REVIEW

Obesity and Asthma

J Delgado,[1] P Barranco,[2] S Quirce[2]

[1] Allergy Service, University Hospital Virgen Macarena, Sevilla, Spain
[2] Allergy Service, Hospital La Paz, Madrid, Spain
[3] Asthma Committee of the Spanish Society of Allergology and Clinical Immunology (MJ Álvarez, I Antépara, V Gutiérrez, RM Muñoz, JM Olaguibel, A Parra, MJ Pascual, J Quiralte, M Rodríguez, J Sastre, JM Vega)

Abstract

Asthma and obesity have a considerable impact on public health and their prevalence has increased in recent years. Numerous studies have linked these disorders. Most prospective studies show that obesity is a risk factor for asthma and have found a positive correlation between baseline body mass index and the subsequent development of asthma. Furthermore, several studies suggest that whereas weight gain increases the risk of asthma, weight loss improves the course of the illness.
Different factors could explain this association. Obesity is capable of reducing pulmonary compliance, lung volumes, and the diameter of peripheral respiratory airways as well as affecting the volume of blood in the lungs and the ventilation-perfusion relationship. Furthermore, the increase in the normal functioning of adipose tissue in obese subjects leads to a systemic proinflammatory state, which produces a rise in the serum concentrations of several cytokines, the soluble fractions of their receptors, and chemokines. Many of these mediators are synthesized and secreted by cells from adipose tissue and receive the generic name of adipokines, including IL-6, IL-10, eotaxin, tumor necrosis factor-α, transforming growth factors-ß1, C-reactive protein, leptin, and adiponectin. Finally, specific regions of the human genome related to both asthma and obesity have been identified.
Most studies point out that obesity is capable of increasing the prevalence and incidence of asthma, although this effect appears to be modest. The treatment of obese asthmatics must include a weight control program.

Key words: Asthma. Obesity. Overweight. Adipocyte. Body mass index.

Resumen

El asma y la obesidad son dos trastornos de gran impacto en la salud pública que han aumentado su prevalencia en los últimos años. Numerosos estudios han intentado relacionar ambas entidades. La mayoría de los estudios prospectivos demuestran que la obesidad es un factor de riesgo para el diagnóstico de asma y, en general, encuentran una asociación positiva entre el índice de masa corporal basal y el posterior desarrollo de asma, lo que sugiere que el exceso de peso favorece el desarrollo de asma. Además, se ha sugerido que la pérdida de peso mejora su evolución.
Distintos factores podrían explicar esta asociación: la obesidad es capaz de reducir la *compliance* pulmonar, los volúmenes pulmonares y el diámetro de las vías respiratorias periféricas, así como alterar los volúmenes sanguíneos pulmonares y la relación ventilación-perfusión. Además, el aumento de la fisiología normal del tejido adiposo en sujetos obesos conduce a un estado proinflamatorio sistémico, con un aumento de las concentraciones séricas de numerosas citocinas y quimiocinas. Muchos de estos mediadores son sintetizados y secretados por células del tejido adiposo y reciben el nombre genérico de adipocinas (IL-6, IL-10, eotaxina, TNF-α, TGB-ß1, PCR, leptina y adiponectina).
Concluimos que la mayoría de los estudios apuntan que la obesidad es capaz de aumentar la prevalencia y la incidencia de asma, aunque este efecto parece ser moderado. El tratamiento de los asmáticos obesos debe incluir un programa de control de peso.

Palabras clave: Asma. Obesidad. Sobrepeso. Adiposito. Índice de masa corporal

Introduction

Asthma and obesity have an enormous impact on public health. It has been estimated that up to 65% of the adult population of the United States is obese or overweight [1], whilst in Spain about 15% of the population is obese and 39% is overweight, and these figures have increased progressively in recent years. Although bronchial asthma affects a smaller percentage of people, its prevalence has also increased since the 1960s. According to the Centers for Disease Control and Prevention [2], the prevalence of asthma in North American children increased from 3.6% in 1980 to 5.8% in 2003.

Both asthma and allergic diseases are associated with a western lifestyle and their prevalence has increased in developed countries. This can be seen clearly from the rapid increase in the prevalence of asthma in children who have emigrated from developing to developed countries [3] and, more recently, the rapid rise in the prevalence of allergic diseases in the former East Germany shortly after German reunification [4]. The factors in western lifestyles that have been considered responsible for this increased prevalence are greater exposure to allergens in the home and changes in contact with different microorganisms (the hygiene hypothesis).

In recent years, many studies [5] in developed countries have suggested a relationship between asthma and factors such as changes in diet and obesity. Although the exact nature of this association has not been fully elucidated, epidemiological data have led researchers to suggest that obesity precedes asthma, increases both its prevalence and severity, and may lessen the efficacy of those drugs normally used in its treatment.

Epidemiological Observations

Cross-Sectional Studies

Several cross-sectional studies have found an increase in the prevalence of asthma among obese patients [5]. These studies include a high number of patients and have provided significant epidemiological data on both disorders. However, given that the data on weight and height for the calculation of the body mass index (BMI) were self-reported, they may be inaccurate and biased and should therefore be interpreted with caution. Furthermore, in some studies [5], asthma was diagnosed and classified solely on the basis of a compatible clinical history or acceptance of a previous diagnosis. Finally, both asthma and obesity may be independently associated with other confounding factors such as sleep apnea or gastroesophageal reflux disease, which were not excluded from many of these studies. However, when the studies partially or fully overcame these shortcomings, an association was found between elevated BMI and asthma [6-8].

A further potential limitation of cross-sectional studies is the difficulty in establishing causality: patients presenting with asthma may develop obesity for a variety of reasons, including inactivity or the side effects of systemic corticosteroids. Without control of these factors in a longitudinal study, it is difficult to establish whether asthma is the cause of obesity or the result.

Prospective Studies

In recent years, numerous prospective studies [9-13] including a high number of patients (> 300 000 in those published in the last 8 years) have been carried out. These studies generally include a fairly rigorous definition of asthma and have the additional benefit of being able to establish the direction of the association.

Most prospective studies show that obesity is a risk factor for the de novo diagnosis of asthma, with the risk increasing between 1.1-fold and 3-fold [9-11]. In the prospective study with the highest number of subjects enrolled and with the longest follow-up (135 000 Norwegian men and women who were followed for 21 years) [11], the incidence of asthma increased 10% and 7% per unit increase in BMI in men and women, respectively. In general, prospective studies find a positive association between baseline BMI and the subsequent development of asthma, thus suggesting that excess weight could favor the development of asthma. However, no unanimity exists regarding results: a recent cohort study [12] including 591 adults who were monitored for 20 years found an association between asthma and obesity, but multivariate analysis revealed that asthma was a risk factor for obesity and not the other way round.

Most of these studies show that the incidence of asthma and increased BMI are frequently related. In general, the more BMI increases, the more the incidence of asthma rises, and this effect is generally stronger among women than among men. However, this difference is always very small and seems to be related to the degree of adiposity in women. One study [13] carried out in a cohort of 1000 individuals found a significant association between the percentage of body fat and asthma in women but not in men. However, bronchial inflammation, as measured by exhaled nitric oxide, was not associated with body fat in either women or men. The study concluded that adiposity was associated with asthma and airway obstruction in women and that this does not appear to be due to inflammation of the airways.

Studies in the Pediatric Population

Studies carried out in the pediatric population are much more heterogeneous both in terms of the strength of their results and in the direction of the asthma-obesity relationship. One study [14] of 9828 children aged between 6 and 14 years who were followed for 5 years showed that obesity increased the risk of suffering from asthma, a trend that was particularly pronounced in girls (those in the top quintile of adiposity had a 2.2-times greater risk of incident asthma in subsequent years). However, another study [15] carried out at practically the same time with the participation of 3792 children found that overweight and obesity increased the risk of bronchial asthma, more so in boys than in girls. A Finnish study [16], which included 4719 participants born in 1996, showed that obesity at age 14 increased the risk of suffering from asthma in adulthood (31 years of age). Those participants who were obese both at 14 and 31 years of age were twice as likely to be asthmatics in adult life as those who were not obese at either of these ages. However, some studies do not show a significant association between obesity and asthma [17].

The most recent prospective study [18] carried out in children included 4393 children with no symptoms of asthma during the first 2 years of their lives. These children were followed for 14 years and the study found that the group with elevated BMIs (above the 85th percentile) at the time of recruitment had a 2.4-times greater risk for subsequent development of asthma than those children who had low BMIs. These data indicate that obesity is a risk factor for the appearance of asthma in early infancy, which is when a large number of patients develop the disease.

Pediatric studies, however, do not show a consistent relationship between obesity and atopy. In the children participating in the *National Health and Nutrition Examination Study III* (NHANES III) [19], a significant relationship was only found between BMI and asthma, but not with atopy, defined as the presence of atopic disease and positive skin tests.

Far fewer studies have attempted to link BMI and different features of asthma: analysis of the data from the cohort study *Childhood Asthma Management Program* (CAMP) [20] shows no relationship between BMI and different indicators of the control of asthma such as absenteeism from school, visits to emergency departments, need for systemic corticosteroids, need for hospitalization, eosinophilia, and levels of immunoglobulin (Ig) E. However, a weak correlation was found with coughing and exercise-induced wheezing. In any case, the low power of these results makes generalization difficult.

Studies Including Weight Change

Results from several studies suggest that just as weight gain increases the risk of asthma, so weight loss improves its outcome. The *Nurse Health Study* [9] concluded that, for people who gained more than 25 kg from 18 years of age, the relative risk of asthma increased by 4.7 in comparison with those whose weight remained stable.

In contrast, several studies show that weight loss improves asthma, at least in adults. Weight loss resulting from surgery produced improvements in the severity of asthma, drug use, and hospitalization [21]. Similarly, weight loss achieved by dieting is capable of increasing lung function in obese asthmatic patients: a loss of 15% of body weight led to better results in peak expiratory volume tests such as forced expiratory volume in the first second of expiration (FEV_1) and forced vital capacity (FVC), lower symptom scores, and less frequent use of medication [22].

Hypotheses That Justify the Association

Obesity and Lung Physiology

Obesity can lead to a reduction in pulmonary compliance, lung volumes, and the diameter of peripheral airways, and it can affect the volume of blood in the lungs and the ventilation-perfusion relationship

Pulmonary compliance is reduced for several reasons in obese subjects, including fat compression and infiltration of the thorax or the increase in lung blood volumes. All of these factors produce a subjective increase in dyspnea [23]. Furthermore, obesity can also lead to limitations in airflow, with reduction in both FEV_1 and FVC. However, this reduction is typically symmetrical, with the FEV_1/FVC ratio remaining unchanged. Some authors have even found a restrictive model in obese subjects with an increased FEV_1/FVC ratio [24]. Such changes in lung physiology lead to superficial respiration in obese patients, with a reduction in lung volumes, especially expiratory reserve volume. This reduction in lung volumes is associated with a reduction in the diameter of peripheral airways that can lead to changes in the function of bronchial smooth muscle. This in turn leads to a change in the actin-myosin cross-bridge cycle, which can potentially increase both obstruction and bronchial hyperreactivity (BHR) [25].

Obesity and Inflammatory Mediators

The increase in the normal functioning of adipose tissue in obese subjects leads to a systemic proinflammatory state. In obese patients, serum concentrations of numerous cytokines, and soluble fractions of their receptors and chemokines have all been found to be increased [26]. Many of these mediators are synthesized and secreted by cells from adipose tissue and have been given the generic name of adipokines. This group includes IL-6, IL-10, eotaxin, tumor necrosis factor (TNF)-α, TGF-ß1, C-reactive protein, leptin, and adiponectin.

TNF-α has been shown to be present in adipocytes and is directly related to body fat. Furthermore, TNF-α is known to be elevated in asthma and is linked to the production of T_H2 cytokines (IL-4, IL-6) in bronchial epithelium, as a result of which higher TNF-α levels would lead to higher levels of these cytokines.

Serum levels of IL-6 are elevated in obese subjects and such levels have been associated with the severity of asthma [27]. Reductions in BHR have been found in obese mice treated with anti–IL-6, although not in normal-weight mice receiving the same treatment [28].

Many recently published articles dealing with the relationship between asthma and obesity have focused on the role of leptin. Leptin is a hormone that is largely produced by adipocytes, although it is also expressed in the hypothalamus, the ovaries, and the placenta, and is found to be elevated in obese patients. It is believed that leptin acts as a lypostate—when the amount of fat stored in the adipocytes increases, leptin is released into the bloodstream. This constitutes a negative feedback signal for the hypothalamus, which responds by releasing anorexigenic peptides and suppressing the production of orexigenic peptides. Energy expenditure thus increases, as does the baseline metabolic rate and body temperature. At the same time, the point of hormonal balance for the reduction of lipogenesis and increase in lipolysis in adipose tissue is modified.

Leptin seems to play a fundamental role in inflammation in obese subjects: it possesses considerable structural homology with long-chain cytokines such as IL-6, and is capable of regulating the proliferation and activation of T cells, promoting angiogenesis, and recruiting activated monocytes and macrophages [29]. Furthermore, leptin is important for the normal development of the lung, as it is a critical mediator in the differentiation between lipofibroblasts and fibroblasts,

and in the synthesis of lung surfactant [30]. In animal models, it has been shown that the exogenous administration of leptin increases lung inflammation produced by exposure to ozone [31], alters serum IgE titers, and increases BHR caused by allergens [32]. In humans, it has been suggested that leptin levels could be used to predict the development of asthma in children [33]. In a population of 5876 women, those with asthma were found to have higher levels than those who did not [34]. This study also found that the relationship between BMI and asthma did not change with serum leptin levels, thus suggesting that this protein may be considered a predictive, although independent, factor for asthma.

Unlike other adipokines, serum levels of adiponectin are reduced in obese subjects [35]. It has been shown that this hormone possesses anti-inflammatory properties, even in the airways [36], with the result that the lower levels in asthmatic subjects could play a role in the obesity-asthma relationship.

A systematic increase in eotaxin has also been found in obese individuals. Part of this chemokine is synthesized in adipocytes, and this suggests a potential role in the increased risk of asthma in obese patients [37].

Genetic Factors

It is well known that, as a result of genetic pleomorphism, genes may exert several different effects. Thus, it is biologically possible to suggest that certain genes that are linked to one particular illness may also be linked to another. Specific regions of the human genome are linked to both asthma and obesity, for example, chromosomes 5q, 6, 11q13, and 12q [38].

Chromosome 5q contains the genes *ADRB2* and *NR3C1*. The *ADRB2* gene, which codes for the $ß_2$-adrenergic receptor exerts an influence on the sympathetic nervous system and is important for the control of tone in the airways and also for baseline metabolism. It has been postulated that the glucocorticoid receptor gene *NR3C1* has been involved in the inflammatory responses associated with obesity and asthma [38]

Chromosome 6 contains the genes of the main histocompatability complex and of TNF-α, which affect immune and anti-inflammatory responses in both asthma and obesity (see above). Chromosome 11q13 contains the genes for the uncoupling proteins UCP2-UCP3 and for the receptor of low-affinity IgE. The UCP2-UCP3 proteins influence baseline metabolism but not asthma. In contrast, the receptor of low-affinity IgE forms part of the inflammatory response of T_H2 cells, whose levels increase in asthma, but not in obesity. Chromosome 12q contains the genes for inflammatory cytokines linked both with asthma (IFN-γ, LTA4H, nitric oxide synthase-1) and with obesity (STAT6, type 1 insulinoid growth factor, CD36L1).

In addition, the $ß_3$-adrenergic receptor, located primarily in adipose tissue, is involved in the regulation of lipolysis and thermogenesis, and morbidly obese patients with a genetic mutation in the gene for the $ß_3$-adrenergic receptor have an increased capacity to gain weight [39]. Polymorphisms in the $ß_2$-adrenergic receptor, which is located in chromosome 5q31-q32, have been associated with different asthma phenotypes, different levels of severity, and a response to ß-agonists [40]. The change of Gln27 for Glu in this receptor has also been associated with obesity [41]

Hormonal Factors

Ever since the first longitudinal studies were carried out, there has been evidence of a greater effect of obesity on asthma in women than in men [9]. We know that the enzyme aromatase, which is responsible for converting androgens into estrogens, is present in adipose tissue. In obesity, the production of estrogens is generally increased and this is associated with early menarche in women and delay in the onset of puberty in men [42,43].

In the Tucson cohort, Castro-Rodríguez et al [44] found that the prevalence of asthma was greater in those obese girls who had early menarche (before 11 years of age) than amongst those who underwent menarche at a later age. This would seem to suggest that obesity disrupts the production (or peripheral sensitivity) of the hormones related to puberty in girls and that an increased production of female hormones (or sensitivity to them) disrupts lung development and the regulation of airway tone in pubertal girls.

The Influence of Diet

Several diet-related factors have been reported to influence the prevalence of asthma in adults and children. For example, the antioxidants (vitamins C and E), carotene, riboflavin, and pyridoxin can all exert an important effect by increasing immune function, reducing the symptoms of asthma/eczema, and improving lung function. Recently, Romieu et al [45] have reported that adult women who consumed fruit and vegetables (tomatoes, carrots, and leafy vegetables) had a lower prevalence of asthma. Higher consumption of trans fatty acids in a pediatric population has also been linked to a reduction in the prevalence of asthma [46]. However, it is important to highlight that the studies on diet and asthma were carried out in patients already diagnosed with asthma.

It is not known whether maternal diet during gestation can influence the development of obesity in children, but it is interesting to point out that the relationship between weight at birth (regardless of gestational age) and the risk of asthma follows a U-shaped curve, that is, both low and high weights at birth increase the risk of asthma [47,48]. Similarly, the same U-shaped curve is seen in the relationship in males between low and high BMIs and greater BHR [49]. This suggests that "fetal programming" may have repercussions on the subsequent development of obesity and asthma.

Implications for Treatment

Data published in recent years indicate that obesity may affect the response of asthmatic patients to their normal treatment. Peters-Golden et al [50] analyzed patient response in relation to BMI in 3000 asthmatic patients given 1 of the following 3 treatments: placebo, inhaled corticosteroids (beclomethasone), and leukotriene receptor antagonists (montelukast). Whilst in the patients receiving beclomethasone there were no changes in drug efficacy as related to patient weight, in the patients receiving placebo the number of days

during which asthma was under control (days with less than 2 puffs of ß$_2$ antagonists, and no nocturnal awakenings or asthma attacks) was greater in normal-weight patients than in overweight or obese patients, even after adjustment for asthma severity. FEV$_1$ values also improved after the administration of placebo in lean, but not in obese, subjects. Given that the response to placebo is, probably, the result of more contact with health care personnel, improvement in breathing techniques, and greater avoidance of asthma triggers, these results may indicate that asthma in obese patients is less sensitive to this type of intervention.

However, in those patients with high BMIs who received montelukast, the clinical benefit was greater than in lean patients, which suggests that leukotrienes play a more important role as mediators of symptoms in obese patients.

Another double-blind study [51] compared the efficacy of placebo, montelukast, and theophyllines in asthmatics in relation to patient weight: in the patients treated with theophyllines, the relative risk of worsening symptoms was greater in obese asthmatics than in lean individuals.

Taken together, these results suggest that BMI is one of the variables that should be taken into consideration in asthmatic patients.

Conclusions

Most of the epidemiological data indicate that obesity can increase the prevalence and incidence of asthma, although this effect appears to be modest and depends on factors such as age and sex. It is clear that the treatment of obese asthmatics must include a weight control program, and it must be borne in mind that obesity may disrupt the response to normal anti-asthmatic treatments.

The complex interrelation between obesity and asthma is an example of the interaction between genes and the environment in the pathogenesis of both disorders and it is very likely that more than 1 biological mechanism is involved. Obesity, by means of inflammatory mechanisms or changes in lifestyle, can trigger asthmatic symptoms in susceptible individuals. The combination of diet and genes may alter the normal patterns of body growth (giving rise to obesity), the tone of the airways (giving rise to asthma), or both. Clearly, more research is needed to further elucidate these 2 phenomena and the multiple interrelationships that exist between them.

References

1. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents and adults. 1999-2002. JAMA. 2004;291:2847-50.
2. Health, United States, 2005. Hyattsville, MD: National Center for Health Statistics, December 8, 2005:63.
3. Waite DA, Eyles EF, Tonkinn SL, O'Donnell TV. Asthma prevalence in Tokelauan children in two environments. Clin Allergy. 1980;10:71-75.
4. Von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. Lancet. 1998;351:862-6.
5. Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol 2005;115:897-909.
6. Beckett WS, Jacobs DR Jr, Yu X, Iribarren C, Williams OD. Asthma is associated with weight gain in females but not in males, independent of physical activity. Am J Respir Crit Care Med. 2001;164:2045-50.
7. Guerra S, Sherrill DL, Bobadilla A, Martínez FD, Barbee RA.The relation of body mass index to asthma, chronic bronchitis, and emphysema. Chest. 2002;122:1256-63.
8. Shaheen SO, Sterne JA, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. Thorax 1999;54:396-402.
9. Camargo CA Jr, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. Arch Intern Med. 1999;159:2582-88.
10. Ford ES, Mannino DM, Redd SC, Mokdad AH, Mott JA. Body mass index and asthma incidence among USA adults. Eur Respr J. 2004;24:740-4.
11. Nystad W, Meyer HE, Nafstad P, Tverdal A, Engeland A. Body mass index in relation to adult asthma among 135,000 Norwegian men and women. Am J Epidemiol. 2004;160:969-76.
12. Hasler G, Gergen PJ, Ajdacic V, Gamma A, Eich D, Rössler W, Angst J. Asthma and body weight change: a 20-year prospective community study of young adults. Int J Obes (Lond). 2006 Jul;30(7):1111-8.
13. McLachlan CR, Poulton R, Car G, Cowan J, Filsell S, Greene JM, Taylor DR, Welch D, Williamson A, Sears MR, Hancox RJ. Adiposity, asthma, and airway inflammation. J Allergy Clin Immunol. 2007 Mar;119 (3):634-9.
14. Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. Pediatr Pulmonol. 2003;36:514-21.
15. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, Avol E, Peters JM. Obesity and the risk of newly diagnosed asthma in school-age children. Am J Epidemiol. 2003;158:406-15.
16. Xu B, Pekkanen J, Laitinen J. Body build from birth to adulthood and risk of asthma. Eur J Public Health. 2002;12:166-70.
17. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? Thorax. 2001;56:845-50.
18. Mannino DM, Mott J, Ferdinands JM, Camargo CA, Friedman M, Greves HM, Redd SC. Boys with high body masses have an increased risk of developing asthma: findings from the National Longitudinal Survey of Youth (NLSY). Int Obes (Lond) 2006;30:6-13.
19. Von Mutius, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. Thorax. 2001;56:835-8.
20. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL; Childhood Asthma Management Program Research Group. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP) Thorax. 2003 Dec; 58(12):1036-41.
21. Spivak H, Hewitt MF, Onn A, Half EE. Weight loss and improvement of obesity-related illness in 500 US patients following laparoscopic adjustable gastric banding procedure. Am J Surg. 2005;189:27-32.

22. Stenius-Aarniala B, Poussa T, KKvarnström J, Grönlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. BMJ. 2000;320:827-32.
23. 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.
24. Biring MS, Lewis MI, Liu JT, Mohsenifar Z. Pulmonary physiologic changes of morbid obesity. Am J Med Sci. 1999;318:293-7.
25. Fredberg JJ, Inouye DS, Mijailovich SM, Butler JP. Perturbed equilibrium of myosin binding in airway smooth muscle and its implications in bronchospasm. Am J Resp Crit Care Med. 1999;159:959-67
26. Shore SA. Obesity and asthma: cause for concern. Curr Opin Pharmacol. 2006;6:230-6.
27. Dixon AE, Shade DM, Cohen RI, Skloot GS, Holbrook JT, Smith LJ, Lima JJ, Allayee H, Irvin CG, Wise RA. Effect of obesity and clinical presentation and response to treatment in asthma. J Asthma. 2006;43:553-8.
28. Lang JE, Williams E, Flynt L. IL-6 contributes to airway responses to acute ozone exposure in lean and obese mice [abstract]. Proc Am Thorac Soc. 2006;3:A821.
29. Sierra-Honigmann MR, Nath AK, Murakami C, García-Cardeña G, Papapetropulos A, Sessa WC, Madge LA, Schechner JS, Schwabb MB, Polverini PJ, Flores-Riveros JR. Biological action of leptin as an angiogenetic factor. Science. 1998;281:1683-6.
30. Torday JS, Sun H, Wang L. Leptin mediates the parathyroid hormone-related protein paracrine stimulation of fetal lung maturation. Am J Physiol Lung Cell Mol Physiol. 2002;282:L405-L410.
31. Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. J Appl Physiol. 2003;95:938-45.
32. 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.
33. Guler N, Kirerleri E, Ones U, Tamay Z, Salmayenli N, Darendelifer F. Leptin: does it have any role in childhood asthma? J Allergy Clin Immunol. 2004;114:254-9.
34. Sood A, Ford ES, Camargo CA. Association between leptin and asthma in adults. Thorax. 2006;61:300-5.
35. Yamauchi T, Kamon J, Waki H, Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezak O, Akanuma Y, Gabrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tobe K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T.Yamauchi T, Kamon J, Waki H, Yamauchi T. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med. 2001;7:941-6.
36. 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.
37. Lilly CM, Woodruff PG, Camargo CA Jr, Nakamura H, Drazen JM, Nadel ES, Hanrahan JP. Elevated plasma eotaxin levels in patients with acute asthma. J Allergy Clin Immunol. 1999;104:786-90.
38. Tantisira KG, Weiss ST. Complex interactions in complex traits: obesity and asthma. Thorax. 2001;56 Suppl 2:64-73.
39. Clément K, Vaisse C, Manning BS, Basdevant A, Guy-Grand B, Ruiz J, Silver KD, Shuldiner AR, Froguel P, Strosberg AD. Genetic variation in the beta 3-adrenergic receptor and an increased capacity to gain weight in patients with morbid obesity. N Engl J Med.1995 Aug 10;333(6):352-4.
40. Hall IP, Wheatley A, Wilding P, Liggett SB. Association of Glu 27 beta 2-adrenoceptor polymorphism with lower airway reactivity in asthmatic subjects. Lancet. 1995 May 13; 345(8959):1213-4.
41. Ishiyama-Shigemoto S, Yamada K, Yuan X, Ichikawa F, Nonaka K. Association of polymorphisms in the beta2-adrenergic receptor gene with obesity, hypertriglyceridaemia, and diabetes mellitus. Diabetologia.1999 Jan;42 (1):98-101.
42. Cooper C, Kuh D, Egger P, Wadsworth M, Barker D. Childhood growth and age at menarche. Br J Obstet Gynaecol. 1996;103:814-7.
43. Kaplowitz P. Delayed puberty in obese boys: comparison with constitutional delayed puberty and response to testosterone therapy. J Pediatr. 1998;133:745-9.
44. Castro-Rodríguez JA, Holberg CJ, Morgan WJ, Wright AL, Martínez FD. Increased incidence of asthma-like symptoms in girls who become overweight or obese during the school years. Am J Respir Crit Care Med. 2001;163:1344-49.
45. Romieu I, Varraso R, Avenel V, Leynaert B, Kauffmann F, Clavel-Chapelon F. Fruit and vegetable intakes and asthma in the E3N study. Thorax. 2006;61:209-15.
46. Weiland SK, Von Mutius E, Husing A, Asher MI. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. ISAAC Steering Committee. Lancet. 1999;353:2040-1.
47. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ. 1991;303:671-5.
48. Svanes C, Omenaas E, Heuch JM, Irgens LM, Gulsvik A. Birth characteristics and asthma symptoms in young adults: results from a population-based cohort study in Norway. Eur Respir J. 1998;12:1366-70.
49. Litonjua AA, Sparrow D, Celedon JC. Association of body mass index with the development of methacholine airway hyperresponsiveness in men. Thorax. 2002;57:581-5.
50. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. Eur Respir J. 2006;27:495-503.
51. Dixon AE, Shade DM, Cohen RI, et al. Effect of obesity and clinical presentation and response to treatment in asthma. J Asthma. 2006;43:553-8.

Manuscript received April 25, 2008; accepted for publication June 13, 2008.

Julio Delgado Romero

Allegy Service, University Hospital Virgen Macarena
Avda. Dr Fedriani, 3
41009 Sevilla, Spain
E-mail: juliodelgadoromero@gmail.com