

Obesity in asthma: Location or hormonal consequences?

Emilio Arteaga-Solis, MD, PhD, and Meyer Kattan, MD New York, NY

Key words: Asthma, obesity, obesity measures, adipokines

Obesity has reached epidemic proportions worldwide. In US children and adolescents aged 2 to 19 years, the prevalence of obesity, as defined by a body mass index (BMI) of the 95th percentile or greater of the BMI-for-age/sex standard US Centers for Disease Control and Prevention charts, increased to 16.9% in 2010.¹ Obesity has been linked to the development of cardiometabolic diseases (ie, atherosclerosis, dyslipidemia, hypertension, and type 2 diabetes). In addition, numerous studies in adults and children have demonstrated a strong positive relationship between obesity and asthma.² Prospective studies have shown that obesity predates asthma and that the relative risk of asthma increases with increasing BMI.² These studies demonstrated causality and dissociate the notion that the more sedentary lifestyle of asthmatic patients caused by their increased respiratory symptoms with exercise led to obesity. Obese asthmatic patients are reported to have a 5-fold higher risk of hospitalization compared with nonobese asthmatic patients, and obesity leads to 250,000 new cases of asthma per year in the United States.² Another consequence of obesity is that obese asthmatic patients are less responsive to inhaled corticosteroids.³

BMI has been commonly used as an indicator of adiposity in asthma studies because it is relatively easy and inexpensive to obtain. However, BMI does not differentiate between lean mass and fat mass. Girls have greater body fat than boys at the same level of BMI. In adults BMI correlates better with lean mass in male subjects, whereas in female subjects it correlates better with fat mass.⁴ Furthermore, Daniels et al⁵ found that the relationship between BMI and body fat was dependent on maturation stage, race, sex, and waist/hip ratio in adolescents. In part, these limitations with BMI might explain the observation in large epidemiologic studies of the effect of obesity on asthma in female but not male subjects. Therefore more direct measurements of body fat might provide greater insight into the relationship between obesity and asthma.

In this issue of the *Journal*, Forno et al⁶ examine the relationships among atopy, asthma, and measures of adiposity in children in Puerto Rico. Whereas BMI was significantly associated with asthma, as has been consistently demonstrated in previous studies, the association between percentage of

body fat (PBF), waist circumference (WC), and waist/hip ratio and asthma were not significant. PBF and BMI, but not WC, were associated with urgent care visits. BMI, PBF, and WC had a significantly positive correlation with forced vital capacity (FVC), but only BMI had a significantly positive correlation with FEV₁.

Of all the asthma-related measures of control, only exercise-induced symptoms in the prior year were associated with the other measures of adiposity, although not with BMI. Conclusions from cross-sectional studies of asthma severity and control are limited because of the variable nature of asthma symptoms over time and recall bias. Consistent with other studies in children, airway obstruction is unlikely to account for these symptoms because FEV₁ is greater in obese compared with nonobese children. The reduced FEV₁/FVC ratio reflects a higher FVC in obese children. Increased bronchial reactivity with exercise might explain the increased exercise symptoms, but evidence for increased reactivity in obese asthmatic patients is inconsistent. The question as to whether the reported exercise symptoms in obese subjects are related to asthma or are a reflection of the perception of symptoms or poor fitness remains unanswered.

WC was the only measure that correlated with increased total IgE levels and allergic rhinitis, whereas BMI, PBF, and WC were associated with various skin test reactivity, with the exception of dust mite. The finding that atopy can mediate the effect of adiposity is of interest and requires further study.

Several mechanisms have been proposed to explain the relationship between asthma and obesity. These include direct mechanical effects on the airways, inflammation associated with airway narrowing, increased airway reactivity to environmental allergens, and, more recently, disruption of the autonomic nervous system mediated by leptin.^{7,8} In adults emerging data indicate that abdominal obesity independent of BMI is a risk factor for asthma.^{9,10} In addition, the reduction in functional residual capacity associated with obesity, which is postulated to promote asthma because of the resulting reduction in airway size and increase in airway hyperresponsiveness,¹¹ is inversely related to abdominal obesity.¹² These findings are consistent with central obesity being an established risk factor for cardiometabolic diseases.¹³ In fact, in 2005, an expert panel organized by the National Heart, Lung, and Blood Institute recommended the use of WC for the initial assessment and efficacy of weight loss.¹⁴ Another expert panel also recommended WC as an assessment of obesity.¹³ However, the study by Forno et al⁶ did not find an association between WC and asthma status in children.

The study by Forno et al⁶ does not provide strong evidence that adding adiposity measures other than BMI would broaden our understanding of the asthma-obesity link. However, the data need to be interpreted with caution. This was a cross-sectional study of prepubertal and postpubertal children between the ages of 6 and 14 years. The major changes in the natural history of asthma and in adipose tissue-derived and sex hormones taking

From the Pediatric Pulmonary Division, Columbia University Medical Center.

Disclosure of potential conflict of interest: M. Kattan has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases.

E. Arteaga-Solis declares that he has no relevant conflicts of interest.

Received for publication January 16, 2014; accepted for publication January 29, 2014.

Available online March 15, 2014.

Corresponding author: Meyer Kattan, MD, Pediatric Pulmonary Division, Columbia University Medical Center, 3959 Broadway, CHC 7-752, New York, NY 10032.

E-mail: mk2833@columbia.edu.

J Allergy Clin Immunol 2014;133:1315-6.

0091-6749/\$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2014.01.036>

place during this age range confound conclusions that can be drawn regarding the asthma-obesity association.

The prevalence of asthma decreases in postpubertal boys but not girls, with most studies indicating that the association between asthma and obesity is stronger in female than in male subjects. There is evidence that estrogen increases bronchial reactivity. In addition to changes in sex hormones in this age group, there are changes in adipokines (ie, adiponectin and leptin). Adiponectin levels decrease in postpubertal female subjects, and leptin levels increase. Clinical studies have demonstrated that adiponectin is associated with decreased asthma symptoms, but the mechanism is not clearly understood.¹⁵ Leptin, a molecule that was thought to have a proinflammatory role in asthmatic patients, was recently demonstrated to inhibit parasympathetic signaling, resulting in bronchodilation in animal models.⁷ By using various genetic and diet-induced obese models, the investigators demonstrated that it is the lack of leptin signaling as a result of leptin resistance associated with obesity that leads to increased parasympathetic signaling and asthma. As a result of the changes associated with puberty and their potential contribution to asthma, there is a need for a better understanding of the role of sex hormones and adipokines.

It is not unexpected that studies of adiposity measures and asthma have been inconsistent because of differences in body habitus and distribution of body fat in children, adolescents, and adults. Age and sex are important variables that need to be taken into account when conducting studies of asthma and obesity. Longitudinal studies taking into account hormones, adipokines, atopy, environment, and genetics are needed to improve our understanding of the complex link between obesity and asthma.

REFERENCES

- Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. NCHS data brief, no 82. Hyattsville (MD): National Center for Health Statistics; 2012.
- Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007; 175:661-6.
- 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.
- Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)* 2008;32:959-66.
- Daniels SR. The use of BMI in the clinical setting. *Pediatrics* 2009;124(suppl 1): S35-41.
- Forno E, Acosta-Perez E, Brehm JM, Han YY, Alvarez M, Colon-Semidey A, et al. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. *J Allergy Clin Immunol* 2014;133:1308-14.
- Arteaga-Solis E, Zee T, Emala CW, Vinson C, Wess J, Karsenty G. Inhibition of leptin regulation of parasympathetic signaling as a cause of extreme body weight-associated asthma. *Cell Metab* 2013;17:35-48.
- Dixon AE, Holguin F, Sood A, Salome CM, Pratley RE, Beuther DA, et al. An official American Thoracic Society Workshop report: obesity and asthma. *Proc Am Thorac Soc* 2010;7:325-35.
- Von Behren J, Lipsett M, Horn-Ross PL, Delfino RJ, Gilliland F, McConnell R, et al. Obesity, waist size and prevalence of current asthma in the California Teachers Study cohort. *Thorax* 2009;64:889-93.
- Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: the HUNT study. *Eur Respir J* 2013;41:323-9.
- Ding DJ, Martin JG, Macklem PT. Effects of lung volume on maximal methacholine-induced bronchoconstriction in normal humans. *J Appl Physiol* 1987;62:1324-30.
- Sutherland TJ, Goulding A, Grant AM, Cowan JO, Williamson A, Williams SM, et al. The effect of adiposity measured by dual-energy X-ray absorptiometry on lung function. *Eur Respir J* 2008;32:85-91.
- Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, et al. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Diabetes care* 2007;30:1647-52.
- Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 2005;81:555-63.
- Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ, et al. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol* 2010;125:584-92.