Symposium on obesity and asthma – November 2, 2006

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Asthma and obesity are frequently associated, and obesity has been considered a factor contributing to both an increase in severity of asthma and to its development. The present document summarizes the proceedings of a symposium held in Montreal, Quebec, on November 2, 2006, under the auspices of the Réseau en santé respiratoire du Fonds de la recherche en santé du Québec in collaboration with the McGill University – Strauss Severe Asthma Program, Université Laval (Québec City) and Université de Montréal. It includes an overview of the various aspects of the relationships between asthma and obesity with regard to animal models; genetic, hormonal and physiological determinants; influence of comorbidities (eg, sleep apnea syndrome); epidemiology; clinical and psychological features; and management of asthma in the obese population.

Key Words: Airway inflammation; Asthma; Body mass index; Lung function; Obesity; Sleep apnea syndrome

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The present report was an initiative of the Réseau en santé respiratoire du Fonds de la recherche en santé du Québec in collaboration with the McGill Strauss Severe Asthma Program, Université Laval and Université de Montréal

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Asthma and obesity are two increasingly common conditions worldwide (1). In the past two decades, large amounts of data have been published on the relationships between these two major health problems (2,3). Recently, the Réseau en santé respiratoire du Fonds de la recherche en santé du Québec has developed a working group to explore current and potential future research initiatives on the relationships between asthma and obesity. As an initial step, a symposium was held in Montreal, Quebec, on November 2, 2006, under the auspices of the Réseau en santé respiratoire du Fonds de la recherche en santé du Québec, in collaboration with the McGill University – Strauss Severe Asthma Program, Université Laval and Université de Montréal, with the additional support of unrestricted educational grants from AstraZeneca Canada, GlaxoSmithKline and Merck Frosst Canada.

The goals of the present symposium were to review current data available, to discuss research needs, and to explore possible collaborative studies in the field of obesity and asthma. Investigators involved in research on obesity and respiratory diseases from the province of Quebec and internationally were therefore invited to this brainstorming session. In the present document, summaries of the presentations and discussions on possible future initiatives in this field of research are reported. Topics included animal models of asthma and obesity; genetic, mechanical, hormonal and other factors by which obesity can influence asthma, as well as the influence of comorbidities, such as sleep apnea syndrome, on this relationship; epidemiological, clinical and psychological features; and, finally, management of asthma in the obese.

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OBESITY AND ASTHMA: LESSONS FROM ANIMAL MODELS

Stephanie A Shore PhD

Epidemiological data indicate that obesity is a risk factor for asthma (1,2). These data are supported by observations in several murine models of obesity. Obese ob/ob, db/db and Cpefat mice, as well as mice with diet-induced obesity, exhibit innate airway hyper-responsiveness, a characteristic feature of asthma. These mice also develop more airway hyper-responsiveness and more pulmonary inflammation than wild-type mice following exposure to ozone, a common asthma trigger (3-6). Gene expression profiling indicates differences in pulmonary gene expression in obese versus lean mice, both before and after ozone exposure. The mechanistic basis for these effects of obesity has not been established, but adipokines, factors synthesized in adipose tissue and released into the blood, may be involved. For example, adiponectin, an anti-inflammatory adipokine that decreases in obesity, has been shown to attenuate allergic airway responses in mice (7). Moreover, allergen challenge reduces both serum adiponectin and adipose tissue expression of adiponectin. Experiments using antitumour necrosis factor-alpha and anti-interleukin-6 antibodies indicated that both of these cytokines may contribute to the innate airway hyper-responsiveness observed in obese mice. The data suggest novel potential therapeutic strategies for the treatment of asthma in the obese, including the use of peroxisome proliferator-activated receptor-gamma agonists, which are known to increase serum adiponectin, as well as tumour necrosis factor-alpha blocking agents.

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BODY MASS INDEX, ADIPOKINES AND AIRWAY OXIDATIVE STRESS

Sushma Komakula MD, Fernando Holguin MD

BACKGROUND: Recently, it has been shown that increasing body mass index (BMI) in asthma is associated with reduced exhaled nitric oxide (NO) (1). The objectives of the present study were to determine whether the BMI-related changes in exhaled NO differ between asthmatic and control subjects, and to determine whether these changes are related to increased airway oxidative stress and systemic levels of leptin and adiponectin.

METHODS: An observational study of the association of BMI, leptin and adiponectin with exhaled NO and exhaled 8-isoprostanes was conducted in 67 nonsmoking patients with moderate to severe persistent asthma during baseline conditions and 47 control subjects. Measurements included plasma levels of leptin, adiponectin, exhaled breath condensates for 8-isoprostanes, exhaled NO, pulmonary function tests, and questionnaires regarding asthma severity and control.

RESULTS: In asthmatic patients, reduced exhaled NO was associated with BMI (β=–0.04 [95% CI –0.07 to –0.01], P=0.003) and ratio of leptin (ng/mL) to adiponectin (μg/mL) (β=–0.0018 [95% CI –0.003 to –0.00034], P=0.01). Also, BMI was associated with increased levels of exhaled 8-isoprostanes (β=0.30 [95% CI 0.003 to 0.6], P=0.03) after adjusting for confounders. In contrast, these associations were not observed in the control group of healthy, nonasthmatic subjects with a similar weight distribution.

CONCLUSIONS: In adults with stable moderate to severe persistent asthma, but not in control subjects, the BMI and the plasma ratio of leptin to adiponectin are associated with reduced exhaled NO. Also, BMI is associated with increased...
exhaled 8-isoprostanes. These results suggest that BMI in asthmatic patients may increase airway oxidative stress and could explain the BMI-related reductions in exhaled NO.

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LUNG FUNCTION IN THE OBESE SUBJECT
Charles G Irvin PhD

The impact of excess body weight on the functioning of the respiratory system is significant. Effects include pathological alterations in mechanical properties, gas exchange, exercise performance and control of breathing (1). Initially, as weight is gained, there is a fall in the functional residual capacity due to chest wall restriction starting at more than 0.5 kg/cm or body mass index greater than 35 kg/m2 (2,3). Total lung capacity is compromised only in the morbidly obese (ie, body mass index of 50 kg/m2 or greater). There are limited data from studies investigating the role of adipose distribution, which may have an important role in the functioning of the respiratory system (4). Obesity has a significant effect on increasing airflow resistance, but this effect appears to be sex specific, being limited to men (5), and is apparently not due to falls in functional residual capacity (6). Sex also affects the impact of obesity on asthma, with boys being more affected than girls (7) and women being more affected than men. Airways hyper-responsiveness is also adversely affected by obesity, in part, due to a fall in lung volume, but other factors may be involved (8). It is not clear that weight loss resolves these profound pathophysiological derangements because the improvement in lung function after weight loss has been disappointing (2,9,10) and suggests mechanisms more than simple chest wall restriction. Taken together, knowledge about the impact of body weight on lung function is surprisingly limited, and a number of unanswered questions regarding the impact of obesity on the functioning of the respiratory system remain to be investigated further.

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Obesity and asthma

GENETICS OF ASTHMA AND OBESITY
Catherine Laprise PhD,
Marie-Claude Vohl PhD

Asthma and obesity are two complex traits that affect patients of all ages, cause important morbidity and mortality, and consequently have critical public health impacts (1). These conditions are increasing in terms of prevalence, and their etiology is under the influence of both genetic and environmental factors. A literature review (1) of the genetic component of these traits reports that many genes are involved, the effects of which may vary in different populations based on genetic background and environmental exposures. In addition, it is important to take into account gene-gene and gene-environment interactions (epigenetics) when evaluating the severity of the clinical manifestations of the diseases. Asthma and obesity pathophysiology involves several cell types, and their respective molecules are involved in different metabolic pathways that affect the disease status. Both asthma and obesity have an important inflammatory component implying a large number of cytokines and chemokines. It will be important to document the common and the specific inflammatory markers to gain a better knowledge of their molecular basis and also to improve our comprehension of these two diseases. Although some of the underlying mechanisms have been elucidated in recent years, much work is needed to gain a clear understanding of the genetic factors that contribute to the development of different forms of asthma and obesity, which may help to clarify the biological link between these two traits.

One can then hypothesize that the development of these traits is under the influence of common inflammatory genes. Based on the literature, an inventory of potential candidate genes for asthma and obesity has been made. For asthma, 12 complete genome scans have been published, identifying a total of 20 chromosomal regions linked to asthma (2). Recent reviews (3,4) report more than 100 genes associated with asthma. Among these, an elite group of 10 genes were replicated in more than 10 independent studies. For obesity, a total of 52 genomic regions harbour quantitative trait loci supported by two or more studies (obesity gene map). Numerous studies report associations between genetic variants and obesity phenotypes with 426 associations within 127 candidate genes (5). A promising observation is that 22 genes are each supported by at least five positive studies.

Expression studies using microarrays identified 79 genes differentially expressed in bronchial biopsies of four asthmatic subjects compared with four control subjects. These included 21 genes previously implicated in asthma (NOS2A and GPX3), as well as new candidates (ALOX15, CTSC, SERPINB2 and C3CR1) (6). Similar experiments have been performed on human adipose tissue to compare the gene expression profiles of subcutaneous and visceral adipose tissues of 10 nondiabetic, normolipidemic obese men (7). A total of 409 transcripts were differentially expressed, including genes involved in lipolytic stimuli and cytokine secretion, genes of the Wnt signalling pathway, as well as the CEPBA and HOX genes. Another study compared the gene expression profiles of obese individuals with and without metabolic complications (8). A total of 489 genes were differentially expressed between the two groups. Of those, 80 were located within a previously identified region of linkage.
The combination of results from linkage and expression studies to identify candidate genes for both asthma and obesity in Quebec studies (data unpublished) indicate that the genes for the human leukocyte antigen cluster, tumour necrosis factor-alpha, peroxisome proliferator-activated receptors, signal transducer and activator of transcription 6, and interleukins, as well as beta-2-adrenergic receptor and high affinity immunoglobulin E receptor (membrane-spanning four domains, subfamily A, member 2), appear to be involved in both conditions, and thus, should be further explored. In perspective, it would be relevant to test for association considering body mass index and waist circumference in the asthma sample. Another interesting avenue could be microarray studies to compare expression profiles of lung tissue of obese asthmatic subjects.

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Physiopathology of Asthma in the Obese
Céline Bergeron MD FRCP MSc, Quayta Hamid MD PhD

Obesity has been suggested to be a risk factor for acquiring asthma (1,2) and a factor for modifying asthma (3-5). A number of mechanisms have been proposed to explain the influence of obesity on asthma, such as low-grade systemic inflammation, modified lung mechanics (6) and altered response to asthma controller agents (7). Obesity is an inflammatory state in which adipose tissue is a source of cytokines and chemokines, including leptin, interleukin-6, tumour necrosis factor-alpha, transforming growth factor-beta and eotaxin (8-10). The exact influence of this systemic inflammation on asthma pathology is unknown. Our data analysis reported no significant differences in the number of sputum eosinophils and neutrophils in obese compared with nonobese moderate and severe asthmatic patients. In the same cohort, airway remodelling features, including smooth muscle mass area, subepithelial fibrosis and epithelium integrity, were similar between obese and nonobese asthmatic patients. However, the chubby appearance of the airways on bronchoscopy and the existence of fat loculation on bronchial biopsies of morbidly obese subjects were suggestive of airway fat infiltration. The consequence of airway fat infiltration is unknown, but it may be associated with corticosteroid insensitivity. In fact, visceral fat tissues from obese subjects express high levels of the dominant negative isoform of the glucocorticoid receptor-beta (11), which is a mechanism of corticosteroid insensitivity reported in severe asthma (12,13).

Airway pathology in obese asthmatic patients is characterized by fat infiltration, which does not appear to influence airway inflammatory cells and remodelling. However, obese asthmatic patients have less well-controlled asthma, suggesting that obesity and/or airway fat infiltration may influence the response to asthma treatment. Comprehensive studies are needed to properly depict the differences in pathology between obese and nonobese asthmatic patients.

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Obesity and Asthma Control
Pierre Ernst MD

Various studies in adults and children have suggested that obese asthmatic subjects experience poorer asthma control than nonobese subjects with asthma. For example, Belamarich et al (1) reported that among children aged four to nine years in the inner-city asthma study, obese subjects had more symptoms, used more oral corticosteroids in the previous three months (30% versus 24%) and experienced more emergency department visits during a nine-month follow-up (39% versus 31%) than nonobese subjects. Saint-Pierre et al (2) reported on 406 asthmatic patients followed in specialty clinics. Obese subjects were one-half as likely as nonobese subjects to achieve acceptable control according to Canadian guidelines.
It remains unclear, however, whether this excess in symptoms, health care use and need for medications represents more severe asthma or rather the presence of more severe asthma-like symptoms. Sin et al (3) found that among 16,171 subjects with asthma in the third National Health and Nutrition Examination Survey (NHANES III), subjects whose body mass index was 31 kg/m² or greater reported more symptoms and bronchodilator use than subjects with a body mass index between 20 kg/m² and 25 kg/m²; however, they had less airway obstruction on spirometry. A population-based survey of 1971 subjects with asthma by Schachter et al (4) found that obese subjects had more symptoms and medication use than nonobese subjects but similar forced expiratory volume in 1 s (FEV₁) forced vital capacity and similar bronchial hyperresponsiveness (BHR). Most importantly, obese subjects were 3.3 times more likely to have wheeze without BHR. Studies of weight loss have also shown an improvement in symptoms and spirometric volumes without convincing evidence of improvement in airway obstruction or BHR (5,6).

The most obvious interpretation of these results is that obese subjects have more asthma-like symptoms (not worse asthma) due to any number of factors, such as mechanics, deconditioning, gastroesophageal reflux disease and sleep disorders. These factors will not improve with usual asthma therapy such that patients appear refractory. In extreme cases, they may be inappropriately treated with oral corticosteroids, causing more weight gain.

More studies of the effects of weight on objective clinical parameters, such as induced sputum and endobronchial biopsies, are needed.

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EPIDEMIOLOGY OF OBESITY AND ASTHMA: SEX ISSUES

Yue Chen MD PhD

Both obesity and asthma are common in Canada. Sex is an important determinant for asthma, and asthma occurrence associated with sex varies considerably over a lifespan (1), suggesting that there are different determinants for asthma in different sex and age subpopulations. In Canada, asthma was found to be positively associated with increasing body mass index in women both cross-sectionally (2) and longitudinally (3). The association was less marked in men. The increased risk of asthma associated with obesity was stronger in women than in men, even when body weight and height were objectively measured (4). The association between obesity and asthma was robust to the anthropometric measures, and using waist circumference as an indicator of abdominal obesity showed a similar result (4). Obesity is likely to have a larger effect on nonallergic asthma. The greater prevalence of nonallergic asthma in women may explain the stronger obesity-asthma association seen in women compared with men and children, who have a greater prevalence of allergic asthma (5,6).

Asthmatic patients are not consistently inactive compared with nonasthmatics. Leisure-time physical activity cannot, therefore, explain the positive association between obesity and asthma (7).

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ASTHMA AND OBESITY: A SPECIFIC PHENOTYPE?
Louis-Philippe Boulet MD FRCPc

The prevalence of both obesity and asthma has increased in the past 20 years (1). Not only can obesity increase the severity of asthma, but it may also contribute to its development through various mechanisms involving common genotypes, mechanical influences, and modulation or increase of immune responses (2). Obesity is associated with significant changes in lung physiology, such as a reduction in expiratory reserve volume (breathing closer to the closing volume of the airways) and total respiratory system compliance, increased work of breathing and reduced effort tolerance (3). Changes in lung volumes and variations in tidal volume (eg, after exercise) may result in a change in obese patients’ airway smooth muscle plasticity, which may explain the lack of bronchoprotective response to deep inspiration manoeuvres in these patients, a feature that may increase their risk of airway hyper-responsiveness or its clinical expression (4). Otherwise, human adipose tissue expresses and releases proinflammatory cytokines. Various markers of chronic inflammation are increased in obese subjects, such as C-reactive protein (5). Visceral adiposity is associated with the increased production of cytokines and chemokines, such as leptin, interleukin-6, tumour necrosis factor-alpha, transforming growth factor-1 and eotaxin. Increased leptin and reduced adipokines may also influence airway inflammatory features, although direct measures of airway inflammation remain to be obtained in obese asthmatic patients (6). Comorbidities favoured by obesity, such as sleep apnea syndrome, gastroesophageal reflux or cardiac problems, may influence respiratory symptoms and assessment of asthma control. Weight loss in obese subjects is associated with a
OBESITY AND ASTHMA: IS SLEEP APNEA THE LINK?  
R John Kimoff MD FRCP


OBESITY, OBSTRUCTIVE SLEEP APNEA AND ASTHMA  
Mihaela Teodorescu MD

Obesity represents an important risk factor for both incident and poorly controlled asthma. Sleep-disordered breathing has been proposed as one possible causative intermediary (1,2). The spectrum of obstructive sleep-disordered breathing comprises a continuum of common conditions, for which obstructive sleep apnea (OSA) is a prototype that alone affects 9% to 24% of middle-aged adults (3). Recently, a high prevalence of OSA symptoms was reported in a clinic-based asthma population presenting for routine visits (4). A large proportion of these patients (44%) met criteria for OSA (4) on a well-validated OSA risk-assessment instrument (5). Polysomnography has demonstrated an unexpectedly high prevalence (95.5%) of OSA among patients with difficult-to-control asthma (6). Excess weight is a powerful risk factor for the development of OSA in general (7), and in asthmatics as well. However, asthma itself (8), common comorbid conditions (such as gastroesophageal

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disease and nasal congestion) and medications used to treat asthma (systemic [6] and inhaled corticosteroids) are all associated with OSA symptoms (Teodorescu et al, unpublished data). Conversely, continuous positive airway pressure for OSA improves asthma symptoms, peak flow rates and disease-specific quality of life (9-11). Furthermore, OSA is an important risk factor for frequent exacerbations in difficult-to-control asthma (12). These observations suggest a high prevalence of OSA among asthmatics and improved asthma outcomes when comorbid OSA is treated. Taken together, these data support an important role for OSA in the relationship between obesity and asthma. Longitudinal and interventional study designs are now warranted to elucidate the precise roles of excess weight and other factors promoting OSA in asthmatics, and the mechanisms through which OSA may exacerbate asthma.

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ASTHMA CONTROL AND OBESITY: A BEHAVIOURAL PERSPECTIVE
Kim I Lavoie PhD, Simon I Bacon PhD

Despite important advances in diagnosis and treatment, the prevalence of asthma has increased in recent years in both Canada and the United States. Between 1980 and 1994, the number of people with asthma increased by over 100% (1). In 2001, Canadian statistics showed that only 43% of asthmatic patients were well controlled according to Canadian consensus guidelines (2). This indicates that more than one-half of all asthmatic patients in Canada have poorly controlled or uncontrolled asthma and are experiencing symptoms at a level that interferes with daily activities and reduces overall quality of life.

In the past three decades, the prevalence of obesity has also risen in both the United States and Canada. Recent (1998) statistics estimate the rate of obesity, defined as having a body mass index (BMI) of 30 kg/m2 or greater, at over 30% in the United States (3) and 15% in Canada (4). The health consequences of obesity are varied and well established. Obesity has been shown to either increase risk for or exacerbate many serious illnesses, including hypertension, diabetes, hypercholesterolemia, sleep apnea, restrictive lung disease and coronary artery disease (5-7).

The concurrent rise in asthma morbidity and obesity rates has prompted researchers to investigate associations between the two disorders. Cross-sectional studies have found evidence of an association between asthma and obesity in both children (8,9) and adults (10,11). This association points to a shared underlying mechanism linking these two disorders, which has been speculated to be physiological (12,13). However, it is equally plausible that the shared underlying mechanism may be behavioural because both uncontrolled asthma and obesity are associated with poor self-management skills. The epidemic rise in obesity over the past three decades is disproportionately due to poor dietary choices, overconsumption of high-calorie foods and physical inactivity, all of which are behavioural factors. Poor asthma control has also been related to important behavioural factors, such as treatment nonadherence and failure to implement action plans (14-16). As such, one would expect to observe a stronger link between obesity and measures of asthma control (a modifiable behavioural factor) than between obesity and measures of asthma severity (a nonmodifiable physiological factor). A study by Lavoie et al (17) demonstrated a significant association between increasing BMI and asthma control levels, but not asthma severity, in a sample of 382 adult asthmatics. It is also noteworthy that the findings linking increasing BMI to worse asthma control were found while controlling for age, sex and asthma severity, which further strengthens the significance of these results.

These findings suggest important avenues for asthma management and control initiatives that focus on modifying behavioural risk factors for chronic disease. Behavioural interventions could be designed to target improvements in both asthma control behaviours (eg, adherence to inhaled corticosteroids) and weight-related behaviours (eg, diet and exercise). Given that there is currently no information in the Canadian consensus guidelines for asthma regarding behavioural interventions, it may be time to focus greater efforts on this initiative.

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Some have speculated that obese asthmatics have symptoms related to deconditioning and mechanical factors. A study by Sin et al (1) found that obesity was associated with dyspnea but not with airflow limitation. However, Dixon et al (2) found that obese and nonobese clinical trial participants with physician-diagnosed asthma had similar airflow limitation and a similar prevalence of comorbidities (eg, rhinitis) associated with asthma; physician-diagnosed asthmatic patients had a similar clinical syndrome irrespective of obesity.

Although the obese and nonobese patients had similar disease characteristics, they responded differently to therapy: obese individuals had worsening of their asthma when given theophylline (2). Peters-Golden et al (3) reported that obese and nonobese individuals respond differently to medication, but it is speculated that it may be related to the fact that adipokines are important mediators of asthma in the obese patient. Future studies are needed to investigate the effect of medications that alter adipokine-mediated inflammation in the treatment of asthma in the obese patient.

have a similar clinical syndrome, they have altered responses to medications. This may be related to the fact that adipokines are important mediators of asthma in the obese patient. Future studies are needed to investigate the effect of medications that alter adipokine-mediated inflammation in the treatment of asthma in the obese patient.

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CONCLUSIONS
Although an increasing amount of data have been gathered on the relationship between asthma and obesity, and the mechanisms by which the interaction may occur, much remains to be done clearly establish how those two conditions may influence each other (Figure 1). Mechanical and other influences linked to obesity can induce symptoms mimicking asthma or influencing the clinical expression of this disease. Much needs to be learned regarding the influence of obesity on the development of asthma and evaluation of the influence of current asthma medications in the obese.

It is also essential to establish studies that examine the link between sleep apnea (an obesity-related disease) and asthma. A follow-up symposium in the fall of 2007 is being planned to discuss the relation between sleep apnea, asthma and inflammation.
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