pattern of results in terms of significance remained the same (Table 2).

In investigating the discrimination value of leptin, adiponectin, and ghrelin concentrations and L/A ratio, three of them indicated an ability to discriminate between asthmatics and controls: leptin [AUC = 0.735 (95% confidence interval (CI) = 0.599–0.871)], L/A ratio [AUC = 0.736 (95% CI = 0.602–0.870)], and ghrelin [AUC = 0.827 (95% CI = 0.704–0.949)] (Figure 1).

TABLE 2.—Current asthma association with serum leptin, adiponectin, and ghrelin concentrations and L/A ratio.

	Asthma ($N = 32$) mean ± SD	Controls ($N = 22$) mean ± SD	*P*-value	*P* value*
Leptin (ng/ml)	24.8 ± 14.8	13.7 ± 10.0	0.003	.035
Adiponectin (ng/ml)	13.5 ± 9.2	10.1 ± 6.4	0.162	.147
Ghrelin (pg/ml)	524.8 ± 274.8	777.3 ± 261.5	0.001	.010
L/A ratio	3.9 ± 4.5	1.8 ± 1.2	0.002	.003

Note: *Adjusted for age, BMI, and atopic status.

Leptin, Adiponectin, and Ghrelin Association with Asthma Severity

Asthma group was divided into two groups: severe asthma and mild to moderate asthma. As shown in Table 3, patients with severe asthma had lower adiponectin concentrations ($p = .015$) and higher L/A ratio ($p = .024$) compared with patients with mild to moderate asthma. Leptin levels also tended to be higher in severe asthma patients than in mild-to-moderate asthma patients ($p = .051$), whereas ghrelin concentrations did not change significantly along with asthma severity.

After adjustment for possible effect modifiers, such as age, BMI, FM, atopic status, and ICS dose, the significance of the difference between the two groups was altered for leptin when the effect of age was considered ($p = .04$). For adiponectin, the effect of BMI and FM diminished the significance of the difference ($p = .07$ and $p = .17$, respectively). Similarly, for the L/A ratio, the effect of BMI and FM diminished the significance of the difference ($p = .09$ and $p = .21$, respectively). For ghrelin, none of the examined effect modifiers changed the pattern of significance.

Finally, leptin and adiponectin concentration levels and L/A ratio may discriminate patients with severe asthma from mild to moderate asthmatics: AUC = 0.733 (95% CI = 0.553–0.913), AUC = 0.751 (95% CI = 0.574–0.928), and AUC = 0.749 (95% CI = 0.570–0.928), respectively (Figure 2).

In patients with mild to moderate asthma, serum leptin levels were inversely correlated with both FEV_1/FVC ($r = -0.514$, $p = .035$) and $FEF_{25–75}$ ($r = -0.493$, $p = .046$).

Leptin, Adiponectin, and Ghrelin Association with Airway Inflammation Parameters

Patients with severe asthma had lower EBC-pH values versus mild to moderate asthma patients ($p = .031$) (Table 1). Ghrelin levels and EBC-pH were significantly

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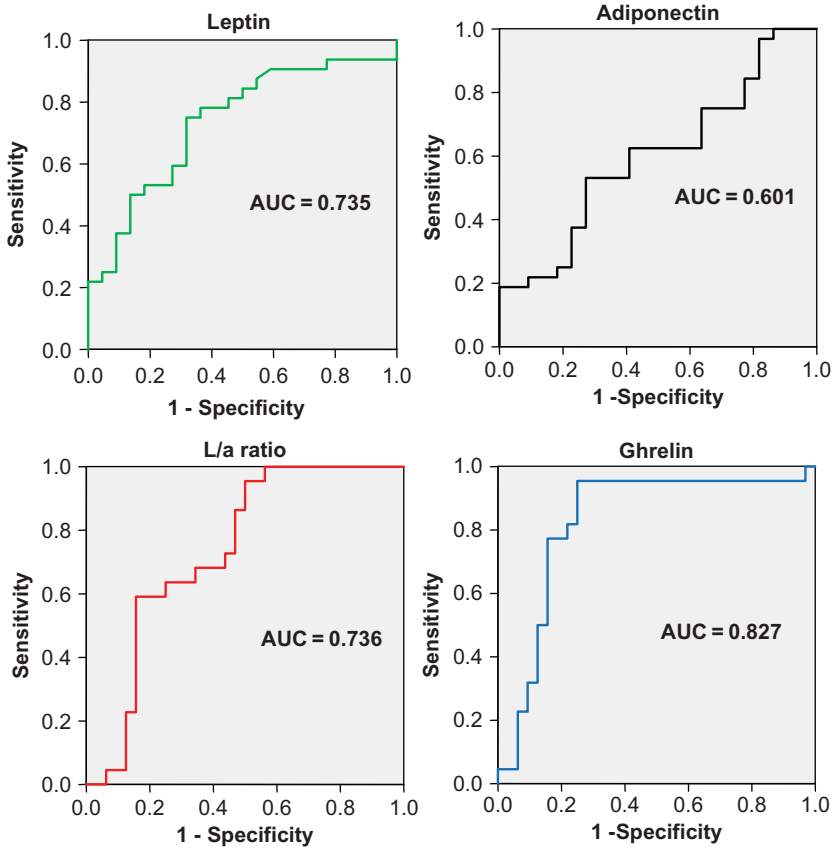

FIGURE 1.—ROC analysis of leptin, adiponectin, L/A ratio, and ghrelin for discriminating asthma patients from controls.

TABLE 3.—Asthma severity association with serum leptin, adiponectin, and ghrelin concentrations and L/A ratio.

	Severe asthma ($N = 15$) Mean ± SD	Mild to moderate asthma ($N = 17$) Mean ± SD	*P* value
Leptin (ng/ml)	31.1 ± 15.5	19.2 ± 12.1	.051
Adiponectin (ng/ml)	9.8 ± 7.8	16.6 ± 9.3	.015
Ghrelin (pg/ml)	513.6 ± 364.4	534.7 ± 172.9	.296
L/A ratio	5.6 ± 4.8	2.3 ± 3.5	.024

correlated in asthmatics ($r = 0.414$, $p = .019$). This correlation was confined entirely to patients with severe asthma ($r = 0.561$, $p = .029$). We did not find any correlation of leptin and adiponectin levels or L/A ratio with EBC-pH in asthma. Additionally, FeNO levels were not significantly correlated with leptin, adiponectin, and ghrelin concentrations or L/A ratio.

Association of Leptin with Atopic Status

Patients with combined asthma and atopy had significantly higher serum leptin and total IgE levels than healthy subjects ($p = .005$ and $p = .002$, respectively), whereas similar differences were not observed for nonatopic asthmatic patients compared with controls. Subgroup analysis also revealed a significant difference in total serum IgE levels between atopic and nonatopic patients with asthma (means ± SDs: 115.3 ± 120.6 vs 30.8 ± 13.4, respectively; $p = .001$) despite similar BMI (Figure 3). Moreover, total serum IgE levels correlated positively with serum leptin levels in the overall group of asthmatic patients ($r = 0.358$, $p = .044$); again, this correlation was confined entirely to atopic asthmatic patients ($r = 0.505$, $p = .046$).

Levels of Leptin, Adiponectin, and Ghrelin at Asthma Exacerbation

The characteristics of patients with asthma exacerbation are shown in Table 4. During asthma exacerbation, leptin levels and L/A ratio were elevated compared to measurements taken 8 weeks later ($p < .0001$). In contrast, serum concentrations of adiponectin and ghrelin presented a significant decrease on admission when a comparison was made 8 weeks later ($p < .0001$ and $p = .0003$, respectively) (Figure 4). The same pattern was seen when adipokines levels were adjusted for BMI. Moreover, the L/A ratio was inversely correlated with Partial Pressure of Oxygen in Arterial Blood (PaO_2) during exacerbation ($r = -0.717$, $p = .030$).

DISCUSSION

In this study we showed that high leptin concentrations, high L/A ratio and low ghrelin levels were associated with current asthma in postmenopausal women. These

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TABLE 4.—Clinical characteristics of patients admitted with acute exacerbation of asthma and followed up 8 weeks later.

$N = 37$	Acute exacerbation	Week 8	P value
Age (years)	51.24 ± 14.50		–
BMI (kg/m^2)	29.25 ± 6.047		–
FEV_1 (%pred)	65.7 ± 22.6	88.0 ± 22.1	<.0001
FEV_1/FVC (%)	65.9 ± 17.2	86.2 ± 10.7	<.0001
$FEF_{25–75}$ (%pred)	42.0 ± 24.9	56.7 ± 23.7	<.0001
FeNO (ppb)	15.0 (9.5–28.8)	11.0 (8.0–15.0)	.244
Leptin (ng/ml)	19.8 (15.2–29.1)	9.8 (6.1–16.2)	<.0001
Adiponectin (ng/ml)	7.9 ± 3.2	15.0 ± 7.0	<.0001
L/A ratio	2.6 (1.9–4.6)	0.6 (0.4–1.1)	<.0001
Ghrelin (pg/ml)	662.6 ± 227.5	884.0 (660.4–1018)	.0003

Notes: BMI, body mass index; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; $FEF_{25–75}$, forced mid-expiratory flow; FeNO, fraction of exhaled nitric oxide; ppb, parts per billion; L/A ratio, leptin-to-adiponectin ratio.
Values are expressed as mean ± SD or median (interquartile ranges) for normally distributed and skewed data, respectively.

associations occurred independent of obesity. In addition, we observed higher leptin and lower adiponectin levels, and thus higher L/A ratio, in patients with severe asthma. Of more interest, both leptin level and L/A ratio were found to discriminate asthma patients from controls and severe from mild to moderate asthmatics. Moreover, our study demonstrated for the first time that asthma exacerbations are characterized by increased leptin and decreased adiponectin and ghrelin levels. A significant correlation was found between leptin and the degree of airway obstruction in patients with mild to moderate asthma. In severe asthmatics, ghrelin levels were positively associated with EBC-pH. Finally, in individuals with atopic asthma, there was a positive correlation between serum leptin and total IgE concentrations.

The elevated leptin levels in asthma patients observed in our study are in association with previous studies that have also reported increased leptin concentrations in asthmatic children (14, 34) and adults (25). In adjusting for possible effect modifiers, BMI did not modify the association between current asthma and serum leptin concentrations. Based on the AUCs and their 95% CI, ROC curves for serum leptin concentrations suggested that leptin can differentiate asthma patients, especially those with severe asthma, from healthy individuals. Thus, in patients with asthma, leptin may be operating beyond the regulation of energy balance.

To our knowledge, this is the first study describing an inverse correlation between serum leptin levels and both FEV_1/FVC and $FEF_{25–75}$ in patients with mild to moderate asthma. A previous study reported that leptin-positive cells within the bronchial wall inversely correlated with FEV_1 and FEV_1/FVC in Chronic Obstructive Pulmonary Disease (COPD) subjects. Authors suggested that leptin may play a cytokine-like role within the airways associated with airflow impairment (35). Although leptin receptor expression has been demonstrated in human airways (35), the effects

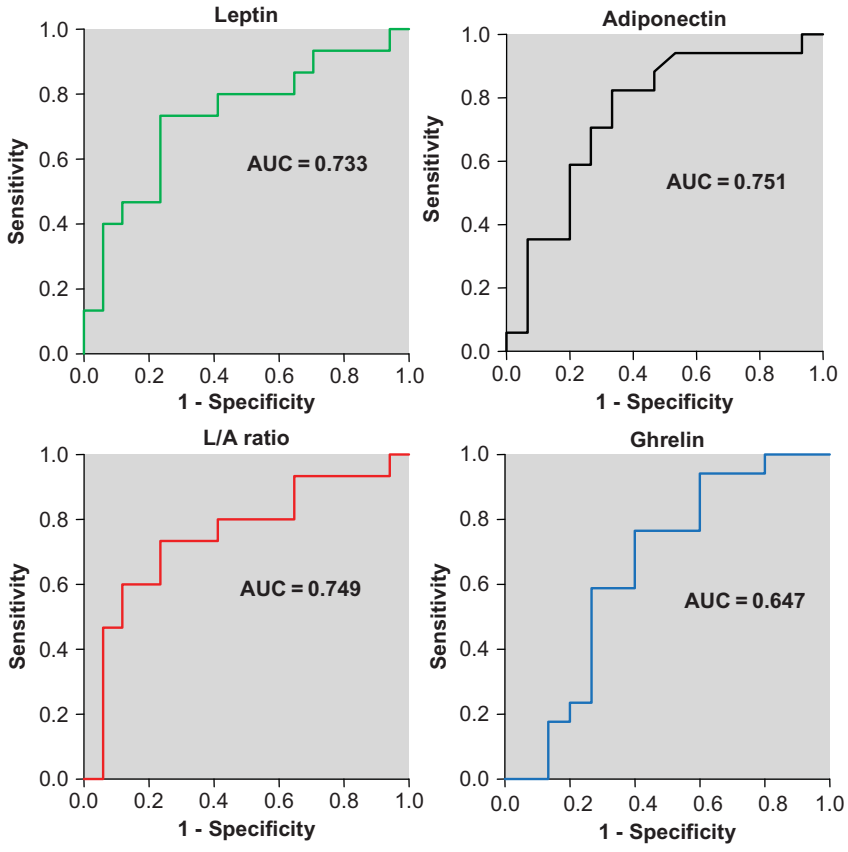

FIGURE 2.—ROC analysis of leptin, adiponectin, L/A ratio, and ghrelin for discriminating severe from mild to moderate asthma.

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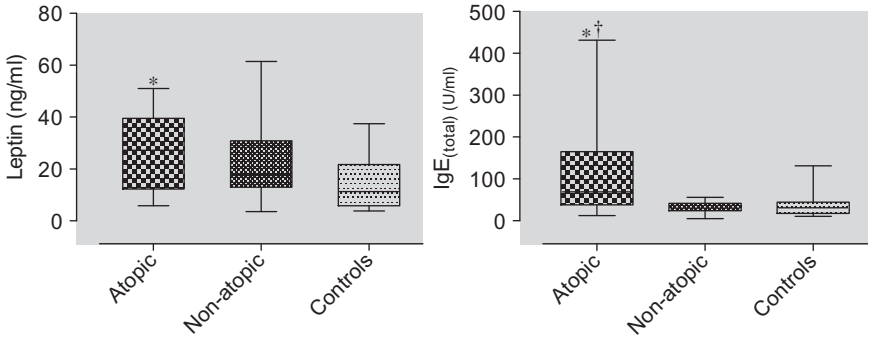

FIGURE 3.—Serum leptin and $IgE_{(total)}$ in atopic and nonatopic patients with asthma.
Note: $^{*}P < .05$ compared with controls; $^{\dagger}P < .05$ compared with mild to moderate asthmatics.

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of leptin on human ASM functions are conflicting. Nair et al., (36) demonstrated that leptin inhibited ASM proliferation and migration induced by platelet-derived growth factor and eotaxin production induced by IL-13; but, leptin did not stimulate proinflammatory cytokine release from ASM cells. However, recent data have shown that leptin induces VEGF release from ASM cells (13); VEGF is also leading to an asthma-like phenotype characterized by mucus hyperplasia, subepithelial fibrosis, smooth muscle hyperplasia and AHR (12, 37). Therefore, although leptin is unlikely to have a direct effect on ASM functions, if the measured levels of leptin in the present study had been more closely allied to the local inflammation within the airways, a different picture might have emerged.

There is some evidence that not only local but also systemic inflammation occurs in bronchial asthma (38). In the setting of obesity, the ability of adipose tissue to elaborate proinflammatory cytokines, including leptin, increases, while the synthesis of adiponectin, which possess anti-inflammatory properties, declines. Inflammatory mediators produced in adipose tissue spill over into the peripheral circulation and contribute to a low-grade state of chronic systemic inflammation (39, 40). Moreover, adipose tissue can respond to proinflammatory stimuli initiated in the lung and exacerbate adipokines production (41–44). However, clear evidence of either an additive or a synergistic pathologic interaction between obesity and asthma is lacking in humans. Interestingly, we did not find obesity to affect significantl serum leptin concentrations in the asthma group; this suggests that leptin secretion may be dysregulated due to the disease.

Furthermore, in the present study we demonstrated that asthma severity was associated with increased L/A ratio, resulting from increased leptin and decreased adiponectin observed in severe asthma. The AUC was 0.749 and 95% CI was 0.570–0.928, suggesting that changes in serum L/A

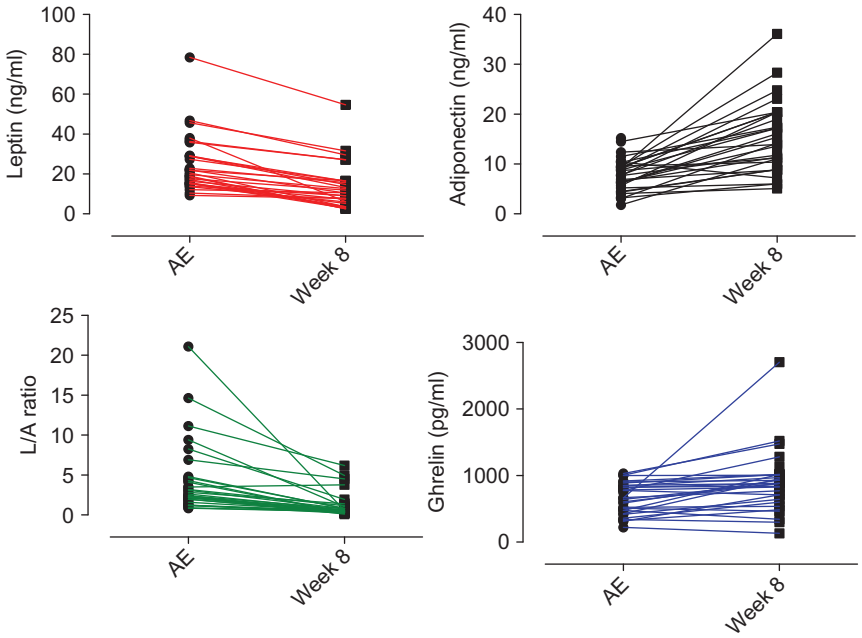

FIGURE 4.—Changes of serum leptin, adiponectin, L/A ratio, and ghrelin during acute exacerbation of asthma.
Note: AE: acute exacerbation, week 8: 8 weeks after AE.

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ratio may have a direct relation to asthma severity. The L/A ratio may reflect the balance between proinflammatory and anti-inflammatory factors secreted by the adipose tissue, and may be linked to asthma severity by modulating airway inflammation. This is in agreement with other authors, who have reported that alterations of leptin/adiponectin balance may be related to the presence of leukotriene inflammation, speculating a link between systemic and local inflammation in asthmatics (45). Komakula et al., have also showed that in asthmatics, the plasma L/A ratio is associated with reduced exhaled NO, possibly reflecting an increase in airway oxidative stress (46).

Literature lacks data regarding the role of ghrelin in adult asthma. Our study is the first to demonstrate the ability of ghrelin to discriminate between asthmatics and controls (AUC = 0.827, 95% CI = 0.704–0.949). Moreover, a significant positive correlation exists between ghrelin concentrations and EBC-pH in severe asthmatics. EBC-pH is one of the robust biomarkers of asthma associated airway inflammation and oxidative stress (47). Ghrelin exerts anti-inflammatory effects through inhibition of the production of proinflammatory cytokines (48). Ghrelin receptors are expressed in lung parenchyma (49). Therefore, one could hypothesize that ghrelin may have protective role in the lung. Experimental data have shown that intravenous administration of ghrelin after the onset of sepsis in rats increases pulmonary levels of ghrelin, ameliorates lung histology, reduces lung water content, elevates lung blood flow, decrease pulmonary levels of proinflammatory cytokines, and improves survival.

Most studies focus on chronic inflammation comparing stable patients with controls. Our study is the first to explore the relationship between adipokines and ghrelin and asthma exacerbations. Asthma attacks are associated with transient increase in leptin and a decrease in adiponectin and ghrelin levels. Our findings are in agreement with animal studies showing a decrease in adiponectin (26) and increase in leptin (4) following ovalbumin (OVA) challenge. The systemic inflammatory response associated with the exacerbation may induce leptin production and downregulate adiponectin and ghrelin expression in the lung systemically. Proinflammatory mediators, e.g., TNF-α, suppress adiponectin production by adipocytes (50), while leptin expression is upregulated by proinflammatory markers, including IL-1 (6). Ghrelin production decreases significantly in acute inflammatory processes like sepsis (51) and acute lung injury (49). Additional studies are warranted in order to elucidate the mechanisms responsible for the disturbances in leptin, adiponectin, and ghrelin levels during asthma attacks.

Regardless of how the alteration of leptin, adiponectin, and ghrelin concentrations comes about in asthma exacerbations, it may have important functional implications. Leptin may induce accumulation of eosinophils and may enhance inflammatory processes at sites such as the airways and thereby augment airway responses (10, 52). Leptin-treated animals exhibit augmented responses to metacholine and increased levels of IgE, following OVA challenge (4). Leptin augments alveolar macrophage leukotriene synthesis (10) and induces the release of IL-1 from eosinophils and IL-6 from macrophages (52), suggesting that leptin may exacerbate airway inflammation and symptoms in asthma (4, 13). On the other hand, adiponectin can attenuate airway allergic reactions (26). Thus, the reduction of adiponectin, associated with asthma attacks, may result in the loss of the beneficial effects of adiponectin regarding airway inflammation.

Finally, in our study atopic asthmatics had significantly higher serum leptin levels than healthy subjects, whereas that was not the case for nonatopic asthmatic patients compared with controls. A positive correlation between serum leptin and total IgE was also found in atopic asthmatics. Similar data have come from previous studies examining the relation between leptin and parameters of atopy and asthma in children (34) and adults (53). Regarding the relationship between obesity and atopic asthma, some controversy exists. In particular, data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES) reports suggested that obesity was associated with both atopic and nonatopic asthma (54). Recently, in a retrospective study of 246 adults with asthma, obesity was found to be associated with increased asthma prevalence, worsened asthma severity and increased serum IgE; the authors suggested that obesity in inner-city adults may be both a risk and exacerbating factor for atopic asthma (55). In contrast, Chen et al., revealed a stronger association between obesity and asthma among nonatopic subjects (56). Other data from the literature supported that obesity may lead to systemic inflammation that in turns leads to an increased risk of asthma in nonatopic individuals. There is no evidence of a relationship between systemic inflammation and asthma among atopic youth (57). In a cluster analysis performed by Haldar et al., the early-onset atopic asthma with concordant eosinophilic airway inflammation and the obese noneosinophilic asthma phenotype were described as two distinct entities (58). Although the prevalence of atopy did differ significantly between clusters, atopic status was not identified as a significant discriminator influencing cluster membership. These findings suggest that systemic and allergic inflammation may operate independently on the pathway to asthma. Actually, none of the later studies assessed the implication of leptin in obesity–asthma association.

Laboratory studies have indicated that leptin can polarize T-helper (Th) cells toward a Th_1 response (59) and can also augment OVA-induced IgE production in sensitized mice (4). In view of atopic diseases, the IgE-mediated reaction is a well-known pathogenic model. Radon et al. have shown a linear positive association between serum leptin levels and prevalence of allergic sensitization in adults, independent of obesity (60). Overall, leptin acts on a variety of immune cells related to allergic response and may also activate eosinophils via differential intracellular signaling cascades (52). Thus, the positive correlation between leptin and IgE in atopic asthmatics documented in our study may be designating the latent allergic disposition rather than mediating the obesity–asthma association.

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One could argue that since we included only postmenopausal women, our results may have limited external validity. However, since studies have shown that hormonal factors may be involved in the severity of asthma (17), we believe that by eliminating this potential confounder we provide evidence for the relation of adipokines with severe asthma. The main limitation is that our sample size might be considered relatively low. This fact probably makes our findings rather unstable and accumulation of more data is needed to further explore the diagnostic and prognostic utility of leptin, adiponectin, and ghrelin in the setting of asthma.

In conclusion, leptin, adiponectin, and ghrelin are associated with asthma and asthma severity. Interestingly, the underlying interacting pathogenic mechanisms occur independent of obesity. In particular, asthma induces changes in serum concentrations of adipokines and ghrelin, which in turn may worsen the disease clinical profile, and may have significant pathophysiological implications during stable and exacerbation periods. The balance of the aforementioned hormones in the circulation may reflect the intensity of the asthma-related inflammation rather than expressing the nutritional status. More prospective studies are warranted in order to determine the temporal relationship (causal direction) of the association of leptin, adiponectin, and ghrelin with asthma.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Luder E, Ehrlich RI, Lou WY, Melnik TA, Kattan M. Body mass index and the risk of asthma in adults. Respir Med 2004; 98:29–37.
2. Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther 2006; 110:83–102.
3. Lugogo NL, Kraft M, Dixon AE. Does obesity produce a distinct asthma phenotype? J Appl Physiol. 2010 Mar; 108(3):729–34.
4. Shore SA, Schwartzman IN, Mellema MS, Flynt L, Imrich A, Johnston RA. Effect of leptin on allergic airway responses in mice. J Allergy Clin Immunol 2005; 115:103–109.
5. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372:425–432.
6. Malli F, Papaioannou AI, Gourgoulianis KI, Daniil Z. The role of leptin in the respiratory system: an overview. Respir Res. 2010 Oct 31; 11:152.
7. Zarkesh-Esfahani H, Pockley AG, Wu Z, Hellewell PG, Weetman AP, Ross RJM. Leptin indirectly activates human neutrophils via induction of TNF-alpha. J Immunol 2004; 172:1809–1814.
8. Shirshev SV, Orlova EG. Molecular mechanisms of regulation of functional activity of mononuclear phagocytes by leptin. Biochemistry (Mosc) 2005; 70:841–847.
9. Raso GM, Pacilio M, Esposito E, Coppola A, Di Carlo R, Meli R. Leptin potentiates IFN-gamma-induced expression of nitric oxide synthase and cyclo-oxygenase-2 in murine macrophage J774A.1. Br J Pharmacol 2002; 137:799–804.
10. Mancuso P, Canetti C, Gottschalk A, Tithof PK, Peters-Golden M. Leptin augments alveolar macrophage leukotriene synthesis by increasing phospholipase activity and enhancing group IVC iPLA2 (cPLA2gamma) protein expression. Am J Physiol Lung Cell Mol Physiol 2004; 287:L497–L502.
11. Bhandari V, Choo-Wing R, Chapoval SP, Lee CG, Tang C, Kim YK, Ma B, Baluk P, Lin MI, McDonald DM, Homer RJ, Sessa WC, Elias JA. Essential role of nitric oxide in VEGF-induced, asthma-like angiogenic, inflammatory, mucus, and physiologic responses in the lung. Proc Natl Acad Sci USA 2006; 103:11021–11026.
12. Kanazawa H, Hirata K, Yoshikawa J. Involvement of vascular endothelial growth factor in exercise induced bronchoconstriction in asthmatic patients. Thorax 2002; 57:885–888.
13. Shin JH, Kim JH, Lee WY, Shim JY. The expression of adiponectin receptors and the effects of adiponectin and leptin on airway smooth muscle cells. Yonsei Med J 2008; 49:804–810.
14. Mai XM, Bottcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. Pediatr Allergy Immunol 2004; 15:523–530.
15. Sood A, Ford ES, Camargo CA Jr. Association between leptin and asthma in adults. Thorax 2006; 61:300–305.
16. Kim KW, Shin YH, Lee KE, Kim ES, Sohn MH, Kim K-E. Relationship between adipokines and manifestations of childhood asthma. Pediatr Allergy Immunol 2008; 19:535–540.
17. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. Am J Respir Crit Care Med 2005; 171:334–339.
18. Diez JJ, Iglesias P. The role of the novel adipocyte-derived protein adiponectin in human disease: an update. Mini Rev Med Chem. 2010 Aug; 10(9): 856–69.
19. Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, Maeda K, Nagaretani H, Kishida K, Maeda N, Nagasawa A, Funahashi T, Matsuzawa Y. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation 2004; 109:2046–2049.
20. Donnelly RP, Dickensheets H, Finbloom DS. The interleukin-10 signal transduction pathway and regulation of gene expression in mononuclear phagocytes. J Interferon Cytokine Res 1999; 19:563–573.
21. Fiorentino DF, Zlotnik A, Mosmann TR, Howard M, O'Garra A. IL-10 inhibits cytokine production by activated macrophages. J Immunol 1991; 147:3815–3822.
22. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001; 19:683–765.
23. Schottelius AJ, Mayo MW, Sartor RB, Baldwin AS Jr. Interleukin-10 signaling blocks inhibitor of kappaB kinase activity and nuclear factor kappaB DNA binding. J Biol Chem 1999; 274:31868–31874.
24. Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? Allergy 2007; 62:1205–1213.
25. Sood A, Ford ES, Camargo CA Jr. Association between asthma and serum adiponectin concentration in women. Thorax 2008; 63:877–882.
26. Shore SA, Terry RD, Flynt L, Xu A, Hug C. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. J Allergy Clin Immunol 2006; 118:389–395.
27. Summer R, Little FF, Ouchi N, Takemura Y, Aprahamian T, Dwyer D, Fitzsimmons K, Suki B, Parameswaran H, Fine A, Walsh K. Alveolar macrophage activation and an emphysema-like phenotype in adiponectin-deficient mice. Am J Physiol Lung Cell Mol Physiol 2008; 294:L1035–L1042.
28. Medoff BD, Okamoto Y, Leyton P, Weng M, Sandall BP, Raher MJ, Kihara S, Bloch KD, Libby P, Luster AD. Adiponectin deficiency increases allergic airway inflammation and pulmonary vascular remodeling. Am J Respir Cell Mol Biol 2009; 41:397–406.
29. Cummings DE, Overduin J. Gastrointestinal regulation of food intake. J Clin Invest 2007; 117:13–23.
30. Suzuki K, Jayasena CN, Bloom SR. Obesity and appetite control. Exp Diabetes Res. 2012; 2012: 824305.
31. Souza-Moreira L, Campos-Salinas J, Caro M, Gonzalez-Rey E. Neuropeptides as pleiotropic modulators of the immune response. Neuroendocrinology. 2011; 94(2): 89–100.
32. Matsuda K, Nishi Y, Okamatsu Y, Kojima M, Matsuishi T. Ghrelin and leptin: a link between obesity and allergy? J Allergy Clin Immunol 2006; 117:705–706.

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33. Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HAM, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Szefler SJ, Sullivan SD, Thomas MD, Wenzel SE, Reddel HK. A new perspective on concepts of asthma severity and control. Eur Respir J 2008; 32:545–554.
34. 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; 114:254–259.
35. Bruno A, Chanez P, Chiappara G, Siena L, Giammanco S, Gjomarkaj M, Bonsignore G, Bousquet J, Vignola AM. Does leptin play a cytokine-like role within the airways of COPD patients? Eur Respir J 2005; 26:398–405.
36. Nair P, Radford K, Fanat A, Janssen LJ, Peters-Golden M, Cox PG. The effects of leptin on airway smooth muscle responses. Am J Respir Cell Mol Biol 2008; 39:475–481.
37. Asai K, Kanazawa H, Otani K, Shiraishi S, Hirata K, Yoshikawa J. Imbalance between vascular endothelial growth factor and endostatin levels in induced sputum from asthmatic subjects. J Allergy Clin Immunol 2002; 110:571–575.
38. Jousilahti P, Salomaa V, Hakala K, Rasi V, Vahtera E, Palosuo T. The association of sensitive systemic inflammation markers with bronchial asthma. Ann Allergy Asthma Immunol 2002; 89:381–385.
39. Sethi JK, Vidal-Puig AJ. Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res 2007; 48:1253–1262.
40. Tilg H, Moschen AR. Role of adiponectin and PBEF/visfatin as regulators of inflammation: involvement in obesity-associated diseases. Clin Sci (Lond) 2008; 114:275–288.
41. Johnston RA, Schwartzman IN, Shore SA. Macrophage inflammatory protein-2 levels are associated with changes in serum leptin concentrations following ozone-induced airway inflammation. Chest 2003; 123:369S–370S.
42. Johnston RA, Theman TA, Lu FL, Terry RD, Williams ES, Shore SA. Diet-induced obesity causes innate airway hyperresponsiveness to methacholine and enhances ozone-induced pulmonary inflammation. J Appl Physiol 2008; 104:1727–1735.
43. Mancuso P, Huffnagle GB, Olszewski MA, Phipps J, Peters-Golden M. Leptin corrects host defense defects after acute starvation in murine pneumococcal pneumonia. Am J Respir Crit Care Med 2006; 173:212–218.
44. Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, Cai Y, Ostrowski MC, Lu B, Parthasarathy S, Brook RD, Moffatt-Bruce SD, Chen LC, Rajagopalan S. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 2009; 119:538–546.
45. Giouleka P, Papatheodorou G, Lyberopoulos P, Karakatsani A, Alchanatis M, Roussos C, Papiris S, Loukides S. Body mass index is associated with leukotriene inflammation in asthmatics. Eur J Clin Invest. 2011 Jan; 41(1): 30–8.
46. 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 higher exhaled 8-isoprostanes in asthmatics. Respir Res 2007; 8:32.
47. Kazani S, Israel E. Exhaled breath condensates in asthma: diagnostic and therapeutic implications. J Breath. Res 2010 Dec; 4(4): 047001.
48. De Vriese C, Delporte C. Ghrelin: a new peptide regulating growth hormone release and food intake. Int J Biochem Cell Biol 2008; 40:1420–1424.
49. Wu R, Dong W, Zhou M, Zhang F, Marini CP, Ravikumar TS, Wang P. Ghrelin attenuates sepsis-induced acute lung injury and mortality in rats. Am J Respir Crit Care Med 2007; 176:805–813.
50. Fantuzzi G. Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol 2008; 121:326–330.
51. Wu R, Dong W, Zhou M, Cui X, Hank Simms H, Wang P. Ghrelin improves tissue perfusion in severe sepsis via downregulation of endothelin-1. Cardiovasc Res 2005; 68:318–326.
52. Wong CK, Cheung PF, Lam CW. Leptin-mediated cytokine release and migration of eosinophils: implications for immunopathophysiology of allergic inflammation. Eur J Immunol 2007; 37:2337–2348.
53. Kilic H, Oguzulgen IK, Bakir F, Turktas H. Asthma in obese women: outcomes and factors involved. J Investig Allergol Clin Immunol. 2011; 21(4): 290–6.
54. Ma J, Xiao L, Knowles SB. Obesity, insulin resistance and the prevalence of atopy and asthma in US adults. Allergy. 2010 Nov; 65(11):1455–63.
55. Fitzpatrick S, Joks R, Silverberg JI. Obesity is associated with increased asthma severity and exacerbations, and increased serum immunoglobulin E in inner-city adults. Clin Exp Allergy. 2012 May; 42(5): 747–59.
56. Chen Y, Dales R, Jiang Y. The association between obesity and asthma is stronger in nonallergic than allergic adults. Chest 2006; 130:890–895.
57. Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, Calatroni A, Zeldin DC. Association of childhood obesity with atopic and nonatopic asthma: results from the National Health and Nutrition Examination Survey 1999–2006. J Asthma. 2010 Sep; 47(7): 822–9.
58. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008; 178:218–224.
59. Martin-Romero C, Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin enhances activation and proliferation of human circulating T lymphocytes. Cell Immunol 2000; 199:15–24.
60. Radon K, Schulze A, Schierl R, Dietrich-Gumperlein G, Nowak D, Jorres RA. Serum leptin and adiponectin levels and their association with allergic sensitization. Allergy 2008; 63:1448–1454.

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