Body Mass and Glucocorticoid Response in Asthma

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Rationale: Obesity may alter glucocorticoid response in asthma.

Objectives: To evaluate the relationship between body mass index (BMI, kg/m²) and glucocorticoid response in subjects with and without asthma.

Methods: Nonsmoking adult subjects underwent characterization of lung function, BMI, and spirometric response to prednisone. Dexamethasone (DEX, 10⁻⁶ M)-induced mitogen-activated protein kinase phosphatase-1 (MKP-1) and baseline tumor necrosis factor (TNF)- α expression were evaluated by polymerase chain reaction in peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage cells. The relationship between BMI and expression of MKP-1 and TNF- α was analyzed.

Measurements and Main Results: A total of 45 nonsmoking adults, 33 with asthma (mean [SD] FEV₁% of 70.7 [9.8]%) and 12 without asthma were enrolled. DEX-induced PBMC MKP-1 expression was reduced in overweight/obese versus lean patients with asthma, with mean ($\pm$ SEM) fold-induction of 3.11 ($\pm$ 0.46) versus 5.27 ($\pm$ 0.66), respectively ($P = 0.01$). In patients with asthma, regression analysis revealed a -0.16 ($\pm$ 0.08)-fold decrease in DEX-induced MKP-1 per unit BMI increase ($P = 0.04$). PBMC TNF- α expression increased as BMI increased in subjects with asthma, with a 0.27 unit increase in log (TNF- α [ng/ml]) per unit BMI increase ($P = 0.01$). The ratio of PBMC log (TNF- α):DEX-induced MKP-1 also increased as BMI increased in patients with asthma ($+0.09 \pm 0.02$; $P = 0.004$). In bronchoalveolar lavage cells, DEX-induced MKP-1 expression was also reduced in overweight/obese versus lean patients with asthma (1.36 ± 0.09 -fold vs. 1.76 ± 0.15 -fold induction; $P = 0.05$). Similar findings were not observed in control subjects without asthma.

Conclusions: Elevated BMI is associated with blunted *in vitro* response to dexamethasone in overweight and obese patients with asthma.

Keywords: asthma; therapy; obesity

An increasing body of literature suggests an interaction between obesity and asthma (1). Epidemiologic studies have suggested that overweight (defined as a body mass index [BMI, kg/m²] of 25–29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) increase asthma incidence (2) and skew prevalent asthma toward a more difficult-to-control phenotype (3). Despite these observations, the mechanisms by which obesity modifies asthma risk or phenotype remain unclear, as do the clinical implications of this interaction (4).

In a subset of obese individuals, enhancement of normal adipose tissue immune function leads to a systemic inflammatory state (5), with elaboration of proinflammatory molecules, such as leptin, tumor necrosis factor (TNF)- α , and IL-6 (6, 7), and associated metabolic and cardiovascular complications, such as insulin resistance and atherosclerosis. Many of these

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Obesity may alter glucocorticoid (GC) response in asthma.

What This Study Adds to the Field

These data suggest that *in vitro* response to GCs is reduced in overweight and obese patients with asthma. This phenomenon may lead to reduced clinical efficacy of GC therapy in patients with asthma who are overweight or obese.

same cytokines have also been associated with the development of glucocorticoid (GC) insensitivity in asthma (8), and are present in obese mice that develop airway hyperresponsiveness after exposure to ozone or sensitization and challenge with ovalbumin (9). This raises the possibilities both that the proinflammatory environment of obesity could possibly modify response to GCs and that controller agents other than inhaled GCs could be more appropriate for patients with asthma with comorbid obesity.

In this regard, two recent reports (10, 11) indicate that overweight and obese patients with asthma may not respond as well as their lean counterparts to inhaled GCs, the most effective asthma controller therapy (12, 13). Peters-Golden and colleagues, in a *post hoc* analysis of clinical trials randomizing subjects to beclomethasone, montelukast, or placebo, reported that clinical response to beclomethasone (as reflected by asthma control days, a composite of rescue β -agonist use, nighttime awakenings, and concurrent asthma exacerbation) was reduced as BMI increased, a trend not observed with montelukast (11). A separate *post hoc* analysis of clinical trial data by Boulet and Franssen also demonstrated a reduction in asthma control achieved in response to fluticasone as BMI increased; their pooled analysis of 1,242 subjects with asthma allocated to either fluticasone, 100 μ g twice daily, or fluticasone/salmeterol, 50 μ g/100 μ g twice daily, suggested that obese patients with asthma treated with GC-containing regimens were less likely to achieve asthma control than were their lean counterparts (10).

Although these reports suggest a reduction in clinical response to GC-containing therapeutic regimens in overweight and obese patients with asthma, the mechanisms by which this insensitivity to GCs might occur have not been elucidated. One potential mechanism by which this could be hypothesized to occur is altered molecular response to GCs due to systemic inflammation. GCs inhibit proinflammatory gene expression, in part through negative regulation of mitogen-activated protein kinase (MAPK) signaling pathways by molecules such as MAPK phosphatase (MKP)-1 (14). Given that proinflammatory cytokines, such as IL-1, IL-6, and TNF- α , are increased in many obese individuals, and given that these same cytokines are regulated by and potential regulators of p38 MAPK (14), it is possible that this proinflammatory environment might modify

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GC function in obese patients with asthma. We hypothesized that overweight and obese patients with asthma would demonstrate evidence of reduced molecular responsiveness to GCs (manifested by reduced induction of MKP-1 expression in response to GC treatment *in vitro*) in immune cells derived from both the peripheral blood and lung, a process potentially mediated by enhanced expression of or sensitivity to TNF- α . We further hypothesized that this effect would be specific to asthma, and would not be observed in overweight and obese subjects without asthma.

METHODS

We enrolled nonsmoking adults (age ≥ 18 yr) with asthma (12), defined by: (1) a clinical history of asthma; (2) airflow limitation (baseline FEV₁ $\leq 80\%$ predicted); and either (3) airway hyperresponsiveness (PC₂₀ methacholine $< 8\text{mg/ml}$); or (4) bronchodilator responsiveness ($>12\%$ and 200 ml improvement in FEV₁ after 180 μg metered-dose inhaler albuterol). Control subjects without asthma (normal spirometry, no history of asthma) were also enrolled. Assessment of lung function and airway hyperresponsiveness were performed according to published guidelines and interpreted according to reference values (15–18). Subjects had not received systemic GCs for 1 month or longer before evaluation, and used less than the equivalent of 800 μg inhaled beclomethasone (CFC) on a daily basis. Spirometric GC response was determined by measuring percent change in pre-bronchodilator FEV₁ after the administration of prednisone, 20 mg by mouth twice daily for 7 days, with adherence assessed by pill count. Subjects were categorized as GC insensitive if prebronchodilator FEV₁ improved by less than 12% after oral GC challenge (19). Prednisone absorption and clearance were examined in GC-insensitive subjects as per Hill and colleagues (20). Subjects with impaired prednisone absorption or accelerated prednisolone clearance were excluded. BMI was calculated as kg/m^2 , and subjects were characterized as lean if BMI was less than 25 kg/m^2 and overweight/obese if BMI was 25 kg/m^2 or greater. All participants underwent skin prick testing to 13 aeroallergens and positive/negative controls, and were excluded if found to be skin test positive.

To evaluate *in vitro* GC sensitivity, peripheral blood mononuclear cells (PBMCs) were isolated from 45 ml heparinized blood by Ficoll-Hypaque (Pharmacia Biotech, Piscataway, NJ) gradient centrifugation (21), and (in a subset of subjects) airway cells were isolated from bronchoalveolar lavage (BAL) (19) obtained via fiberoptic bronchoscopy performed according to published guidelines (22). After isolation, 2×10^6 cells were treated with either culture medium or dexamethasone (DEX) 10^{-6} M for 4 hours. RNA was extracted, transcribed into cDNA, and analyzed by real-time polymerase chain reaction via the dual-labeled fluorogenic probe method (ABI Prism 7000; Applied Biosystems, Foster City, CA) (23) using primers and probes for human MKP-1. TNF- α expression was measured using similar methods both in DEX-untreated cells and after treatment with either culture medium or DEX 10^{-6} M for 4 hours. Standard curves were generated for target genes from serial dilutions of total cDNA of the highest expression sample, with normalization of each target gene to corresponding levels of the house-

keeping genes 18sRNA and/or GAPDH in each sample. Changes in DEX-induced MKP-1 expression were expressed as fold change (19).

Unadjusted between-group comparisons were performed using Student's *t* or chi-square tests. Log transformation was used when data were not normally distributed. To determine the association between BMI and biomarkers of GC response, least-squares regression was used. To avoid overfitting the model, models were adjusted only for the potentially confounding effects of sex. Where appropriate, analyses were performed with and without inclusion of a single significant outlying value. All analyses were performed using JMP 7.0 (SAS Institute, Cary, NC).

All research was approved by the National Jewish Institutional Review Board, with informed consent obtained from all subjects.

RESULTS

Subject Characteristics

A total of 33 adult subjects with asthma and a mean (SD) age of 40.0 (10.9) years were recruited. Mean BMI was 28.7 (5.3) kg/m^2 , with a mean FEV₁ % predicted of 70.7 (9.8)%. A total of 12 adult subjects without asthma were also recruited, with a mean age of 41.7 (7.7) years and mean BMI of 27.1 (6.6) kg/m^2 . Additional demographic features of the study population are reported in Table 1.

BMI and PBMC DEX-induced MKP-1 Expression

In PBMCs from subjects with asthma, blunted induction of MKP-1 expression by DEX (10^{-6} M) was observed in overweight/obese versus lean patients with asthma, with mean ($\pm$ SEM) fold-induction of 3.11 (± 0.46) in overweight/obese subjects versus 5.27 (± 0.66) in lean subjects ($P = 0.01$ for the comparison; Figure 1A). When BMI was evaluated continuously, induction of PBMC MKP-1 expression was reduced as BMI increased, with a mean 0.16 (± 0.08)-fold ($P = 0.04$) reduction in MKP-1 expression observed for each one-unit increase in continuous BMI (Figure 1B). After exclusion of a single outlying subject from the regression model, the observed effect of BMI remained statistically significant in both the categorical and continuous BMI analysis, with a reduction in the mean value in the lean group to 4.32 (± 0.39) ($P = 0.02$ for the comparison, categorical analysis) and a 0.10 (± 0.04)-fold reduction ($P = 0.03$) per unit BMI (continuous analysis). Clinical GC insensitivity was related to blunted induction of PBMC MKP-1, with only a 3.04 (± 0.53)-fold increase observed in GC-insensitive subjects versus a 4.77 (± 0.58)-fold increase in GC-sensitive subjects ($P = 0.04$ for comparison), a finding not modified substantially by exclusion of the outlier data point (4.05 ± 0.34 ; $P = 0.03$).

In contrast to subjects with asthma, subjects without asthma did not demonstrate a relationship between BMI and DEX-induced MKP-1 expression; comparison of MKP-1 expression between BMI categories revealed a mean 2.83 (± 0.32)-fold

TABLE 1. PHYSIOLOGIC AND DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS

	Control Subjects without Asthma (<i>n</i> = 12)	Subjects with Asthma (<i>n</i> = 33)	Subjects with Asthma, BMI < 25 (<i>n</i> = 11)	Subjects with Asthma, BMI ≥ 25 (<i>n</i> = 22)	<i>P</i> Value
Age, yr	41.7 (7.7)	40.0 (10.9)	36.5 (7.5)	41.8 (12.0)	0.2
Female, %	67	48	36	55	0.3*
BMI, kg/m^2	27.1 (6.6)	28.7 (5.3)	23.5 (1.4)	31.2 (4.6)	<0.0001
FEV ₁ , L	3.14 (0.5)	2.45 (0.6)	2.72 (0.6)	2.32 (0.6)	0.1
FEV ₁ % predicted	95.8 (11.3)	70.7 (9.8)	72.1 (9.8)	70.0 (10.0)	0.6
FEV ₁ response to albuterol, %	N/A	+13.4 (12.2)	+18.0 (8.4)	+11.1 (13.3)	0.1
FEV ₁ response to prednisone, %	N/A	+11.4 (15.4)	+12.2 (12.3)	+11.0 (16.9)	0.8

Definition of abbreviations: BMI = body mass index.

Data are reported as mean (SD) or percent. All *P* values for comparison between asthmatic BMI categories using Student's *t* test, except* using Pearson chi-square test.

Figure 1. (A) Reduced dexamethasone (DEX)-induced mitogen-activated protein kinase phosphatase (MKP)-1 expression in peripheral blood mononuclear cells (PBMCs) from overweight/obese (gray) versus lean (black) subjects with asthma. Data are presented as mean $\pm$ SEM. (B) PBMCs from patients with asthma demonstrates significantly reduced DEX-induced MKP-1 expression with increased body mass index (BMI). Lines represent regression with (solid line) and without outlying data point (arrow).

induction in lean control subjects without asthma ($n = 6$) versus 3.03 (± 0.32)-fold induction in overweight/obese control subjects without asthma ($n = 6$) ($P = 0.7$ for the comparison; Figure 2A). Regression modeling indicated only a 0.01 (± 0.04)-fold reduction in MKP-1 expression per unit BMI increase, a finding that was not statistically significant ($P = 0.8$; Figure 2B).

BMI, TNF- α , and MKP-1 Expression in PBMCs

TNF- α mRNA expression (ng/ml per ng/ml of GAPDH) was assayed in a subset of PBMCs from patients with asthma ($n = 11$) and control subjects without asthma ($n = 11$). Increasing BMI was associated with enhanced TNF- α mRNA expression only in patients with asthma, and not in control subjects without asthma, with a 0.27 (± 0.09) unit increase in log (TNF- α [ng/ml]) for each unit increase in BMI ($P = 0.01$) in subjects with asthma (Figure 3A), and a 0.14 (± 0.1) unit increase in log (TNF- α [ng/ml]) per unit BMI ($P = 0.3$) in subjects without asthma (Figure 3B). To analyze the impact of this BMI-dependent increase in TNF- α mRNA expression, the ratio of log (TNF- α [ng/ml]) to DEX-induced MKP-1 expression was evaluated versus BMI, and subjects with asthma were found to manifest a significant increase in this ratio as BMI increased (Figure 4A), with a 0.09 (± 0.02) increase in the ratio per unit BMI ($P = 0.004$), indicating that, in asthma, increasing BMI is associated with an increase in TNF- α mRNA expression relative to DEX-induced MKP-1 expression. This

Figure 2. (A) Dexamethasone (DEX)-induced MKP-1 expression in peripheral blood mononuclear cells (PBMCs) of lean (black) versus overweight/obese (gray) subjects without asthma. Data are presented as mean $\pm$ SEM. (B) PBMCs from subjects without asthma do not demonstrate significantly reduced DEX-induced MKP-1 expression with increased body mass index (BMI).

effect of BMI on TNF- α mRNA and DEX-induced MKP-1 expression was not observed in subjects without asthma (Figure 4B), in whom the unit increase in the ratio with increasing BMI was 0.06 (± 0.04) per unit BMI ($P = 0.2$). Of note, the degree of DEX-induced suppression of TNF- α mRNA expression was similar between subjects with and without asthma (5.41 $\pm$ 0.74-fold vs. 5.84 $\pm$ 0.71-fold suppression; $P = 0.7$), and did not differ within these groups according to BMI. This suggests that the differential relationship between baseline TNF- α mRNA and the ability of DEX to induce MKP-1 expression in patients with asthma versus subjects without asthma was not due to a differential relationship effect of GCs on TNF- α mRNA expression in these two groups.

MKP-1 and TNF- α Expression in BAL Cells of Subjects with Asthma

To explore whether similar alterations of DEX-induced MKP-1 expression were operative in the airways of patients with asthma, in addition to the peripheral blood, a subset of subjects with asthma ($n = 11$) underwent fiberoptic bronchoscopy with BAL, with analysis of MKP-1 and TNF- α mRNA expression in BAL immune cells. No difference in BAL cell yield or differential was found between overweight/obese and lean patients with asthma (data not shown). As was observed in PBMCs, DEX-induced MKP-1 expression differed between BMI categories, with a 1.36 (± 0.09)-fold induction in overweight and obese subjects versus a 1.76 (± 0.15)-fold induction in lean subjects

Figure 3. (A) Peripheral blood mononuclear cells (PBMCs) from patients with asthma demonstrate significantly increased log (TNF- α) mRNA expression with increasing body mass index (BMI). (B) PBMCs from subjects without asthma do not demonstrate significantly increased log (TNF- α) mRNA expression with increasing BMI.

($P = 0.05$ for comparison; Figure 5A). Furthermore, DEX-induced MKP-1 expression in BAL cells was reduced as BMI increased (Figure 5B), with a $0.04 (\pm 0.01)$ -fold reduction ($P = 0.03$) in BAL cell MKP-1 expression observed for each unit increase in continuous BMI. A trend toward increased expression of TNF- α by BAL cells was observed as BMI increased, with a $0.23 (\pm 0.09)$ -unit increase ($P = 0.03$) in log (TNF- α) for every one-unit increase in BMI after exclusion of a single outlier (inclusion of the outlier yielded a similar estimate of effect [0.21 ± 0.12], but with $P = 0.1$).

DISCUSSION

These data indicate that *in vitro* biomarkers of GC insensitivity increase in both the lung and peripheral blood as body mass increases in individuals with asthma, but not in control subjects without asthma. This effect is manifested by reduced induction of MKP-1 expression in response to DEX in both PBMCs and BAL cells, and is related to enhanced expression of TNF- α in both peripheral and lung immune cells as body mass increases, suggesting a scenario in which one or more molecular pathways governing GC responses are modified in both the airway and peripheral blood in overweight and obese patients with asthma.

Figure 4. (A) Peripheral blood mononuclear cells (PBMCs) from patients with asthma demonstrate a significantly increased ratio of log (TNF- α) mRNA to dexamethasone (DEX)-induced MKP-1 expression with increasing body mass index (BMI). (B) PBMCs from subjects without asthma do not demonstrate a significantly increased ratio of log (TNF- α) mRNA to DEX-induced MKP-1 expression with increasing BMI.

These findings are statistically robust, particularly with regard to the findings in PBMCs. Although our BAL data are restricted to a smaller subset of the participants with asthma, the sample facilitated detection of differences in the BAL that mirrored our findings in the peripheral blood, suggesting that the mechanisms underlying altered MKP-1 and TNF- α expression are operative in the lung as well. With regard to limitations of this work, it should be noted that subjects with asthma manifested a clinically significant degree of airflow limitation, suggesting that we have evaluated a population of patients with moderate-to-severe asthma, and raising the possibility that our findings may not apply to subjects with mild or intermittent asthma. This can also be interpreted as a potential strength, however, in that it provides observations likely to be relevant to a population of patients with asthma who are more challenging to manage. Our evaluation of molecular biomarkers related to GC response was focused on the MKP-1 pathway, and its potential modulation by TNF- α , allowing the possibility that other unmeasured mechanisms influencing GC signaling could also be operative in overweight and obese patients with asthma. Finally, because we relied on self-report of cigarette smoking, it is possible (although unlikely) that some subjects could have smoked during the study—a behavior known to modify oral GC response (24).

Figure 5. (A) Reduced dexamethasone (DEX)-induced MKP-1 expression in bronchoalveolar lavage (BAL) cells from overweight/obese (gray) versus lean (black) patients with asthma. Data are presented as mean $\pm$ SEM. (B) BAL cells from patients with asthma demonstrate significantly reduced DEX-induced MKP-1 with increasing body mass index (BMI).

As noted previously, the mechanisms by which obesity exerts its effects on asthma remain unclear (4), although potential interactions other than an effect on response to therapy include an increased risk of developing asthma in the setting of obesity, or a skewing toward a more severe phenotype in the overweight or obese individual with asthma. A recent meta-analysis (2) of prospective epidemiologic studies of BMI and asthma incidence indicated that overweight and obesity increase asthma incidence, with a statistically significant increase in the overall odds ratio for incident asthma in overweight and obese subjects to approximately 1.5, along with the suggestion of dose dependency in asthma risk as BMI increased, a phenomenon echoed in the findings of this study with regard to GC response. Studies of the relationship between BMI and asthma in patients with prevalent asthma are less common, but a recent report from the National Heart, Lung, and Blood Institute-funded Severe Asthma Research Program (25) indicated that, in approximately 250 subjects with severe asthma (26), obesity was not more prevalent in severe versus moderate asthma, leading to questions about the role of obesity as a modifier of asthma severity.

Most relevant to our data is the possibility that the inflammatory environment in obesity modifies either clinical or biologic response to GCs. In obesity, enhancement of normal adipose tissue immune function leads to a systemic inflammatory state (5), and many of the cytokines found to be elevated in obesity-related systemic inflammation are also associated with development of GC insensitivity in asthma (8), and may be

critical components of the mechanisms by which this phenomenon occurs in overweight and obese patients with asthma. The mechanisms of GC insensitivity are complex, reflecting the multiple steps involved in GC action, but most important with regard to our findings are the effects of MAPK activation on GC receptor function. Phosphorylation modulates the function of the GC receptor (27, 28), and prior studies have demonstrated that cytokine-induced phosphorylation of the GC receptor, mediated by p38 MAPK or other pathways, is associated with loss of GCR nuclear translocation and reduced responsiveness of T cells to DEX (29, 30). GCs have also been reported to increase expression of a key regulator of MAPK inactivation, MKP-1 (14, 31, 32). The observed attenuation of MKP-1 expression in overweight and obese patients with asthma may allow persistent MAPK activation (14), thereby reducing molecular response to GCs and resulting in an associated reduced clinical response to these agents.

Research over the last decade has demonstrated that TNF- α is overexpressed in the adipose tissue and muscle of obese humans (33–36), a phenomenon that may be of relevance to the treatment of patients with GC-insensitive asthma, both with regard to the potential impact on MAPK signaling pathways noted in the INTRODUCTION, and with regard to the findings of the recent clinical trial by Berry and colleagues, which demonstrated an increase in expression of membrane-bound TNF- α , TNF- α receptor 1, and TNF- α -converting enzyme in PBMCs from patients with severe asthma, in which clinical surrogates of GC insensitivity are the major defining criteria (26). This study demonstrated a beneficial effect of soluble TNF- α receptor etanercept in these patients, as shown by improvements in airway hyperresponsiveness, FEV₁, and asthma-related quality of life (37), raising the possibility that controller agents other than corticosteroids may be more appropriate for patients with asthma characterized by obesity and GC insensitivity. Although our data are not conclusive, they do suggest that increased TNF- α in overweight and obese patients with asthma might be one signal by which down-regulation of MKP-1 expression is controlled.

Additional clinical and basic research is necessary to elucidate the mechanisms by which overweight and obesity modify response to GC therapy in asthma, and we suggest that our research has identified but one potential mechanism by which obesity could alter response to controller therapy in asthma. Recognition of this phenomenon may help identify asthma patients at risk for suboptimal response to controller therapy over the long term, and lead to the development of alternative effective strategies for this prevalent subgroup of patients with asthma.

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