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 (Quebec 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*

Symposium sur l'obésité et l'asthme – le 2 novembre 2006

L'asthme et l'obésité sont fréquemment associés et l'obésité est considérée comme un facteur impliqué tant dans l'augmentation de la sévérité que dans le développement de l'asthme. Ce document est un compte-rendu des présentations effectuées dans le cadre d'un symposium du Réseau en santé respiratoire du Fonds de la recherche en santé du Québec qui a eu lieu à Montréal le 2 novembre 2006, en collaboration avec le *McGill University – Strauss Severe Asthma Program*, l'Université Laval (Québec) et l'Université de Montréal. Au cours de cette rencontre, divers aspects de la relation entre obésité et asthme ont été abordés, en regard des modèles animaux, des influences génétiques, hormonales et physiologiques, de l'influence des comorbidités (ex : syndrome d'apnée du sommeil), de l'épidémiologie, des aspects cliniques et psychologiques et, enfin, du traitement de l'asthme chez la personne obèse.

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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: PROCEEDINGS OF A SYMPOSIUM

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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; epidemiology, clinical and psychological features; and, finally, management of asthma in the obese.

REFERENCES

1. Weiss ST. Obesity: Insight into the origins of asthma. Nat Immunol 2005;6:537-9.
2. Schaub B, von Mutius E. Obesity and asthma, what are the links? Curr Opin Allergy Clin Immunol 2005;5:185-93.
3. Tantisira KG, Weiss ST. Complex interactions in complex traits: Obesity and asthma. Thorax 2001;56(Suppl 2):ii64-73.

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 *Cpe^{fat}* mice, as well as mice with diet-induced obesity, each 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.

REFERENCES

1. Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol 2005;115:897-909.
2. Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther 2006;110:83-102.
3. Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. J Appl Physiol 2003;95:938-45.
4. Lu FL, Johnston RA, Flynt L, et al. Increased pulmonary responses to acute ozone exposure in obese *db/db* mice. Am J Physiol Lung Cell Mol Physiol 2006;290:L856-65.
5. Johnston RA, Theman TA, Shore SA. Augmented responses to ozone in obese carboxypeptidase E-deficient mice. Am J Physiol Regul Integr Comp Physiol 2006;290:R126-33.
6. Shore SA. Obesity and asthma: Lessons from animal models. J Appl Physiol 2007;102:516-28.
7. Shore SA, Terry RD, Flynt L, Xu A, Hug C. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. J Allergy Clin Immunol 2006;118:389-95.

BODY MASS INDEX, ADIPOKINES AND AIRWAY OXIDATIVE STRESS

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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 asthmatics 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 –0.1], 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.

REFERENCES

1. Barros R, Moreira A, Fonseca J, et al. Obesity and airway inflammation in asthma. J Allergy Clin Immunol 2006;117:1501-2.

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/m^2 (2,3). Total lung capacity is compromised only in the morbidly obese (ie, body mass index of 50 kg/m^2 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.

REFERENCES

1. Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. Can Respir J 2006;13:203-10.
2. Ray CS, Sue DY, Bray G, Hansen JE, Wasserman K. Effects of obesity on respiratory function. Am Rev Respir Dis 1983;128:501-6.
3. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. Chest 2006;130:827-33.
4. Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. Effects of mass loading the respiratory system in man. J Appl Physiol 1964;19:959-66.
5. Rubinstein I, Zamel N, DuBarry L, Hoffstein V. Airflow limitation in morbidly obese, nonsmoking men. Ann Intern Med 1990;112:828-32. (Erratum in 1990;113:334).
6. Yap JC, Watson RA, Gilbey S, Pride NB. Effects of posture on respiratory mechanics in obesity. J Appl Physiol 1995;79:1199-205.
7. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). Thorax 2003;58:1036-41.
8. Wang YL, Cerny FJ, Kufel TJ, Grant BJ. Simulated obesity-related changes in lung volume increases airway responsiveness in lean, nonasthmatic subjects. Chest 2006;130:834-40.
9. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M. Immediate and long term effect of weight reduction in obese people with asthma: Randomized controlled study. BMJ 2000;320:827-32. (Erratum in 2000;320:984).
10. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effect of weight loss on peak flow variability, airways obstruction and lung volumes in obese patients with asthma. Chest 2000;118:1315-21.

GENETICS OF ASTHMA AND OBESITY

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Asthma and obesity are two complex traits that afflict 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 *CX3CR1*) (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 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.

REFERENCES

1. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. Am J Respir Crit Care Med 2006;174:112-9.
2. Blumenthal MN. The role of genetics in the development of asthma and atopy. Curr Opin Allergy Clin Immunol 2005;5:141-5.
3. Hoffjan S, Nicolae D, Ober C. Association studies for asthma and atopic diseases: A comprehensive review of the literature. Respir Res 2003;4:14.
4. Ober C, Hoffjan S. Asthma genetics 2006: The long and winding road to gene discovery. Genes Immun 2006;7:95-100.
5. Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: The 2005 update. Obesity (Silver Spring) 2006;14:529-644.
6. Laprise C, Sladek R, Ponton A, Bernier MC, Hudson TJ, Laviolette M. Functional classes of bronchial mucosa genes that are differentially expressed in asthma. BMC Genomics, 20045:21.
7. Vohl MC, Sladek R, Robitaille J, et al. A survey of genes differentially expressed in subcutaneous and visceral adipose tissue in men. Obes Res 2004;12:1217-22.
8. Bouchard L, Tchernof A, Deshaies Y, et al. ZFP36: A promising candidate gene for obesity-related metabolic complications identified by converging genomics. Obes Surg 2007;17:372-82.

PHYSIOPATHOLOGY OF ASTHMA IN THE OBESE

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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.

REFERENCES

1. Guerra S, Sherrill DL, Bobadilla A, Martinez FD, Barbee RA. The relation of body mass index to asthma, chronic bronchitis, and emphysema. Chest 2002;122:1256-63.
2. Chinn S, Jarvis D, Burney P. Relation of bronchial responsiveness to body mass index in the ECRHS. European Community Respiratory Health Survey. Thorax 2002;57:1028-33.
3. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med 2006;100:648-57.
4. Cassol V, Rizzato TM, Teche SP, et al. Obesity and its relationship with asthma prevalence and severity in adolescents from southern Brazil. J Asthma 2006;43:57-60.
5. Akerman MJ, Calacanis CM, Madsen MK. Relationship between asthma severity and obesity. J Asthma 2004;41:521-6.
6. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). Thorax 2003;58:1036-41.
7. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006;27:495-503.
8. Vasudevan AR, Wu H, Xydakis AM, et al. Eotaxin and obesity. J Clin Endocrinol Metab 2006;91:256-61.
9. Maachi M, Pieroni L, Bruckert E, et al. Systemic low-grade inflammation is related to both circulating and adipose tissue TNFalpha, leptin and IL-6 levels in obese women. Int J Obes Relat Metab Disord 2004;28:993-7.
10. van Dielen FM, van't Veer C, Schols AM, Soeters PB, Buurman WA, Greve JW. Increased leptin concentrations correlate with increased concentrations of inflammatory markers in morbidly obese individuals. Int J Obes Relat Metab Disord 2001;25:1759-66.
11. Boullu-Ciocca S, Paulmyer-Lacroix O, Fina F, et al. Expression of the mRNAs coding for the glucocorticoid receptor isoforms in obesity. Obes Res 2003;11:925-9.
12. Bergeron C, Fukakusa M, Olivenstein R, et al. Increased glucocorticoid receptor-beta expression, but not decreased histone deacetylase 2, in severe asthma. J Allergy Clin Immunol 2006;117:703-5.
13. Christodoulopoulos P, Leung DY, Elliott MW, et al. Increased number of glucocorticoid receptor-beta-expressing cells in the airways in fatal asthma. J Allergy Clin Immunol 2000;106:479-84.

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/m^2 or greater reported more symptoms and bronchodilator use than subjects with a body mass index between 20 kg/m^2 and 25 kg/m^2; 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/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.

REFERENCES

1. Belamarich PF, Luder E, Kattan M, et al. Do obese inner-city children with asthma have more symptoms than nonobese children with asthma? Pediatrics 2000;106:1436-41.
2. Saint-Pierre P, Bourdin A, Chanez P, Daures JP, Godard P. Are overweight asthmatics more difficult to control? Allergy 2006;61:79-84.
3. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med 2002;162:1477-81.
4. Schachter LM, Salome CM, Peat JK, Woolcock AJ. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. Thorax 2001;56:4-8.
5. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. Chest 2000;118:1315-21.
6. Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. Chest 2004;125:2046-52.

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).

REFERENCES

1. Chen Y, Stewart P, Johansen H, McRae L, Taylor G. Sex difference in hospitalization due to asthma in relation to age. J Clin Epidemiol 2003;56:180-7.
2. Chen Y, Dales R, Krewski D, Breithaupt K. Increased effects of smoking and obesity on asthma among female Canadians: The National Population Health Survey, 1994-1995. Am J Epidemiol 1999;150:255-62.
3. Chen Y, Dales R, Tang M, Krewski D. Obesity may increase the incidence of asthma in women but not in men: Longitudinal observations from the Canadian National Population Health Surveys. Am J Epidemiol 2002;155:191-7.
4. Chen Y, Rennie D, Cormier Y, Dosman J. Sex specificity of asthma associated with objectively measured body mass index and waist circumference: The Humboldt study. Chest 2005;128:3048-54.
5. Chen Y, Dales R, Jiang Y. The association between obesity and asthma is stronger in nonallergic than allergic adults. Chest 2006;130:890-5.
6. Chen Y. Obesity and asthma in children. J Pediatr 2004;144:146-7.
7. Chen Y, Dales R, Krewski D. Leisure-time energy expenditure in asthmatics and non-asthmatics. Respir Med 2001;95:13-8.

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

reduction in asthma symptoms, a reduction in medication needs and improved control (7,8). However, current asthma therapy seems less effective in obese patients (9). Indeed, overweight subjects are less likely to achieve acceptable asthma control and seem to present a reduced response to agents, such as inhaled corticosteroids (9). This reduced response to asthma therapy may be due to the absence of asthma, with symptoms being related to an asthma-like condition due to obesity; a different asthma pathophysiology, with a less responsive inflammatory process; the presence of comorbidities; or other factors. Research is needed to better define the asthma phenotype in obese subjects and its optimal treatment.

REFERENCES

1. Weiss ST. Obesity: Insight into the origins of asthma. Nat Immunol 2005;6:537-9.
2. Tantisira KG, Weiss ST. Complex interactions in complex traits: Obesity and asthma. Thorax 2001;56(Suppl 2):ii64-73.
3. Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. Can Respir J 2006;13:203-10.
4. Boulet LP, Turcotte H, Boulet G, Simard B, Robichaud P. Deep inspiration avoidance and airway response to methacholine: Influence of body mass index. Can Respir J 2005;12:371-6.
5. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. Am J Respir Crit Care Med 2006;174:112-9.
6. Mai XM, Bottcher MF, Leijon I. Leptin and asthma in overweight children at 12 years of age. Pediatr Allergy Immunol 2004;15:523-30.
7. Simard B, Turcotte H, Marceau P, et al. Asthma and sleep apnea in patients with morbid obesity: Outcome after bariatric surgery. Obes Surg 2004;14:1381-8.
8. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. Chest 2000;118:1315-21.
9. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006;27:495-503.

OBESITY AND ASTHMA: IS SLEEP APNEA THE LINK?

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Obstructive sleep apnea-hypopnea (OSAH) is characterized by recurrent episodes of upper airway obstruction during sleep leading to hypoxemia and sleep fragmentation. There is emerging evidence linking OSAH and asthma. Several studies (1,2) have pointed to an increased prevalence of snoring and OSAH among asthmatics. A recent McGill University study (3) identified OSAH among 88% of 26 severe asthmatics and 71% of 21 moderate asthmatics. There are also data suggesting that OSAH contributes to asthma exacerbations in difficult asthmatics (4) and that continuous positive airway pressure treatment of OSAH may improve asthma control (5,6). There is a diversity of mechanisms by which OSAH and asthma may interact, and obesity may be a common factor in several of them. OSAH has a well-established relationship to obesity; population prevalence of OSAH increases with increasing body mass index, and OSAH severity decreases with weight loss (7). Acid-pepsin reflux, which is linked to obesity, occurs frequently in OSAH patients (8,9) and may be an exacerbating factor in asthma. Oral corticosteroid use in asthma may contribute to obesity and, thereby, reduce upper airway calibre, and may adversely affect upper airway dilator muscle function (10). Upper airway inflammation has been demonstrated in OSAH, which may contribute to reduced upper airway calibre and neuromuscular dysfunction (9,11,12). Inflammation may result from mechanical trauma during apneas and hypoxia-reoxygenation-related oxidative stress, but obesity may also be a contributing factor to both local (13) and systemic inflammation in OSAH. The latter could secondarily promote activation of inflammatory pathways in the lower respiratory tract, thereby destabilizing asthma control. While important links appear to exist among asthma, obesity and OSAH, further research is required to elucidate the precise pathways involved in these interactions.

REFERENCES

1. Larsson LG, Lindberg A, Franklin KA, Lundback B. Symptoms related to obstructive sleep apnoea are common in subjects with asthma, chronic bronchitis and rhinitis in a general population. Respir Med 2001;95:423-9.
2. Yigla M, Tov N, Solomonov A, Rubin AH, Harlev D. Difficult-to-control asthma and obstructive sleep apnea. J Asthma 2003;40:865-71.
3. Shannon J, Pepe C, Ernst P, Martin J, Olivenstein R, Kimoff RJ. High prevalence of obstructive sleep apnea in severe and moderate asthma. Am J Respir Crit Care Med 2004;169:A452. (Abst)
4. ten Brinke A, Sterk PJ, Masclee AA, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26:812-8.
5. Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: Role of snoring and obstructive sleep apnea. Am Rev Respir Dis 1988;137:1502-4.
6. Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktas H. Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. Respir Med 2005;99:529-34.
7. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. J Appl Physiol 2005;99:1592-9.
8. Valipour A, Makker HK, Hardy R, Emegbo S, Toma T, Spiro SG. Symptomatic gastroesophageal reflux in subjects with a breathing sleep disorder. Chest 2002;121:1748-53.
9. Payne RJ, Kost KM, Frenkiel S, et al. Laryngeal inflammation assessed using the reflux finding score in obstructive sleep apnea. Otolaryngol Head Neck Surg 2006;134:836-42.
10. Petrof BJ, Hendricks JC. Muscle factors in obstructive sleep apnea. In: Pack AI, ed. Sleep Apnea: Pathogenesis, Diagnosis, and Treatment. New York: Marcel Dekker Inc, 2002:217-34.
11. Boyd JH, Petrof BJ, Hamid Q, Fraser R, Kimoff RJ. Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. Am J Respir Crit Care Med 2004;170:541-6.
12. Bergeron C, Kimoff J, Hamid Q. Obstructive sleep apnea syndrome and inflammation. J Allergy Clin Immunol 2005;116:1393-6.
13. Series F, Chakir J, Boivin D. Influence of weight and sleep apnea status on immunologic and structural features of the uvula. Am J Respir Crit Care Med 2004;170:1114-9.

OBESITY, OBSTRUCTIVE SLEEP APNEA AND ASTHMA

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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

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.

REFERENCES

1. Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther 2006;110:83-102.
2. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. Am J Respir Crit Care Med 2006;174:112-9.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
4. Teodorescu M, Consens FB, Bria WF, et al. Correlates of daytime sleepiness in patients with asthma. Sleep Med 2006;7:607-13.
5. Douglass AB, Bornstein R, Nino-Murcia G, et al. The Sleep Disorders Questionnaire. I: Creation and multivariate structure of SDQ. Sleep 1994;17:160-7.
6. Yigla M, Tov N, Solomonov A, Rubin AH, Harlev D. Difficult-to-control asthma and obstructive sleep apnea. J Asthma 2003;40:865-71.
7. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
8. Teodorescu M, Consens FB, Bria WF, et al. Screening for symptoms of sleep-disordered breathing (SDB) among asthmatics. Sleep 2005;28S:A164. (Abst)
9. Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: Role of snoring and obstructive sleep apnea. Am Rev Respir Dis 1988;137:1502-4.
10. Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktas H. Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. Respir Med 2005;99:529-34.
11. Teodorescu M, Consens FB, Bria WF, et al. Treatment for obstructive sleep apnea in patients with persistent asthma improves quality of life: A randomized-controlled study. Sleep 2006;29S:A160. (Abst)
12. ten Brinke A, Sterk PJ, Masclee AA, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. Eur Respir J 2005;26:812-8.

ASTHMA CONTROL AND OBESITY: A BEHAVIOURAL PERSPECTIVE

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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/m^2 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.

REFERENCES

1. Statistics Canada. Persons with asthma, by age and sex. <http://www40.statcan.ca/l01/cst01/health49b.htm> (Version current at May 3, 2007).
2. Chapman KR, Ernst P, Grenville A, Dewland P, Zimmerman S. Control of asthma in Canada: Failure to achieve guideline targets. Can Respir J 2001;8(Suppl A):35A-40A.
3. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: Prevalence and trends, 1960-1994. Int J Obes Relat Metab Disord 1998;22:39-47.
4. Katzmarzyk PT. The Canadian obesity epidemic, 1985-1998. CMAJ 2002;166:1039-40.
5. Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: A statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: Endorsed by the American College of Cardiology Foundation. Circulation 2004;110:2952-67.
6. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: Impact of cardiorespiratory fitness. Diabetes Care 2005;28:391-7.

7. Ardern CI, Katzmarzyk PT, Janssen I, Ross R. Discrimination of health risk by combined body mass index and waist circumference. Obes Res 2003;11:135-42. (Erratum in 2003;11:491).
8. Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. Arch Pediatr Adolesc Med 1998;152:1197-200.
9. Figuerosa-Munoz JI, Chinn S, Rona RJ. Association between obesity and asthma in 4-11 year old children in the UK. Thorax 2001;56:133-7.
10. Luder E, Ehrlich RI, Lou WY, Melnik TA, Kattan M. Body mass index and the risk of asthma in adults. Respir Med 2004;98:29-37.
11. Kim S, Camargo CA Jr. Sex-race differences in the relationship between obesity and asthma: The behavioral risk factor surveillance system, 2000. Ann Epidemiol 2003;13:666-73.
12. Thomson CC, Clark S, Carmago CA Jr. Body mass index and asthma severity among adults presenting to the emergency department. Chest 2003;124:795-802.
13. Akerman MJ, Calacanis CM, Madsen MK. Relationship between asthma severity and obesity. J Asthma 2004;41:521-6.
14. Cluley S, Cochrane GM. Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids. Respir Med 2001;95:37-9.
15. Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. Eur Respir J 1995;8:899-904.
16. Schmaling KB, Hernandez DV, Giardino ND. Provider and patient adherence with asthma evaluation and treatment. In: Brown ES, ed. Asthma: Social and Psychological Factors and Psychosomatic Syndromes. Advances in Psychosomatic Medicine. Switzerland: Karger, 2003:98-114.
17. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med 2006;100:648-57.

TREATMENT OF ASTHMA IN THE OBESE PATIENT

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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 subjects respond less well to inhaled corticosteroids. It is not known why obese and nonobese individuals respond differently to medication, but it is speculated that it may be related to the pathophysiology of asthma in obese individuals. Studies by Shore et al (4,5) suggest that adipokines released by adipose tissue may affect airway inflammation. Conventional asthma therapies may not be effective against adipose-related inflammation. Preliminary data suggest that theophylline alters cytokine release from adipose tissue explants; if theophylline alters adipose inflammatory pathways important in obesity-associated asthma, unanticipated effects of this medication in obese asthmatics may be seen. The data suggest that although obese and nonobese people with physician-diagnosed asthma 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.

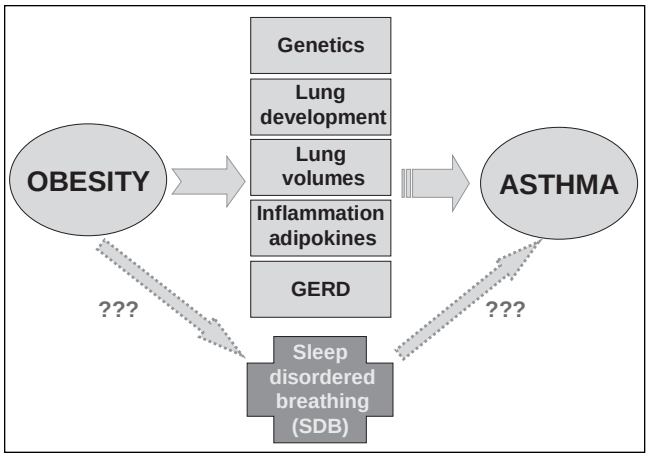

Figure 1) *Potential mechanisms involved in the relationship between obesity and asthma. GERD Gastroesophageal reflux disease*

REFERENCES

1. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med 2002;162:1477-81.
2. Dixon AE, Shade DM, Cohen RI, et al. Effect of obesity on clinical presentation and response to treatment in asthma. J Asthma 2006;43:553-8.
3. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006;27:495-503.
4. Shore SA, Schwartzman IN, Mellema MS, Flynt L, Imrich A, Johnston RA. Effect of leptin on allergic airway responses in mice. J Allergy Clin Immunol 2005;115:103-9.
5. Shore SA, Terry RD, Flynt L, Xu A, Hug C. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. J Allergy Clin Immunol 2006;118:389-95.
6. Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther 2006;110:83-102.

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 to 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.