Published in final edited form as:

J Asthma. 2011 October ; 48(8): 811–817. doi:10.3109/02770903.2011.613507.

Relationship of Adipokines with Immune Response and Lung Function in Obese Asthmatic and Non-Asthmatic Women

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Abstract

Background—Obesity is a risk factor for asthma. Studies in mice suggest that the adipokines leptin and adiponectin affect asthmatic responses. The purpose of this study was to determine if adipokines associated with obesity are (1) altered in obese women with asthma compared to controls and (2) associated with increased cytokines and chemokines involved in allergic inflammation.

Methods—We performed a cross-sectional study of asthmatic and non-asthmatic obese premenopausal women. Participants answered questionnaires and performed lung function tests. Serum and peripheral blood mononuclear cells (PBMCs) were collected for analysis of cytokines and adipokines.

Results—A total of 22 asthmatic (mean body mass index 40.0 ± 5.1 kg/m) and 20 non-asthmatic women (mean body mass index 41.3 ± 5.6 kg/m²) participated. We found no difference in serum adipokine concentrations between asthmatics and non-asthmatics. Serum adiponectin correlated positively with PBMC eotaxin ($r_s = 0.55$, $p = .0003$) and RANTES (regulated upon activation, normal T-cell expressed, and secreted) ($r_s = 0.36$, $p = .03$), whereas serum leptin correlated negatively with PBMC eotaxin ($r_s = -0.34$, $p = .04$). There was a negative correlation between serum adiponectin and PBMC interferon- γ ($r_s = -0.41$, $p = .01$).

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Contribution to Authorship. Dr. A. E. Dixon was involved in all phases of study design, participant recruitment, data collection, data analysis, and writing of manuscript. Dr. S. E. Johnson was involved with data collection, data analysis, and writing of the manuscript. Ms. L. V. Griffes recruited all participants at the University of Vermont, was involved with data collection, and assisted with writing manuscript. Ms. D. M. Raymond performed all the laboratory-based assays. Ms. R. Ramdeo recruited participants at Long Island Jewish, collected data, and assisted with writing manuscript. Ms. A. Soloveichik assisted with recruitment of participants at Long Island Jewish, collected data, and assisted with writing manuscript. Dr. B. T. Suratt assisted with design of laboratory-based assays, data interpretation, and writing of manuscript. Dr. R. I. Cohen was involved in all phases of study design, participant recruitment, data collection, data analysis, and writing of manuscript.

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

Conclusions—Perturbations of adipokines that occur in obesity were correlated with decreased cytokine production typically associated with allergic responses in PBMC of obese premenopausal women. This study suggests that although obese asthmatics may have elements of Th2-mediated inflammation, adipokine derangements in obesity are associated with Th1 rather than Th2 bias. Obesity has complex effects on allergic inflammation and is likely to be important modifier of the pathogenesis of airway disease in asthma.

Keywords

asthma; inflammation; obesity; Th1/Th2

Introduction

The incidence of both obesity and asthma has been increasing in the United States. In the United States alone, it is estimated that 250,000 new cases of asthma per year may be related to obesity (1). This relationship between asthma and obesity has also been reported in other populations (2, 3).

Although there are discrepancies regarding the absolute attributable risk of asthma with obesity, the majority of studies do suggest that obesity, particularly in premenopausal women, is a risk factor for the diagnosis of asthma (4, 5). The mechanisms linking asthma with obesity remain poorly understood, although some studies suggest that obesity-induced systemic inflammation could play a role in asthma expression in obese individuals (6). Studies in obese mice suggest that perturbations in adipokines associated with obesity could exacerbate airway hyperreactivity (7, 8).

Adipokines are produced by adipose tissue and are implicated in the pathogenesis of obesity-related inflammation resulting in the metabolic syndrome and other obesity-related diseases. Two of the best characterized adipokines are leptin and adiponectin. Leptin, originally identified as a mediator of satiety, is elevated in obesity and has been shown to be an important pro-inflammatory mediator through augmentation of Th1-related responses (9, 10). Conversely, adiponectin decreases in proportion to obesity and is traditionally thought of as an anti-inflammatory mediator though recent publications suggest it may have some pro-inflammatory effects (9, 11–13). As leptin and adiponectin levels are altered in obesity, and have effects on the immune system, these two adipokines have been the subject of multiple studies aiming to understand the increased risk of asthma in the obese.

Airway inflammation and bronchial hyperresponsiveness are hallmarks of human asthma. Different populations of activated T-lymphocytes promote different types of inflammation, with Th1 cells producing cytokines (interferon- γ (IFN- γ)) involved in cellular immunity whereas Th2 cells producing cytokines (interleukin-4, interleukin-5) involved in allergic inflammation. The process of cellular inflammation is mediated by various cell types including mast cells, eosinophils, macrophages, and T-lymphocytes, which are recruited to the airways by various chemokines. The chemokine eotaxin recruits eosinophils by inducing its chemotaxis, whereas RANTES (regulated upon activation, normal T-cell expressed, and secreted) recruits T-cells, eosinophils, basophils, and leukocytes into active inflammatory sites. RANTES can also play a role in the activation of natural killer cells in the Th1-

mediated process of cellular immunity. A complex interplay of cells and their signaling pathways leads to the type of imbalance in the cellular environment that causes maladaptive airway inflammation and hyperreactivity. The cells and signaling pathways involved in this imbalance is poorly understood in our population of interest, obese females with asthma.

The purpose of this study was to determine if adipokines associated with obesity are (1) altered in obese women with asthma compared to obese women without asthma and (2) associated with increased levels of the cytokines and chemokines involved in allergic asthmatic inflammation.

Methods and Materials

The study protocol was approved by the University of Vermont Committee on Human Research (Study Number 06-125) and the North Shore-Long Island Jewish Health System Institutional Review Board (Study Number 06.02.008). Informed consent was obtained from all participants prior to any study procedures.

Participants

We enrolled asthmatic obese and non-asthmatic obese women, aged 18–45 years, with body mass indices (BMIs) between 35 and 45 kg/m². Participants were not current smokers and all had less than a 10 pack-year smoking history.

Asthmatic subjects had a physician diagnosis of asthma and physiological evidence of asthma (12% and 200 cc bronchodilator response or a positive methacholine challenge). All had stable disease without exacerbation or change in medication during the 4 weeks preceding enrollment in this study.

Non-asthmatic subjects had no prior diagnosis of asthma, atopy or lung disease, and a negative methacholine challenge test.

We excluded participants with other serious medical conditions that would interfere with study participation. Those on thiazolidinediones (oral hypoglycemic), HMG-A Co-A reductase inhibitor medications (statins), or with a recent weight loss of >10 kg or 10% body weight within the past 3 months were also excluded due to expected confounding effects on adipokine levels. However, subjects with a history of controlled diabetes, hypertension, and hypercholesterolemia were not excluded.

Study Procedures

Participants answered questionnaires related to their medical history and performed lung function testing including spirometry, diffusing capacity, and lung volumes (by body plethysmography) according to American Thoracic Society guidelines. Height, weight, and waist measurements were performed. We obtained a fasting serum blood sample. Samples were collected and stored at –80°C for later analysis.

Isolations of Peripheral Blood Monocytes

Peripheral blood mononuclear cells (PBMCs) were isolated from 20 ml of heparinized blood by Ficoll-Paque™ PLUS density centrifugation as per manufacturer's instructions (GE Healthcare, Piscataway, NJ, USA; 25 minutes at 2200 rpm at room temperature). Mononuclear cells were cultured in RPMI media (Biowhittaker, Walkersville, MD, USA) at a concentration of 1×10^6 cells per well in 48-well culture plates with or without lipopolysaccharide (LPS) (1 µg/ml) at 37°C with 5% CO₂ for 24 hours, after which the culture supernatant was collected and stored at –80°C for later analysis.

Adipokine and Cytokine Assays

Serum and PBMC culture supernatant samples were assayed for IFN- γ , RANTES, Eotaxin, monocyte chemotactic protein 1 (MCP-1), interleukin-6, and interleukin-8 using magnetic-bead-based multiplex assays (Bio-Rad, Hercules, CA, USA). Millipore's Milliplex™ Adipocyte Map Kit (Millipore, Billerica, MA, USA) fluorescently labeled microsphere bead assays were used for assays of adiponectin and leptin.

All assays were performed as per the instructions provided by the manufacturer in one laboratory by an investigator (author, DMR) blinded to study data.

Statistical Methods

This study was powered to detect a significant difference in serum levels of leptin between obese asthmatic and non-asthmatic women. Based on previous data on leptin levels in obese healthy women, and differences of leptin levels between asthmatics and controls (14, 15), we assumed a leptin level of 31.3 ng/ml (standard deviation 24.1 ng/ml) in obese healthy women and 53 ng/ml in obese asthmatic women; thus recruiting 20 subjects in each group would yield an 80% power to detect a significant difference in leptin levels between the asthmatics and non-asthmatics with a two-sided α of 0.05.

Descriptive statistics were first used to describe the study population, followed by parametric (*t*-test) and nonparametric (Kruskal-Wallis) tests for continuous variables, and χ^2 analysis for categorical variables, comparing asthmatics and non-asthmatics. We then determined the correlation between serum adipokine concentration and production of Th1 and Th2 cytokines/chemokines by PBMCs using Spearman's correlation coefficient. All analyses were carried out using STATA® 10.0 (College Station, TX, USA) statistical software.

Results

Baseline Study Participant Characteristics

There were no significant differences between the asthmatic and non-asthmatic groups with respect to age, ethnicity, BMI, waist circumference, or pack years of smoking. As expected, both forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were significantly lower in asthmatics than in non-asthmatics (Table 1). Of the 22 asthmatics, 8 participants had well-controlled asthma, with Juniper asthma control scores of less than 0.75. Another eight participants had poorly controlled asthma with Juniper asthma control

scores of greater than 1.5. Fifteen asthmatics were using combination inhaled corticosteroid/long-acting β -agonist therapy (two were also on a leukotriene modifier), four were using inhaled corticosteroid, three were taking leukotriene modifiers, and two were taking only short-acting β -agonists. Of the 22 asthmatics, 12 reported a history of environmental allergies.

Serum

There were no differences in adiponectin or leptin levels (Table 2), nor leptin to adiponectin ratios (data not shown) between asthmatics and non-asthmatics, though overall leptin levels were higher in asthmatics. Eotaxin levels were significantly higher in asthmatics. There was a trend toward higher levels of IFN- γ in non-asthmatics. There was no difference in the level of RANTES between asthmatics and non-asthmatics (Table 2).

A multivariate regression analysis to study the relationship between serum leptin (log-transformed data), BMI, and the presence or absence of asthma revealed that leptin was statistically significantly related to BMI ($p = .003$), this was true in both asthmatics and non-asthmatics. Asthma was not related in a statistically significant way to leptin even when adjusting for BMI ($p = .4$). Waist circumference was significantly correlated with serum leptin levels ($r_s = 0.48$, $p = .0015$) whereas adiponectin was not ($r_s = -0.13$, $p = .42$).

Supernatant from PBMC

We isolated PBMCs from the blood of participants and determined spontaneous and LPS-stimulated cytokine production from cells in culture. PBMCs were successfully isolated from 18 asthmatics and 19 controls. We found no difference in eotaxin, RANTES, or IFN- γ production between asthmatics and non-asthmatics (Table 3).

In LPS-stimulated PBMC, we found significant increases in interleukin-6, interleukin-8, and MCP-1 production in both asthmatics and non-asthmatics, though this was not different between the two groups (Table 4).

Relationship between Serum Adipokines and Cytokine Production from PBMC+++

We determined the relationship between spontaneous cytokine production from PBMC and serum adipokines to determine whether serum adipokines were associated with alterations in the immune axis. We found a significant positive correlation between serum levels of adiponectin and eotaxin ($r_s = 0.55$, $p = .0003$) and RANTES ($r_s = 0.36$, $p = .026$) produced from PBMC. Conversely, there was a negative relationship between serum adiponectin and IFN- γ produced from PBMC ($r_s = -0.41$, $p = .01$) (Figure 1). We did not find a significant relationship between serum leptin and RANTES or IFN- γ ; however there was an inverse relationship between leptin and serum eotaxin ($r_s = -0.34$, $p = .04$) (Figure 2). We found similar trends when we considered both groups separately (data not shown).

We also studied the relationship between the leptin:adiponectin ratio and PBMC cytokine production, with similar results in that the ratio was inversely related to RANTES and eotaxin, and there was a trend toward a positive relationship with IFN- γ (Table 5). There were similar trends when we considered asthmatics and controls separately, which became

more significant when the groups were combined (related to smaller numbers leading to reduced power in separate groups).

Discussion

We studied a well-characterized cohort of obese premenopausal asthmatic women and an appropriately matched obese group without asthma. We did not find significant differences in serum adiponectin or leptin between asthmatics and non-asthmatics. We found that serum adiponectin, which decreases in obesity, correlated positively with markers of Th2, and negatively with markers of Th1 immune response in PBMC. Serum leptin, which increases in proportion to obesity, correlated negatively with eotaxin production by PBMC. In serum, we found an increase in serum eotaxin, a marker of a Th2 response, in asthmatics. Our findings suggest that perturbations in adipokines associated with obesity (increased leptin and decreased adiponectin) could skew the immune response away from Th2 and enhance Th1 responses. Our data indicate that these findings were not unique to asthma, but were also seen in non-asthmatics. Our findings suggest that a unique phenotype of lung disease may exist in the obese.

Mechanistic studies in mice suggest that leptin and adiponectin influence both airway hyperreactivity and inflammation. In normal-weight allergen-challenged mice, leptin infusion increases airway hyperreactivity, whereas adiponectin infusion decreases airway hyperreactivity (7, 8). Studies in mice also suggest that increased leptin and decreased adiponectin, as occurs in obese, may augment allergic inflammation (7, 8, 16).

The data on the relationship between adipokines and asthma in humans are complicated with conflicting results in different demographic groups suggesting that there is not a simple linear cause–effect relationship between serum adipokines and airway disease (17, 18). Studies in the US population suggest that leptin and adiponectin may be associated with asthma, particularly in premenopausal women, although the role of adipokines may not fully explain this relationship (5, 19). For the purposes of this study, we focused on obese premenopausal women; the group which prior studies suggest has the strongest relationship between adipokines and asthma. However, we failed to detect a significant relationship between adiponectin and leptin with asthma. Our results for leptin are similar to those of Sutherland et al. (6) who also performed a cross-sectional study of premenopausal women and reported that leptin levels were increased in obesity regardless of the presence of asthma.

One of the important questions in human asthma is the mechanism by which these metabolic perturbations alter immune responses and airway inflammation. Our classic understanding of asthma is that it is an inflammatory disease characterized by eosinophilic airway inflammation with Th2 skewing characterized by increases in chemokines such as eotaxin, and decreased levels of the Th1 cytokine IFN- γ (20). In this study, we were interested in understanding whether differences exist in serum adipokine levels between well-matched groups of obese asthmatics and obese non-asthmatics. Although we found no difference between these two groups, our data did yield potentially important insights into the relationship between adipokines and cellular immune responses. Increased serum leptin was

associated with decreased eotaxin, suggesting that leptin could dampen the Th2 response in this obese study group. In addition, lower levels of adiponectin in this obese study group were associated with decreased RANTES and eotaxin, and higher levels of IFN- γ . Taken together, our results suggest that elevated leptin and decreased adiponectin associated with obesity may skew PBMC-mediated inflammatory response toward a Th1 phenotype.

Our data are consistent with numerous previous animal and human studies indicating that leptin and obesity are associated with an augmented Th1 immune response (10, 21, 22). Therefore, our data are consistent both with prior publications that suggest leptin may dampen Th2 responses, and that adiponectin may have pro-inflammatory effects including enhanced allergic responses, though this will require further study.

Our data are also consistent with several publications on the nature of the airway inflammatory response in humans with increasing BMI. These show a flat relationship between airway eosinophilia and BMI, or even an inverse relationship between airway eosinophilia and BMI (6, 23–25), consistent with our findings that markers of Th2 inflammation in PBMCs are inversely associated with the alterations in leptin and adiponectin characteristic of obesity.

We did find increased levels of serum eotaxin in obese asthmatics. This suggests that although metabolic changes in obesity tend to dampen allergic responses, these responses may still be involved in the etiology of asthma in many women who would perhaps have asthma regardless of BMI. Our data further suggest that adipokine derangements in obesity do not aggravate underlying Th2 allergic response, but are perhaps superimposed upon allergic asthma and could alter the characteristics of this disease creating a unique phenotype of asthma. The concept that obesity leads to asthma through different mechanisms than classic allergic asthma in the lean population is also supported by physiological studies which show that asthma and obesity have additive, not synergistic, effects on airway function (26).

There are limitations to this study. We did not find a difference between leptin levels in obese asthmatics and non-asthmatics, which may have been due to sample size. However, we chose our sample size based on power calculations derived from prior studies on this topic. We chose to study a group of individuals that were clearly obese, with BMIs above the threshold used to define obesity, as there appears to be a dose–response effect of obesity on asthma, and we reasoned that this would maximize our ability to observe differences between asthmatics and non-asthmatics. It should be noted that given a setting dominated by obesity, the lack of differences in serum adipokine levels between obese asthmatics and obese non-asthmatics is perhaps not surprising. We studied only obese premenopausal women, therefore our results cannot be generalized to the entire population, but our subjects represent a sub-population in which obesity has most consistently been implicated in the pathogenesis of asthma. The correlation of serum adipokines and inflammatory markers from PBMC does not establish cause and effect, but suggest that serum adipokines may act through effector cells to alter the phenotype of airway inflammation in the obese. In addition, while PBMCs are readily available and well-described surrogates, they are not in fact airway inflammatory cells (27–31). Finally intrinsic factors such as circadian rhythmic

release and reproductive hormone levels may alter circulating levels of leptin and adiponectin and these variables were not controlled for in our data collection.

Conclusions

This study suggests that although obese asthmatics may have elements of Th2-mediated inflammation, adipokine derangements in obesity are associated with Th1 rather than Th2 bias. Obesity has complex effects on allergic inflammation and is likely to be important modifier of the pathogenesis of airway disease in asthma.

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Figure 1.

Relationship between serum adiponectin and chemokines produced by PBMC for (a) eotaxin, (b) RANTES, and (c) interferon- γ , in non-asthmatics (+) and asthmatics (◇).

Figure 2. Relationship between serum leptin and chemokines produced by PBMC for (a) eotaxin, (b) RANTES, and (c) interferon- γ , in non-asthmatics (+) and asthmatics (◇).

Table 1

Patient demographics and lung function.

	Non-asthmatic	Asthmatic	P-value ^a
<i>n</i>	20	22	
Age	37 (± 7.55)	37 (± 9.11)	.92
% Caucasian	65	86	.64
BMI (kg/m ²)	40.0 (± 5.1)	41.3 (± 5.6)	.45
Waist circumference (cm)	107.8 (± 4.8)	114.6 (± 2.7)	.20
Pack years smoking	1.05 (± 2.41)	1.13 (± 3.08)	.93
Combination inhaled corticosteroid/long-acting β -agonists		15	
Inhaled corticosteroid		4	
Leukotriene modifier		3	
Short-acting β -agonist only		2	
Juniper asthma control		1.35 (± 1.17)	
FEV1 (% predicted)	94% (± 11)	81% (± 19)	.01
FVC (% predicted)	95% (± 11)	86% (± 18)	.05
FEV1/FVC	89% (± 9)	85% (± 11)	.25
DLCO (% predicted)	85.7 $\pm$ 21.5	76.4 (± 11.8)	.43
RV (% predicted)	85.4 (30.8)	95.1 (41.3)	.41
TLC (% predicted)	93.3 (19.0)	88.6 (30.4)	.65

Notes:

^aValues shown are mean (SD), *p*-value shown for *t*-test for normally distributed and Kruskal–Wallis for nonparametric continuous variables, and χ^2 for categorical variables.

Table 2

Serum cytokines and adipokines in control and asthmatic participants.

	Non-asthmatic (<i>n</i> = 20)	Asthmatic (<i>n</i> = 22)	P-value
Adiponectin (µg/ml)	20.3 (13.7)	23.9 (15.3)	.18
Leptin (ng/ml)	36.8 (30.3)	50.2 (42.9)	.31
Eotaxin (pg/ml)	76.5 (78.0)	156.5 (95.5)	.04
RANTES (pg/ml)	295.3 (469.3)	235.9 (133.9)	.42
IFN- γ (pg/ml)	13.1 (51.5)	2.7 (16.3)	.11

Note: Values shown are median and IQR, *p*-value shown for Kruskal–Wallis test.

Table 3

Supernatant from un-stimulated peripheral blood mononuclear cell cultures.

	Non-asthmatic (<i>n</i> = 19)	Asthmatic (<i>n</i> = 18)	P-value
Eotaxin (pg/ml)	28.9 (17.0)	23.7 (18.2)	.36
RANTES (pg/ml)	10.7 (17.9)	12.3 (74.8)	.78
IFN- γ (pg/ml)	57.0 (97.8)	88.0 (73.5)	.76
IL-6 (pg/ml)	2.74 (3.27)	3.14 (1.74)	.91
IL-8 (pg/ml)	331 (594)	154 (343)	.33
MCP-1 (pg/ml)	15.64 (23.82)	11.53 (29.5)	.92

Note: Values shown are median and IQR, *p*-value shown for Kruskal–Wallis test. IL-6, interleukin-6; IL-8, interleukin-8.

Table 4

Supernatant from peripheral blood mononuclear cell cultures stimulated with LPS.

	Non-asthmatic (n = 19)	Asthmatic (n = 18)	P-value
Eotaxin (pg/ml)	25.0 (27.1)	19.8 (20.0)	.63
RANTES (pg/ml)	13.2 (73.0)	24.5 (476)	.34
IFN- γ (pg/ml)	53.1 (59.7)	67.3 (115.7)	.56
IL-6 (pg/ml)	1393 (2382)	1481 (2451)	.93
IL-8 (pg/ml)	2545 (197)	2545 (578)	.33
MCP-1 (pg/ml)	82.3 (672.0)	163.8 (215.5)	.50

Note: LPS, lipopolysaccharide; IL-6, interleukin-6; IL-8, interleukin-8.

Table 5

Relationship between leptin:adiponectin ratio and PBMC cytokine production.

	Correlation coefficient (<i>r</i>)	P-value
Combined study groups		
Eotaxin	−0.52	.00
RANTES	−0.31	.06
IFN- γ	0.25	.13
Asthmatics		
Eotaxin	−0.52	.00
RANTES	−0.28	.22
IFN- γ	0.16	.50
Controls		
Eotaxin	−0.52	.00
RANTES	−0.41	.11
IFN- γ	0.39	.13