Relationship between cysteinyl leukotrienes and nitric oxide in the pathogenesis of asthma in obesity

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Abstract

**Background:** Obesity has become a lot more prevalent recently, and its involvement with pathogenesis of asthma is frequently investigated.

**Aims:** We hypothesize that altered plasma adipokines and exhaled nitric oxide (NO) levels in obese subjects upregulate inflammation in asthmatics. We examined the hypothesis that the inflammatory mediators, cysteinyl leukotrienes (cys-LT) which are regulated by leptin and NO, play a role in the pathogenesis of airway inflammation in obese asthmatics.

**Methods:** We studied asthmatics (n=59) and non-asthmatics (n=58), both obese and non-obese, and further analyzed by gender. We examined plasma leptin, and fractional exhaled nitric oxide (FeNO), in obese and non-obese asthmatics and non-asthmatics. In addition, we measured urinary cys-LT levels in these subjects.

**Results:** Plasma leptin was increased in asthmatics compared to non-asthmatics (34.5±31 vs. 27.0±26, p=0.038), specifically in obese female asthmatics compared to obese male asthmatics (65.1±22.5 vs. 26.2±15.9 ng/ml, p=0.01). FeNO were decreased in obese compared to non-obese asthmatics (17.8±9.3 vs. 29.5±22.4, p=0.04), an effect that was most noted in female asthmatics. Urinary cys-LT levels were elevated in female asthmatic (7.2±2.9 vs. 5.0±1.8, p=0.002), especially in older heavier subjects. The ratio of urinary cys-LT to FeNO was elevated in obese female asthmatics.

**Conclusions:** Pro-inflammatory leptin and anti-inflammatory NO are altered in obese asthmatics. These mediators may regulate cys-LT. The group of subjects with elevated cys-LT/FeNO ratios may be a target for selective therapy.

**Keywords:** Obesity, leptin, nitric oxide, eicosanoid, airway

Introduction

There has been a significant increase in the prevalence in obesity in the US, from 18% in the ’80’s to approximately 35% in 2010 [1,2]. Over the same time frame, there has been an increase in the prevalence of asthma from 30.7 to 53.8 per thousand population. A positive independent association between obesity and the incidence of adult-onset asthma was noted in a prospective epidemiologic study [3]. National Health and Nutrition Examination Survey data, demonstrated an independent association between obesity and asthma, both atopic and non-atopic [4]. Obesity is independently associated with increased airway hyper reactivity [5]. Furthermore, weight loss improves airway narrowing and bronchial hyper reactivity [6]. Obesity is disproportionately common among patients with asthma [7,8].

Leukotrienes (LT) are derived from arachidonic acid metabolism and known to play an important role in airway inflammation and the development of asthma [9]. The 5-lipoxygenase enzyme acts on the arachidonic acid pathway producing LTB4 and cys-LT (LT C4, D4 and E4). Cys-LT and LTB4 are released by granulocytes (neutrophils, eosinophils) as well as mast cells, peripheral blood monocytes and macrophages, which are involved in the pathogenesis of airway obstruction [9]. LT synthesis is increased in peripheral blood leukocytes [10,11] airway macrophages and eosinophils [12] from asthmatics compared to healthy controls. Asthma in obese subjects often manifests steroid resistance and is difficult to manage [13]. Other investigators have demonstrated an association between body mass index (BMI) and
urine cys-LT in obese asthmatics [14]. Obese subjects with asthma, have demonstrated reduced responsiveness to inhaled corticosteroids and display a greater improvement to the LT modifier, montelukast, compared to non-obese asthmatics [15]. By deduction, LTs may play a larger role in mechanisms of asthma in obese subjects compared to non-obese patients [15].

Obesity is a pro-inflammatory state, with adipocytes releasing peripheral blood cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6, and many other classical mediators [16]. Adipose tissue also elaborates a number of adipokines, hormones that are structurally similar to cytokines with both pro- and anti-inflammatory properties. Leptin, is one such adipokine, a 16kD protein involved in the regulation of food intake and energy balance [17]. Plasma leptin levels correlate with total body fat stores, with an elevation in obesity and a reduction following weight loss. Leptin is a pro-inflammatory cytokine that upregulates both Th1 cytokines [18] and LT [19,20].

Leptin may promote pulmonary inflammation and bronchoconstriction as shown in murine models of obesity asthmatics [21,22]. However, there are inconsistent data supporting a role for leptin in the pathogenesis of asthma in humans, independent of BMI [23]. We have preliminary data that plasma leptin levels are increased in obese asthmatics [24]. Plasma leptin also tended to be increased in asthmatics compared to non-asthmatics, irrespective of obesity.

FeNO measurements provide information on underlying eosinophilic airway inflammation, and current evidence suggests a role in identifying the phenotype of corticosteroid responsiveness. However, FeNO does not provide information about airway inflammation characterized by neutrophil infiltration, which can be seen in severe asthma. Others have shown that there is a negative correlation between BMI and FeNO in asthma [25]. Investigators have demonstrated increased asymmetric di-methyl arginine compared to L-arginine in obesity [26]. This uncouples NO synthase leading to lowered FeNO. Late-onset asthmatics display higher median plasma asymmetric di-methyl arginine levels (and lower median plasma L-arginine levels) compared with early onset asthma. Log L-arginine/asymmetric di-methyl arginine and FeNO inversely correlated with BMI.

We and others have shown that both endogenous and exogenous nitric oxide (NO) is anti-inflammatory and suppresses 5-lipoxygenase activity and LT synthesis [27-30]. Therefore, reduced FeNO may lead to excess cys-LT synthesis in the airways of asthmatics with obesity and lead to worsening of pulmonary function in this population. There is an increased predictive value of using combinations of biomarkers to predict therapeutic responses. A recent study demonstrated that a high ratio of urinary LTE4 to FeNO was associated with increased responsiveness to LT receptor antagonists compared to inhaled corticosteroids [31]. This group of subjects with comparatively higher cys-LT / FeNO ratio tended to have less allergic, more neutrophil driven airway disease as seen in rhinovirus infections, and smokers [32,33]. We explored the relationship of these two biomarkers in subjects with mild to moderate asthma with obesity compared to non-obese.

**Methods**

**Recruitment**

Recruited subjects, with or without asthma, were 18-65 yr. old, both male and female, and representative of the ethnicity and race distribution of the community’s population. Fully informed written consent was obtained from each subject prior to entry into the study. All procedures were approved by the Institutional Review Board of the University of Michigan. BMI calculations were determined by dividing the weight by the square of the height (kg/m²). Subjects who met inclusion criteria were enrolled consecutively and studied based on BMI, 1) normal BMI (20-24.9 kg/m²) and 2) obese BMI (>30 kg/m²) to optimize potential differences.

Stable asthmatics without exacerbations for 2 months were included. The diagnosis of asthma was based on history, physical exam, and pulmonary function testing. Pulmonary testing included forced expiratory volume in one second (FEV1) measurements were performed pre-bronchodilator on all asthmatic patients. Patients with mild to moderate persistent asthma (Step 1-3) were studied, including subjects on inhaled corticosteroids [34,35]. Vital signs including the BMI values were determined in all subjects on the day of the study.

Exclusion criteria include current smokers within the past 6 months and previous smokers >20 pack years, intercurrent infection, and treatment with LT-modifier drugs, cyclooxygenase-1 inhibitors including aspirin, and oral corticosteroids. Subjects with aspirin exacerbated respiratory disease were excluded because of their tendency to display excess cys-LT synthesis at baseline [36].

**Blood**

Plasma leptin levels were determined spectrophotometrically using commercially-available colorimetric enzyme immunoassay kits (Millipore, MA USA) according to the manufacturer’s instructions [37]. The coefficient of variation for duplicate samples was 3.7% and the lower limit of detection was 0.5 ng/ml. Blood samples were drawn from each patient at the same time of the day, in the morning, and when fasting.

**Exhaled breath**

Subjects were asked to perform two FeNO measurements using the NIOX MINO Airway Inflammation Monitor (NIOX MINO; Aerocrine AB, Solana, Sweden). The NIOX MINO required the subjects to exhale at a constant pressure between 10 and 20 cmH2O and adjusts flow to the American Thoracic Society recommended flow rate of 50 +/- 5 ml/s [38]. The NIOX MINO has previously shown good correlation with traditional NO analyzers [39].

**Urine**

Urine was collected (spot) and kept in a refrigerator until
aliquoting (10 ml) and freezing (−80°C). Urine cysteinyl leukotriene was analyzed by enzyme-linked immunosorbent assay with the detection limit <10 ng/l and the inter-assay variation <12% [40]. Urine cys-LT levels are presented as pg/mg creatinine. These samples were run using the kits from Cayman Chemicals, Ann Arbor.

Statistics
Mean and standard deviations for normally distributed data were calculated and differences between groups determined by the Student t test. For skewed data Mann-Whitney tests were utilized. For the evaluation of possible associations between each study variable (dependent) and BMI (independent), linear regression was performed. We log transformed the data since it was not normally distributed. This log transformation resulted in normalization of the data.

Correlations and partial correlations were performed using Pearson’s coefficient. Multivariable regression analysis was performed for leptin, FeNO and urine cys-LT levels, adjusting for age, gender and asthma. We evaluated the association with BMI categories as well as BMI as a continuous variable.

Multiple comparison of study variables among the four groups were performed with one way analysis of variance (ANOVA) using a Bonferroni correction. The data were log transformed prior to ANOVA. P values <0.05 were considered statistically significant. All statistics were performed on IBM SPSS version 21 statistical software.

Results
We set out to study four groups of subjects: obese asthmatics, non-obese asthmatics; obese non-asthmatics and non-obese non-asthmatics. The total number of subjects studied was 117. By design the BMI of the control and obese subjects were recruited to obtain optimal separation of the groups (Table 1). There was no significant difference in FEV1 between obese and non-obese asthmatics (82.6±14.3 vs. 91.0±14.9 % predicted, p=0.07).

The gender breakdown was 65% female, (35% male). No significant difference occurred in BMI between the genders, obese (39.3±5.9 vs. 38.6 ± 6.5 years male/female), or non-obese (23.0±1.6 vs. 22.8±1.8).

The recruitment age in the subjects, asthma vs. non-asthma, wasn’t significantly different; (Table 1). Males and females displayed no difference in age. Obese subjects were generally older, displaying an age-related increase in fat mass (obese 43.4±12.4 vs. non-obese 30.8 vs±.11.9, p=0.0001). Obese asthmatics were on average older than non-obese asthmatics (44.0±10.3 vs. 29.9±9.8 years, p=0.0001).

Co-morbidities: There is a number of co-morbidities that contribute to exacerbations of asthma. Thirteen of the obese subjects had a diagnosis of obstructive sleep apnea, compared to none in the non-obese population. These were evenly divided among asthmatics and non-asthmatics (8/59 vs. 5/58 subjects). Gastro-esophageal reflux disease was more common in obese subjects than non-obese (13/58 vs. 2/59 subjects). Gastro-esophageal reflux disease was also more common in asthmatics than in non-asthmatics (11/59 vs. 4/58 subjects).

Leptin levels
As expected, fasting plasma leptin levels were higher in obese subjects than non-obese subjects (51.4±25.7 vs. 9.4±8.6 ng/ml, p<0.0001). There was a significant increase in leptin levels in asthmatics compared to non-asthmatics (34.5±31 vs. 27.0±26, p=0.038). Mean leptin levels were higher in females than in males (39.9±29.0 vs. 12.5±15.8 ng/ml, p<0.0001). Female asthmatics had higher leptin levels than males with asthma (42.9±31.0 compared to 17.6±18.8 ng/ml, p=0.004) (Figure 1). Leptin levels were higher in obese female asthmatics compared to obese male asthmatics (65.1±22.5 vs. 26.2±15.9 ng/ml, p=0.01) (Figure 1 and Table 3).

Leptin’s correlation with weight was positive at 0.8, which was significant (p<0.0001). When adjusted for asthma it was 0.8 (p<0.0001). The correlation of leptin with asthma is -0.25 (p=0.07). When adjusted for BMI the correlation was -0.13 (p=0.36). Multivariable linear regression analysis demonstrated a positive correlation between leptin and weight (0.81, p<0.001). There was also a positive correlation between leptin and the female gender (0.44, p<0.001).

Using ANOVA, leptin was significantly different between the four groups: obese asthmatics, non-asthma non-obese, asthma non-obese and non-asthma obese. Obese asthmatics had significantly higher levels than obese non-asthmatics (p<0.0001) (Figure 2).

Urine Cys-LT levels
There was no significant difference in urine cys-LT levels between asthmatics and non-asthmatics (6.7±2.9 vs. 6.5±3.3, p=0.8). Likewise, there was no difference between obese and non-obese subjects (6.9±3.2 vs. 6.3±3.0, p=0.26). Urine cys-LT levels were no different in obese asthma compared non-obese asthmatics (7.2±3.2 vs. 6.3±2.6, p=0.2), but females trended to

Table 1. Demographics of the study population of obese, non-obese, asthmatic and non-asthmatic subjects.

|          | Asthma | Non Asthma | p     |
|----------|--------|------------|-------|
| n        | 59     | 58         |       |
| BMI      | 32.0±9.3 | 29.7±8.3 | >0.95 |
| Age      | 37.3±12.2 | 36.8±14.9 | ≤0.01 |
| M/F      | 18:41  | 22:36      |       |

Subgroups

|          | Obese / Non-obese | Obese / Non-obese |
|----------|--------------------|--------------------|
| n        | 30/29              | 28/30              |
| BMI      | 38.9±6.1 / 22.8±1.7 | 37.7±5.4 / 22.9±1.7 |
| Age      | 44.0±10.3 / 29.9±9.8 | 42.7±13.6 / 31.5±11.6 |
| M/F      | 9.2/9:20           | 7.2/15:15          |

Notes: BMI, body mass index; M/F, male / female. Data presented as mean±SD.
Figure 1. Elevated leptin levels in female asthmatics.
Plasma leptin levels (ng/ml) were increased in female subjects with asthma compared male asthmatics*, irrespective of weight. Obese female asthmatics also demonstrated increased leptin levels compared to obese male asthmatics†.

Figure 2. Increased leptin levels in obese asthmatics compared to non-obese asthmatics and non-asthmatics.
Plasma leptin levels log mean transformed (ng/ml) in subjects with asthma obesity (AO), non-asthma non-obesity (NANO), asthma non-obesity (ANO), non-asthma obesity (NAO). AO had significantly higher leptin levels (ANOVA p<0.05), compared with NANO,*ANO† and NAO$.

Table 2. Mediator levels in obese, non-obese, asthmatic and non-asthmatic subjects.

| Mediator | Obese Asthma | Non-obese Asthma | Obese Non-Asthma | Non-obese Non-Asthma | p |
|----------|--------------|------------------|-------------------|----------------------|---|
| Leptin   | 55.4±26.9    | 24.2±12.9        | 46.5±24.2         | 8.9±8.8              | P=0.0001 |
| U Cys-LT/FeNO | 0.50±0.4 | 0.30±0.21 | 0.44±0.21 | 0.42±0.3 | P=0.06 |

Notes: U Cys-LT/FeNO, ratio urinary cysteinyl leukotrienes to fractional exhaled nitric oxide. Data presented as mean±SD.

Urine cys-LT levels than male asthmatics (7.3±2.9 vs. 5.0±1.8, p=0.002).

Table 3. Role of gender in mediator levels in obese, non-obese, asthmatic and non-asthmatic subjects.

|          | Asthma |          | Non-asthma |          |
|----------|--------|----------|------------|----------|
| Leptin ng/ml | Female | Male | Female | Male | p        |
| Non-obese | 14.3±8.0 | 26.2±19.4 | 14.6±9.4 | 3.3±1.3 | P=0.002 |
| Obese     | 65.1±22.5 | 26.2±15.9 | 53.8±22.3 | 28.1±19.4 | P=0.07 |
| Non-obese | 0.32±0.24 | 0.27±0.18 | 0.51±0.34 | 0.24 | P=0.06 |
| Obese     | 0.57±0.49 | 0.19±0.08 | 0.48±0.22 | 0.34±0.19 | P=0.03 |

Notes: U Cys-LT/FeNO, ratio urinary cysteinyl leukotrienes to fractional exhaled nitric oxide. Data presented as mean±SD.

FeNO
FeNO overall displayed no difference in asthmatics compared to non-asthmatics (23.5±17.8 vs. 20.4±12.4, p=0.4). Interestingly, FeNO levels were decreased in obese compared to non-obese (18.9±9.8 vs. 24.6±18.6, p=0.05) subjects, irrespective of whether they had asthma. FeNO was also significantly reduced in obese asthmatics compared to non-obese asthmatics (17.8±9.3 vs. 29.5±22.4, p=0.04) (Table 2). There was no significant difference in FeNO in females compared to males (19.3±13.0 vs. 26.5±17.7, p=0.13), so the lack of elevation of FeNO in asthmatics compared to non-asthmatics was likely primarily related to obesity.

Linear regression demonstrated that FeNO has a significant negative correlation with BMI at -0.153 (p=0.05). FeNO demonstrated a negative correlation with asthma (-0.175, p=0.036) but did not correlate with FEV1 (0.055, p=0.345). Likewise, FeNO demonstrated a significant negative correlation with the female gender (-0.23, p=0.01). Using multiple linear stepwise regression only asthma and gender (female) had a negative correlation, when the variables: age, gender, BMI and asthma were considered (p=0.02).

Using ANOVA, FeNO was significantly different between the four groups: obese asthmatics, non-asthma non-obese, asthma non-obese and non-asthma obese. Obese asthmatics had significantly lower FeNO levels than non-obese asthmatics (p=0.002) (Figure 3).

Urine cys-LT/FeNO ratio
The high ratio of urine cys-LT to FeNO has been demonstrated...
as a marker of subjects who respond preferentially to LT modifier therapy [32,41]. We calculated the urine cys-LT/FeNO ratio in our subjects to help characterize the usefulness of this marker in the obese asthma population. There was no significant difference in the urine cys-LT/FeNO ratio between asthmatics and non-asthmatics (0.4±0.37 vs. 0.43±0.26, p=0.7) (Table 2). However, female asthmatics demonstrated a significant increase in urine cys-LT/FeNO ratio compared to male asthmatics (0.52±0.35 vs. 0.25±0.16, p=0.012) (Figure 4). Obese female asthmatics had an increased urine cys-LT/FeNO ratio compared to non-obese male asthma (0.57±0.24 vs. 0.27±0.03, p=0.04).

**Discussion**

The findings of this study are: 1) plasma leptin levels are increased in asthmatics compared to non-asthmatics, particularly in obese asthmatics compared to obese non-asthmatics. This was mainly accounted for by higher leptin levels in females, and especially obese female asthmatics. 2) Urine cys-LT levels were elevated in female asthmatics and were increased in older heavier subjects. 3) FeNO levels were significantly reduced in obese compared to non-obese asthmatics. There was also a negative correlation between females and FeNO. 4) The urine cys-LT/FeNO ratio was higher in obese female asthmatics.

The finding of the association between leptin and asthma, and specifically in obese female asthmatics corroborates data from a previous study from our laboratory [24]. Leptin has been noted to be a pro-inflammatory adipokine driving the immune system towards a predominant Th1 phenotype [42]. Leptin may also have an impact in the airway milieu in asthmatics with obesity. It may increase pro-inflammatory phenotype in macrophages [43], augmenting the response to LPS. Leptin deficient mice display reduced LT synthesis, and exogenous leptin augments LT production in macrophages from these animals [19]. Obesity has also been associated with an alteration in adipokines that predispose to neutrophilic inflammation [44]. Recently, it has also been shown that leptin may also affect the airway diameter through non-inflammatory pathways by inhibiting the cholinergic pathway [22]. Population studies have shown no association between leptin and asthma, but they studied non-fasting subjects, smokers, variables that can affect leptin levels, and may explain their different conclusions [45].

The reduced bronchial responsiveness to inhaled corticosteroids in patient with obesity, with a relatively stable response to montelukast, has been previously described [15]. Other investigators have demonstrated an association between BMI and urine cys-LT in obese asthmatics [14]. Obese patients displayed significantly higher values of LTE4/creatinine in urine compared to subjects who were pre-obese and in the normal range. The only significant associations were those between BMI and LTE4/creatinine in urine, considering the BMI when controlling for gender was still significant (0.21, p=0.04). The correlation of cys-LT/FeNO with gender when controlling for BMI 0.3, p=0.01.

Linear regression demonstrated urine cys-LT/FeNO ratio had a correlation with gender 0.28, p=0.002, BMI 0.23 (continuous variable), p=0.009, weight -0.13 (categorical variable obese or non-obese), p=0.08, and leptin 0.24, p=0.007. Using multiple linear stepwise regression only gender (female) and BMI had a positive correlation, when the variables: age, gender, leptin, BMI and asthma were considered (p=0.002).
noted with exhaled breath condensate samples.

In our cohort, subjects with the older obese women phenotype tended to have increased leptin and urine cys-LT levels with worse pulmonary function. Obese female asthmatics had higher leptin levels than obese male asthmatics. Recently, investigators have demonstrated that BMI was associated with the incidence of asthma in women but not in men [46]. Furthermore, adult onset non-atopic asthma has become the most common type of asthma in women [47]. Investigators have demonstrated that both testosterone (negative) and estrogen (positive) were associated with alterations in adipokines, specifically leptin levels [48]. The increase in BMI with age may have offset the effect of any change in estrogen / testosterone levels on adipokine levels as subjects increased in years.

In our study FeNO was not significantly elevated in asthmatics compared to non-asthmatics including both obese and non-obese subjects. This was explained in part by the role of obesity. FeNO was reduced in obese compared to non-obese subjects. It was also decreased in obese asthmatics compared to non-obese asthmatics. Reduced arginine / asymmetric dimethyl arginine ratio in obesity may explain this phenomenon [26]. The negative correlation between FeNO and the female gender (who made up ~65% of subjects) compared to males may also be influencing this finding. Although FeNO levels did not correlate with urine cys-LT levels, the reduction in FeNO levels in obese subjects may contribute to the increased cys-LT levels seen in these subjects in urine measurements [14] as well as in exhaled breath condensate [24].

Urine LTE4/FeNO ratio has been utilized as a marker for subjects that respond preferentially to LT modifier drugs compared to inhaled corticosteroids in the management of children with asthma [32]. These subjects tended to have less IgE sensitivity, lower eosinophil counts and less responsiveness to inhaled corticosteroids. Likewise subjects with exercise-induced asthma with higher urine LTE4/FeNO ratios tended to respond better to LT receptor antagonists than to inhaled corticosteroids [41]. Urine cys-LT/FeNO ratio in our study was higher in obese female asthmatics. This may identify a subgroup of obese female asthmatics who will respond better to LT modifiers.

We documented comorbidities of obstructive sleep apnea and gastro-esophageal reflux disease in asthmatics and non-asthmatics. Poorly controlled obstructive sleep apnea has been shown to worsen asthma control, in part through increased release of pro-inflammatory mediators during episodes of hypoxia and disrupted sleep [49]. Nocturnal gastro-esophageal reflux disease may exacerbate asthma with aspiration of acid, during inhalation against a closed airway, following episodes of upper airway obstruction. Like obstructive sleep apnea, the incidence of gastro-esophageal reflux disease is also increased in obese subjects and may exacerbate airway disease after eating. Gastro-esophageal reflux disease can result in reflex bronchospasm from ir-
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