Obesity and Asthma

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Asthma and obesity are prevalent disorders, each with a significant public health impact, and a large and growing body of literature suggests an association between the two. The systemic inflammatory milieu in obesity leads to metabolic and cardiovascular complications, but whether this environment alters asthma risk or phenotype is not yet known. Animal experiments have evaluated the effects of leptin and obesity on airway inflammation in response to both allergic and nonallergic exposures and suggest that airway inflammatory response is enhanced by both endogenous and exogenous leptin. Cross-sectional and prospective cohort studies of humans have shown a modest overall increase in asthma incidence and prevalence in the obese, although body mass index does not appear be a significant modifier of asthma severity. Studying the obesity–asthma relationship in large cohorts, in which self-reports are frequently used to ascertain the diagnosis of asthma, has been complicated by alterations in pulmonary physiology caused by obesity, which may lead to dyspnea or other respiratory symptoms but do not fulfill accepted physiologic criteria for asthma. Recent investigations toward elucidating a shared genetic basis for these two disorders have identified polymorphisms in specific regions of chromosomes 5q, 6p, 11q13, and 12q, each of which contains one or more genes encoding receptors relevant to asthma, inflammation, and metabolic disorders, including the β_2-adrenergic receptor gene ADRB2 and the glucocorticoid receptor gene NR3C1. Further research is warranted to synthesize these disparate observations into a cohesive understanding of the relationship between obesity and asthma.

Keywords: asthma; epidemiology; inflammation; obesity; pathogenesis

Asthma and obesity are prevalent disorders, each with a significant impact on the public health. Age-adjusted data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) indicate that approximately 65% of United States' adults 20 years or older are either overweight or obese (1), a 10% increase in prevalence versus 1988–1994 (2). Furthermore, 31% of children aged 6 through 19 years are either overweight or at risk for overweight (1). Although asthma affects a smaller proportion of the United States' population than does obesity ($\sim$ 7% of adults in 2002) (3), it, too, exacts a significant toll on individuals and society (4).

An increasing body of literature suggests that there is an association between obesity and asthma. Although the exact nature of this association remains unclear, many investigators have interpreted the data to suggest that obesity both increases the risk of incident asthma (5) and alters prevalent asthma toward a more difficult-to-control phenotype (6). However, others have questioned whether the two disorders are related at all (7). Although the risk of asthma due to obesity remains unclear (8), a theory of causation can be supported, at least tentatively, by animal studies that provide biological underpinnings to an association between the two disorders, by epidemiologic studies that suggest the relationship between these two disorders is clinically important, and by new insights into a shared genetic basis for susceptibility to both disorders.

OBESITY, AIRWAY INFLAMMATION, AND ATOPY

Data from animal and human studies suggest that enhancement of normal adipose tissue functions in obesity leads to a systemic proinflammatory state (9). Adipose tissue from obese individuals expresses a number of proinflammatory molecules, such as leptin, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), transforming growth factor β1 (TGF-β1), and C-reactive protein, and there appears to be significant overlap between the immune function of adipocytes and the functions of T lymphocytes and macrophages, particularly with regard to elaboration of inflammatory cytokines (10, 11). This proinflammatory state has been implicated in leading to a number of the metabolic and cardiovascular complications of obesity, but whether or not this environment can also modulate airway inflammation, alter lung development or physiology, and lead to asthma is not yet known. Although a conclusive relationship between obesity and systemic inflammation, airway inflammation, and asthma has yet to be described, a variety of reported observations suggest that obesity might impact the lung in multiple ways (Figure 1).

Much of the literature focusing on the relationship between obesity and airway inflammation and asthma has focused on the role of leptin. Leptin, the product of the *Ob* gene, is increased in obese humans and is also a central mediator of inflammation in obesity; it shares structural homology with long-chain helical cytokines, such as IL-6, and has been shown to regulate T-cell proliferation and activation, recruit and activate monocytes and macrophages, and promote angiogenesis (12). Leptin is also important for normal lung development, serving as a critical mediator of the differentiation of lipofibroblasts to normal fibroblasts and of pulmonary surfactant phospholipid synthesis (13), and obese mice that are genetically leptin deficient (*ob/ob*) demonstrate profound pulmonary hypoplasia.

Exogenous leptin has been shown to modulate allergic airway responses in mice, independent of obesity. Shore and colleagues sensitized and challenged lean BALB/cJ mice with ovalbumin and then infused either saline or leptin subcutaneously. Leptin infusion led to increased serum leptin levels and was associated with an enhancement of airway hyperresponsiveness (AHR) and an increase in serum IgE after inhaled ovalbumin challenge, responses not observed in animals challenged with inhaled phosphate-buffered saline. There was no effect of leptin administration on

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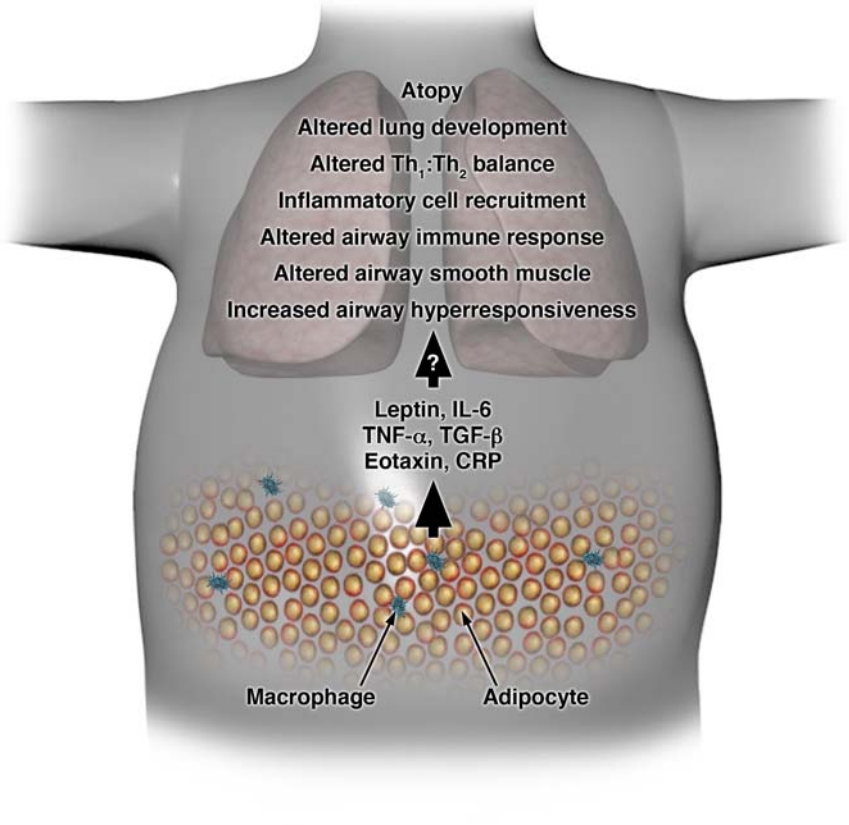

Figure 1. In obesity, visceral adiposity is correlated with circulating levels of proinflammatory cytokines, and adipose tissue propagates inflammation both locally and systemically, in part through recruitment of macrophages via chemokines such as monocyte chemoattractant protein-1 (MCP-1) and in part via elaboration of cytokines and chemokines such as (but not limited to) leptin, interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), transforming growth factor β1 (TGF-β1), and eotaxin. Although the precise relationship between obesity and asthma remains to be determined, modifications of atopy, lung development, Th1–Th2 balance, immune responsiveness, and airway smooth muscle have been hypothesized to be mechanisms by which obesity might increase asthma risk or modify asthma phenotype. CRP = C-reactive protein.

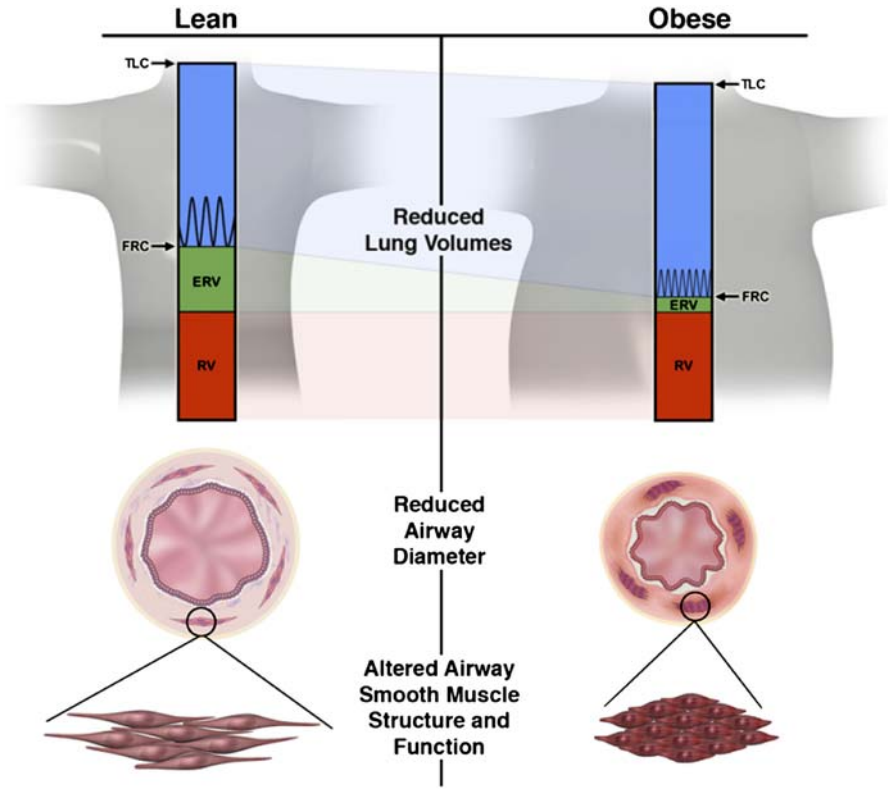

Figure 2. Obesity leads to alterations of lung volumes (*top*), particularly expiratory reserve volume (ERV) and FRC, leading to a rapid, shallow breathing pattern that occurs close to closing volume. Obesity also causes reduced peripheral airway diameter (*middle*), which can lead to increased airway hyperresponsiveness due to alterations of smooth muscle structure and function (59).

bronchoalveolar lavage (BAL) fluid cell counts or lung tissue cytokine mRNA expression, however (14). Interestingly, exogenous leptin administration enhances nonallergic pulmonary immune function as well; Mancuso and colleagues recently reported that the provision of exogenous leptin enhanced bacterial clearance, BAL neutrophils and cytokines, alveolar macrophage bacterial killing, and leukotriene synthesis in a murine pneumococcal pneumonia model (15). Endogenous leptin levels can be increased by overfeeding wild-type lean mice, leading to obesity and enhancing airway inflammatory response. Overfed mice that were subsequently sensitized and challenged with ovalbumin had higher antigen-induced T-cell responses, increased mitogen-induced splenocyte IFN-γ production, and increased number of tracheal mast cells compared with lean control animals, although ovalbumin-specific immunoglobulin levels were paradoxically reduced in obese mice versus lean control mice (16). These studies suggest that leptin appears to have an important immunomodulatory role that is relevant to airway function and immune response, independent of body mass.

The relationship between obesity and enhanced airway inflammation cannot be attributed solely to leptin, however, because the obese leptin-deficient *ob/ob* mouse also demonstrates enhanced airway immune response. In a study of airway response to ozone, Shore and colleagues exposed both lean wild-type C57BL/6J mice and obese *ob/ob* mice to ozone, after which AHR and airway inflammation were evaluated (17). Exposed *ob*/*ob* mice had enhanced AHR when compared with lean control animals, and while BAL levels of the CC chemokine eotaxin (an eosinophil chemoattractant) were increased, a predominantly Th1 inflammatory phenotypic response was observed in *ob*/*ob* mouse, with elevated BAL levels of IL-6 and the neutrophil chemoattractants macrophage inflammatory protein 2 (MIP-2) and KC. In this same study, a subset of both lean and obese mice were given intraperitoneal injections of leptin before and directly after ozone exposure, and although leptin administration did not further enhance inflammatory responses in the *ob*/*ob* mice, leptin did significantly increase BAL levels of IL-6 and KC in lean control mice. This suggests that the mechanisms by which exogenous leptin alters airway immune response might vary between obese and lean animals, dependent on factors such as endogenous leptin concentrations, receptor number or affinity, or other concurrent modifications of inflammatory pathways.

A recent investigation of mice and humans provides compelling evidence for an effect of obesity on eotaxin expression. Vasudevan and colleagues compared adipose tissue eotaxin mRNA levels and serum eotaxin concentrations in lean and overfed obese C57BL/6 mice and determined that obese mice had significantly increased eotaxin mRNA levels in the stromal/vascular fraction of adipose tissue when compared with lean mice, a phenomenon that correlated significantly ($r = 0.778$, $p = 0.008$) with increased serum eotaxin levels in obese versus lean animals. A similar relationship between obesity and plasma eotaxin concentrations was demonstrated in humans, with eotaxin concentrations of 82.6 ± 31.6 versus 44.5 ± 22.0 pg/ml ($p = 0.004$) in obese versus lean subjects. In the obese subjects, weight loss of 8.0 ± 3.8 kg (SD), achieved either via caloric restriction or bariatric surgery, was associated with a reduction in plasma eotaxin concentrations to 62.8 ± 25.3 pg/ml ($p < 0.001$) (18). Only one of the obese participants had asthma, limiting the ability to relate changes in eotaxin to changes in asthma phenotype, but these data suggest that elevated systemic levels of eotaxin are observed in obesity and that the source of the eotaxin is at least in part the adipose tissue, raising the possibility that this obesity-associated increase in eotaxin might play a role in elevating asthma risk or severity (19, 20).

Clinical studies in children provide supporting evidence to the mouse-model observation that leptin may play a role in asthma that is to some extent independent of obesity. Guler and colleagues reported an association between leptin and asthma in a population of 134 Turkish children with a mean age of 6 years, 102 of whom had asthma. These investigators reported that a significant elevation in serum leptin was observed in children with asthma when compared with healthy children (median, 3.53 vs. 2.26 ng/ml; $p = 0.008$), despite similar mean body mass index (BMI; 17.53 vs. 16.98), although this difference appeared to be far more significant in boys than girls. Atopic subjects with asthma had significantly higher leptin levels than did nonatopic subjects, although there were only weak correlations between log IgE and log leptin levels among the children with asthma ($r = 0.231$, $p = 0.02$) (21). In a smaller group ($n = 23$), reported by Mai and colleagues, overweight children with asthma had serum leptin levels that were numerically higher but not statistically different than those seen in obese children without asthma, with median leptin concentrations of 30.8 versus 14.3 ng/ml, respectively ($p = 0.14$) (22). Of note, inhaled corticosteroid therapy has been reported to reduce leptin concentrations in children with asthma. Gurkan and colleagues reported that, in a small cohort ($n = 23$) of children with mild to moderate asthma, treatment with inhaled budesonide resulted in a significant reduction in serum leptin concentrations after 4 weeks, with a mean (± SD) pretreatment leptin concentration of 19.3 ± 5.1 ng/ml compared with 10.6 ± 1.6 ng/ml post-treatment ($p < 0.001$). Although this study did not have an actively treated control group, subjects in the healthy control group had a mean serum leptin concentration of 9.8 ± 1.6 ng/ml, suggesting that, in children with asthma, inhaled corticosteroid therapy reduces leptin concentrations to within the range observed in nonasthmatic control subjects (23).

EPIDEMIOLOGIC OBSERVATIONS

Cross-sectional studies of adults have demonstrated an increased prevalence of asthma in the obese (24–27), and a recent review has examined this literature in detail (28). These studies were able to evaluate large numbers of subjects and have provided important insights into the epidemiology of the two disorders, although some rely on self-reported weight and height to determine BMI, a potential limitation due to inaccuracies or biases related to reporting. However, in studies that use measured rather than self-reported height and weight to define BMI (24, 26, 27), there is still a significant association between elevated BMI and asthma. Another potential limitation is that these studies typically categorize asthma on the basis of a self-reported physician's diagnosis of asthma, rather than formal physiologic evaluation, raising the possibility that respiratory symptoms are in fact due to some obesity-related physiologic impairment other than asthma (29). Furthermore, it is difficult to establish causation or the directionality of the association in prevalence studies; because individuals with asthma may develop obesity due to a variety of factors, including inactivity or side effects of systemic corticosteroids, without controlling for these factors in a longitudinal study it is difficult to understand whether asthma causes obesity or whether it results from it. Obesity and asthma may even each be independently associated with other unmeasured confounding conditions, such as obstructive sleep apnea or gastroesophageal reflux disease (GERD) (30), conditions that are often unmeasured in these studies.

Prospective studies have often included more rigorous definitions of asthma in their study populations (5, 24, 31–36) and have the additional benefit of being able to assess whether antecedent obesity leads to subsequently increased incidence of asthma. In

one of the earliest and largest studies by Camargo and colleagues (5), 85,911 women were monitored for 4 years. In a multivariate model, the relative risk of incident asthma for increasing categories of BMI was 1.0, 1.1, 1.6, 1.7, and 2.7 (p for trend < 0.001). Although a potential weakness of this study was the use of self-reported weight and height, the authors point out that previous studies have validated this approach against measured weight and height, and found differences to be minimal. Two prospective studies by Ford and coworkers (32) and Nystad and colleagues (35) included both men and women, based their description of BMI on measured weight and height, and found associations between elevated BMI and incident asthma of similar strength to studies using self-reported data. Whether anthropomorphic variables were measured or self-reported, the majority of prospective studies have reported that obesity is a risk factor for the development of a new diagnosis of asthma, with risk or odds ratios (ORs) of between 1.1 and 3.0 comparing the highest with lowest BMI categories. Most have shown a steady dose–response relationship with incident asthma and increasing BMI, and most demonstrate the effect to be stronger in women than men. Many of these longitudinal studies also control for diet and physical activity, strengthening the conclusion that it is obesity itself, and not a lack of exercise or a dietary factor, that is associated with asthma. However, in a recent community-based cohort study of 591 adults with and without asthma who were monitored between ages 20 and 40 years, asthma was significantly associated with obesity cross-sectionally (OR, 3.9, 95% confidence interval [1.2–12.2]), but a multivariate analysis revealed that although obesity was not a risk factor for subsequent asthma, asthma was a risk factor for subsequent obesity (37).

Although the dose–response relationship and stronger association often observed between obesity and asthma in women are intriguing, the difference in the point estimates between men and women is usually small, and some studies have shown conflicting results. For example, in Chen and colleagues' 2002 Canadian National Population Health Survey study, the incidence of asthma was associated with the degree of baseline adiposity in women but not men (31). Two other prospective studies showed that the association between obesity and asthma is not stronger in women compared with men (33, 34).

There is more heterogeneity in the pediatric epidemiologic literature regarding the strength and direction of the obesity–asthma relationship. A prospective study of 9,828 children aged 6 to 14 years showed that, after a mean follow-up of 5 years, obesity increased the risk of incident asthma (38). Similar to some of the adult studies, the effect may have been stronger in girls than boys, with a 2.2 times greater risk of asthma in the highest compared with leanest BMI quintile in girls, and only a 1.4 times greater risk in boys. However, the association between BMI and asthma in boys was bimodal, with an increase in asthma incidence in both the lowest and highest BMI quintiles in boys. When comparing the fifth with the third BMI quintile in girls and boys, the relative risk of asthma was 3.11 and 3.81, respectively, suggesting there is no difference between the sexes, or that perhaps the risk is higher in boys. A 2003 report of 3,792 participants in the Children's Health Study showed that overweight and obesity increased the risk of incident asthma (risk ratio, 1.52 [1.14–2.03] and 1.60 [1.08–2.36], respectively), with obese boys having an increased risk of asthma compared with girls (39), counter to the relationship observed in adults but possibly congruent with the findings of Guler and colleagues described above. Not all studies of children show a significant association, however. Chinn and colleagues reported that, in a group of British schoolchildren, the annualized odds of developing asthma was 1.09 [1.07–1.11] for both boys and girls, a number that did not change significantly when adjusting for BMI (40). The cause of the heterogeneity in the sex dependence of this relationship in pediatric and adult studies is not clear, but some investigators have suggested that BMI does not measure adiposity equally well in children versus adults and men versus women due to differences in factors such as muscle mass (41), and it can be reasonably postulated that other factors, such as lung development and growth or pre- versus postpubertal sex hormone differences, are operative as well.

Pediatric studies have also not shown a consistent relationship between obesity and atopy. In children participating in the NHANES III survey, the prevalence of asthma and atopy (evaluated by reported prevalence of atopic disease and skin-prick testing) increased with increasing BMI, but after adjusting for confounding factors, only the relationship between BMI and asthma remained significant (OR, 1.77 [1.44–2.19]); there was no relationship between BMI and atopy (42). In contrast, a New Zealand study found that, in girls, BMI was significantly associated with positive skin tests and elevated IgE (43). This association was modest (OR, 1.14 [1.10–1.30]), and not seen in boys.

Evaluations of the relationship between BMI and asthma phenotype in patients with well-characterized asthma are far less prevalent in the literature. Analysis of data from the Childhood Asthma Management Program (CAMP) cohort (in which participants' asthma phenotype was carefully defined by means of symptoms, lung function, and testing for atopy and AHR) suggested that there was not a statistically significant relationship between BMI and many markers of asthma control, including school absenteeism, emergency department care, or requirement for corticosteroids or hospitalizations, although there was a weak relationship with exertional cough or wheeze. BMI did not appear to impact eosinophil counts or IgE concentrations, and although there was a weak inverse relationship between BMI and bronchodilator reversibility ($\beta = -0.003$, $p = 0.02$), there was no impact of BMI on AHR to methacholine (44). The generalizability of these data is somewhat limited, however, by the observation that most participants were prepubertal and that the median BMI was 17.09, and additional data from the extended follow-up phase of CAMP are needed to shed light on the relative contributions of body mass, age, sex hormones, and other variables to overall asthma phenotype and severity.

GERD and sleep-disordered breathing (SDB) are two conditions that are commonly associated with both obesity and asthma. Two epidemiologic investigations offer insight into the possible confounding effect of these disorders on the obesity–asthma relationship. In a follow-up questionnaire study of the European Community Respiratory Health Survey, involving over 16,000 respondents, Gunnbjornsdottir and colleagues found that both self-reported GERD symptoms and self-reported asthma symptom onset increased in prevalence with increasing BMI, but that when GERD was controlled for, obesity remained significantly related to the onset of asthma (33). With regard to SDB, in a group of 788 children evaluated by Sulit and colleagues, although both SDB and obesity were each associated independently with asthma and wheeze, adjustment for SDB did not significantly alter the strength of the relationship between obesity and asthma (45). Although there are still many unanswered questions about the interactions among these disorders, these two studies do suggest that, although both GERD and SDB are important comorbid conditions in obese individuals with asthma, they do not fully account for the association between obesity and asthma.

OBESITY AND PULMONARY PHYSIOLOGY

Obesity has been recognized to affect lung function for over 50 years (46), and physiologic studies suggest that obesity has

important mechanical effects that can lead to symptoms without necessarily causing the physiologic changes commonly observed in asthma. Obesity causes a reduction in respiratory system compliance, lung volumes, and peripheral airway diameter, as well as an increase in AHR, alteration in pulmonary blood volume, and ventilation–perfusion mismatch.

Respiratory system compliance is reduced by at least three factors in obesity: excess soft tissue weight compressing the thoracic cage, fatty infiltration of the chest wall, and an increase in pulmonary blood volume (47–50). This reduction in respiratory system compliance results in an increased oxygen cost of breathing (51), as well as a subjective increase in dyspnea (52). Obesity also causes airflow limitation, with reduction of both FEV_1 and FVC (53). Unlike asthma, however, these reductions in airflows are typically symmetric and result in a preserved FEV_1/FVC ratio (52). In fact, some authors have shown that the FEV_1/FVC ratio is increased in obesity, consistent with a restrictive physiology (53). These alterations of pulmonary physiology lead obese individuals to breathe shallowly near their closing volume (54). Lung volumes, particularly the expiratory reserve volume (ERV) and FRC (53, 55), are reduced in obesity (Figure 2, *top*), with studies of surgical weight loss demonstrating that clinically significant weight loss is associated with meaningful improvements in ERV, FRC, total lung capacity, residual volume (56), and respiratory muscle function (57).

The reductions in lung volumes observed in obese individuals are associated with a reduction in peripheral airway diameter (58) (Figure 2, *bottom*), a phenomenon that, over time, perturbs smooth muscle function, causing a change from rapidly cycling actin–myosin cross-bridges to slowly cycling latch bridges (59), potentially increasing both airway obstruction and AHR. However, the available clinical data on obesity and AHR are conflicting. In a study of 11,277 participants in the European Community Respiratory Health Survey, AHR increased with increasing BMI in men but not women (60), and in a case-control study, BMI was associated with the development of AHR (61). In contrast, Schachter and colleagues showed that, in a group of 1,971 adults, BMI was associated with a diagnosis of asthma and symptoms of dyspnea and wheeze, but was not associated with either airflow obstruction or AHR (62). Another study of 5,984 children showed that obesity was associated with asthma symptoms and inhaler use, but not AHR (63). Thus, although it is apparent that obesity leads to a number of physiologic perturbations that could cause respiratory symptoms, physiologic studies do not uniformly support the conclusions that obesity leads to airflow limitation, AHR (either via the latch bridge hypothesis or by increasing airway inflammation), or asthma.

Medical weight loss studies in individuals with asthma have demonstrated, however, that weight loss can lead to improvements in both clinical and physiologic parameters. In an observational study of 14 obese patients with asthma before and after an 8-week very-low-calorie diet, weight loss reduced diurnal peak flow variability, increased FRC, and improved measures of airflow limitation (64). In a similarly designed 6-month medical weight loss study of 58 obese women (24 of whom had asthma), weight loss improved lung function as measured by FEV_1 and FVC, but did not affect methacholine responsiveness (65). Finally, in an experimental study of two groups of 19 patients with obesity and asthma, the group randomized to supervised medical weight loss demonstrated improved lung function, asthma symptoms, and health status when compared with control subjects (66).

THE INFLUENCE OF SEX HORMONES AND GENES

The finding in some studies that there are sex differences in the strength of the relationship between obesity and asthma could suggest that sex hormones play a role modulating this relationship. Castro-Rodríguez and colleagues showed that, although there was no association between BMI and asthma at age 6, the development of overweight or obesity between age 6 and 11 was associated with a seven-times increased risk of new asthma symptoms, and the effect was strongest among females beginning puberty before age 11 (67). In adult postmenopausal women, exogenous estrogen in the form of hormone replacement therapy has been associated with an increased risk of asthma (68), and a recent study showed that the association between BMI and asthma severity was stronger in women with early menarche than in women without early menarche (69).

There are no well-established mechanisms to explain the association of sex hormones with asthma, particularly in obesity, but estrogen may play a role in asthma, and may do so by modifying the inflammatory response to favor a Th2 response. Estrogen or progesterone administered to human peripheral blood mononuclear cells induces production of the Th2 cytokines IL-4 and IL-13 (70). Treatment of eosinophils with β-estradiol significantly enhances eosinophil adhesion to human mucosal microvascular endothelial cells, and induces degranulation, whereas testosterone administration reduces eosinophil adhesion and viability (71). This estrogen-induced shift from a Th1 to Th2 response was further demonstrated in a murine model of immune response to purified protein derivatives. In this study, β-estradiol, administered at contraceptive doses, decreased purified protein derivative-specific delayed-type hypersensitivity responses, and during subsequent *in vitro* studies of the draining lymph node cells, β-estradiol suppressed IL-2 and IFN-γ production, while increasing gene expression of the Th2 cytokines IL-4 and IL-10 (72). Finally, when progesterone was administered to BALB/c mice sensitized with ovalbumin, there was an increase in bronchial eosinophilia and enhanced bronchial responsiveness (73). Thus, there may be a mechanistic basis for the association between sex hormones and asthma, although the exact importance of these models in the obesity–asthma relationship in humans remains to be determined.

Obesity and asthma may be determined by common genetic mechanisms. Hallstrand and colleagues reported an analysis of 1,001 monozygotic and 383 dizygotic same-sex twin pairs, and found that the covariation between obesity and asthma is predominantly caused by shared genetic risk factors for both conditions (74). Candidate genes have been identified that are associated with both obesity and asthma (Table 1). The β_3-adrenergic receptor, located primarily in adipose tissue, is involved in the regulation of lipolysis and thermogenesis, and morbidly obese people with a genetic mutation in the gene for the β_3-adrenergic receptor have an increased capacity to gain weight (75). Polymorphisms in the β_2-adrenergic receptor gene, located on chromosome 5q31-q32, have been associated with asthma phenotype, severity, and response to β-agonists (76–78). The Gln27→Glu polymorphism of this receptor has also been associated with obesity (79). In addition, TNF-α gene haplotypes have been associated with asthma and AHR (80) and obesity (81), and the glucocorticoid receptor gene NR3C1 has been postulated to be involved in the inflammatory responses associated with both obesity and asthma.

CONCLUSIONS

Much work remains to be done to elucidate the relationship of obesity and asthma. Although longitudinal adult epidemiologic investigations suggest that there is an association between the two, the overall impact of obesity on asthma incidence and prevalence appears to be modest and modified by factors such as age and sex. In cohorts where asthma has been carefully characterized,

TABLE 1. CANDIDATE GENES OF POTENTIAL RELEVANCE TO BOTH OBESITY AND ASTHMA

Locus	Candidate Genes	Relevance to Asthma	Relevance to Obesity
5q	ADRB2	Controls airway tone	Controls metabolic rate
	NR3C1	Modulates inflammation	Modulates inflammation
6p	TNF, HLA gene cluster	Modulates immune and inflammatory responses	Modulates immune and inflammatory responses
11q13	UCP2, UCP3	Unknown	Controls metabolic rate
	IgE (FCεRB)	Th2 inflammatory response	Unknown
12q	STAT6, IGF1, IL1A, LTA4H	Modulates inflammatory responses	Modulates inflammatory responses

Definition of abbreviations: ADRB2 = β_2-adrenergic receptor; IGF = insulin-like growth factor; IL1A = interleukin 1α; LTA4H = leukotriene A4 hydroxylase; NR3C1 = glucocorticoid receptor; STAT6 = signal transducer and activator of transcription gene; TNF = tumor necrosis factor; UCP = uncoupling protein.

the impact of BMI appears to be even more modest, and careful phenotyping studies in matched cohorts of subjects with and without both asthma and obesity are needed to further elucidate the extent to which airway physiologic and inflammatory phenotypes are modified by obesity and to clarify the extent to which potentially confounding comorbidities, such as SDB and GERD are important. Although the recent focus on mouse models relating obesity of various etiologies to allergic response and airway inflammation is promising, a continued emphasis on well-characterized animal models with regard to the interaction of obesity, environmental exposures (e.g., allergen, infection), host factors (e.g., sex hormones), and airway inflammation is needed to guide further hypothesis development and testing in humans. Finally, ongoing research into the genetic basis for both of these complex traits and increased effort at relating these genes to specific asthma phenotypes should begin to enhance our understanding of the common genetic basis of these disorders.

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