Gabriele Fulgheri*, Grażyna Sypniewska

Department of Laboratory Medicine, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland
*PhD student

Is there a link between asthma and obesity?

Corresponding author:

Grażyna Odrowąż-Sypniewska,
Department of Laboratory Medicine,
Nicolaus Copernicus University,
Collegium Medicum
Sklodowskiej-Curie Street No 9,
85–094 Bydgoszcz, Poland
E-mail: odes@cm.umk.pl

ABSTRACT

The association between obesity and several diseases is well known, but an association with asthma has been much less described. Epidemiological studies have shown that obesity is an independent risk factor for asthma in children and adults. Fundamental is the influence of the definition of the type of asthma on the link between those two diseases. Several reports have shown a stronger association between obesity and clinical asthma phenotypes than with physiological and inflammatory asthma phenotypes. Among the mechanisms that have been proposed to explain the obesity-asthma relationship, the immunological, hormonal and environmental are the most important; however, the impact of genetic factors should also be considered. Environmental factors such as high-calorie and low antioxidant diet, low maternal vitamin consumption and in particular low vitamin D have been recently discussed. Serum concentration of 25(OH)D has been found to be insufficient in children with asthma. Low 25-hydroxyvitamin D concentration leads to increasing asthma severity and requires more intensive glucocorticoids treatment. 25(OH)D may have a protective effect against asthma exacerbations as it enhances steroid responsiveness. The nature of the asthma-obesity relationship is very complex and involves several mechanisms. Among these, bronchial smooth muscle cells dysfunction, inflammatory mediators and oxidative stress, dietary and genetic factors play major roles.

Key words: obesity, asthma, vitamin D, pulmonary diseases

Folia Medica Copernicana 2013; 1 (1): 1–4

Introduction

An association between obesity and several diseases other than pulmonary diseases, is well known [1]. In spite of the fact that the prevalence of both obesity and asthma is increasing concomitantly, an association between them has been much less described and the causes underlying obesity's impact on asthma risk remain a topic for further investigation. Epidemiological studies have shown that obesity is an independent risk factor for asthma in children and adults [2, 3]. Obese children are at increased risk for developing asthma, one of the commonest chronic diseases among this population. Studies reporting the link between asthma risk and overweight / obesity in children and adolescents have produced inconsistent findings. However, it appears that increasing body mass in children and adolescents is not only associated with an increasing prevalence of asthma varying according to race and ethnicity, but also appears to further exacerbate asthma and requires escalating pharmacological intervention [4].

Another issue which should be addressed is the influence of asthma definition on the link between obesity and asthma. It is important to rule out the association dependent on the respiratory symptoms which are caused by obesity. One of the best approaches to define asthma is the measurement of bronchial hyperresponsiveness using a test with methacholine [5]. Cetlin et al. reported no positive association between obesity and asthma defined by symptoms associated with a positive methacholine challenge test. On the contrary, they found an association when the diagnosis of asthma was previously made by a physician [3]. In children, physician-diagnosed asthma has been found to be associated with higher body mass index percentile, body fat and waist circumference [6].

Obese asthmatics

Several reports have supported a stronger association of obesity with self-reported wheeze, use of asthma

medications and other clinically defined asthma phenotypes than with physiological (e.g. airway hyperreactivity or bronchodilator responsiveness of forced expiratory volume in 1 s (FEV$_1$) and inflammatory phenotypes of asthma (such as sputum cell counts and differentials, exhaled nitric oxide) [7–12].

On the other hand, the effect of obesity is not equal in all asthmatics. In adults, obesity is a characteristic feature of females with late-onset asthma having a higher degree of airway eosinophilic inflammation, moderately increased IgE concentrations but less atopy [13]. In early-onset asthma, more allergic symptoms, atopy, higher IgE concentrations and a lower degree of eosinophilic inflammation are typical features. Very recent data suggests that the severity and characteristics of asthma depend on the age of asthma onset. In late-onset asthma, obesity and increased asthma severity are more likely to be causatively associated, whereas in early-onset asthma, more severe asthma symptoms are the effect of significant body weight increase in asthmatics [13]. Asthma has been found to be related to excess body fat, at least in women. However, due to inaccurate measurement of fat deposits in the visceral area by DEXA, it appears that the excess of lean mass better predicts asthma among obese women [1].

Biological mechanisms relating asthma to obesity

Several mechanisms have been proposed that relate asthma to obesity, among them immunological, hormonal and environmental. The immunological mechanism involving Th2 cells and proinflammatory state may link obesity to asthma. Activated CD4+ T helper cells 2 (Th2) release interleukins IL-4, IL-5, IL-13 and regulate immune response by stimulating IgE production. Following allergen inhalation, IgE binds to mast cells and basophils, causing degranulation and the release of preformed and *de novo* synthesised mediators such as leukotrienes, prostaglandins and several proinflammatory cytokines (TNF-α, IL-1, IL-6) causing bronchial spasms and increased mucus production [14]. Enhanced leukotriene synthesis may contribute to the obese asthma phenotype.

Elevated TNF-α in asthma is linked to the production of IL-4 and IL-6 in bronchial epithelium. Serum TNF-α is also increased in obesity. This is especially interesting because this cytokine increases calcium signalling to a variety of contractile agonists in airway smooth muscle cells through TNF receptors expressed on these cells [15]. Single nucleotide polymorphisms in the TNF-α gene have been associated with both asthma and obesity [16]. Plasminogen activator inhibitor (PAI-1), that is elevated in obesity, may promote the devel-

opment of asthma by regulating airway remodelling, airway hyper-responsiveness (AHR) and allergic inflammation [17].

IL-5 is involved in the late phase of allergic reaction, and promotes differentiation of eosinophils and their release. It has been shown that human Th2 cells differentiated *in vitro* are involved in the selective expression of the gene for pro-melanin-concentrating hormone (PMCH), a precursor of orexigenic peptide, melanin concentrating hormone (MCH). PMCH plays an important role, acting in the hypothalamus, to stimulate the appetite in rodents and a receptor for MCH (MCHR1) has been identified [18]. In humans, two MCH receptors are present (MCHR1 and MCHR2) and activated Th2 cells have been shown to release MCH-containing proteins [19]. The proteins derived from PMCH secreted to the circulation following Th2 activation in asthma may increase appetite by stimulating the hypothalamus, which may relate asthma to obesity through a link of allergic inflammation to energy homeostasis.

Another mechanism linking obesity to asthma is the role of mediators of energy metabolism, adipocytokines such as leptin and adiponectin and hormone ghrelin [20]. Leptin, a pro-inflammatory adipocytokine, is expressed not only in adipocytes but also in the lungs [21]. This adipocytokine enhances Th1 cells proliferation, and downregulates the function of other cells associated with asthma, but it also may affect subepithelial neovascularisation and vascular permeability through the action of vascular endothelial growth factor (VEGF) released by airway smooth muscle cells [22, 23]. Adiponectin, an anti-inflammatory adipokine and its four receptors, besides adipocytes, is expressed in multiple cell types in the lung [24]. A decrease of serum adiponectin in obesity suppresses secretion of anti-inflammatory IL-10, whereas a decrease of serum ghrelin causes enhanced release of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α). Altogether, this leads to the susceptibility of hyperactive immune system to the development of allergic diseases. Recent data from children with asthma has shown that obesity worsens the symptoms of asthma, and that moreover leptin, adiponectin and ghrelin are involved in the inflammatory state observed in this disease, especially among obese children [20]. It seems that the contribution of adipokines to the asthma-obesity relationship is small and may depend on their airway concentration [1].

Factors relating obesity to asthma

Among factors relating obesity to asthma, dietary factors, lack of physical exercise, foetal programming and genetics have been recently discussed [16]. Environmental factors such as high-calorie and low

antioxidant diet, and low maternal vitamin consumption, especially low vitamin D, may lead to both obesity and asthma. Asthma may be induced by an increase of proinflammatory mediators and oxidative stress, through toll-like receptors present on airway inflammatory cells and the NF-κB pathway, as a consequence of the excess saturated fats in the diet [16]. In obese adult asthmatics, excess oxidative stress is reflected by increased levels of 8-isoprostane and other biomarkers. These biomarkers are elevated both in the blood and the lungs of obese patients with asthma. Enhanced oxidative stress may worsen the responsiveness to corticosteroid therapy [16].

Moreover, the so-called Western diet contains more omega-6 than omega-3 polyunsaturated fatty acids that enhances proinflammatory effect on the airways and decreases lung function. Serum concentration of 25(OH)D reflecting vitamin D status has been found to be insufficient in children with asthma. Lower 25-hydroxyvitamin D concentration leads to increasing asthma severity and requires more intensive treatment with glucocorticoids. As 25(OH)D may enhance induction of anti-inflammatory IL-10 by glucocorticoids, hypovitaminosis D causes the need for higher corticosteroid use [25].

25-hydroxyvitamin D and asthma

25-hydroxyvitamin D has been shown to exert significant immunomodulatory effects [26]. Hydroxylation of 25(OH)D, catalysed by CYP27B1, to give the active form $1\alpha,25(OH)2D$ has been found not only in the kidneys but also in several other extrarenal cells such as macrophages and dendritic cells. Additionally, vitamin D receptor (VDR) has been identified on B and T lymphocytes. It has been reported that 25(OH)D insufficiency may contribute to the risk of asthma through influence on T cells, diminished maturation and functioning of bronchial smooth muscle cells (airway remodelling early in life), lung function and impaired clearance of respiratory pathogens [16,27]. Possibly $1\alpha,25(OH)2D$ modulates T regulatory cells that increase release of IL-10 and TGF-β which lowers Th2 cytokine production [26]. There has been some criticism concerning the potential protective effect of vitamin D against asthma and its complications. According to Paul et al., currently there is no sufficient evidence of a causal relationship between vitamin D status and asthma, although it seems that vitamin D may have a protective effect against asthma exacerbation as it enhances steroid responsiveness [26].

Finally, vitamin D may influence asthma by regulating the expression of disease susceptibility genes. Of several genes connected to both obesity and asthma, currently five are of interest [16]. The gene *ADRB2* on chromosome 5q codes for the adrenergic β2 receptor and influences on sympathetic nervous system as well as regulation of airway tone and resting metabolic rate. Polymorphism of this gene has been linked to different asthma phenotypes, severity and response to treatment. Other genes related to obesity-asthma phenotypes include NR3C1, which codes for the glucocorticoid receptor, TNF-α and the lymphotoxin–A genes with a possible role in mediation of allergic responses, several variants of vitamin D receptor (VDR) gene and protein kinase C-a (PRKCA). The association of SNPs within the protein kinase Ca gene with BMI was found by Murphy et al. [28]. This enzyme not only plays a role in cellular proliferation and differentiation, cell cycle regulation, adhesion, survival and apoptosis, but also inhibits pre-adipocyte differentiation and insulin signalling which are important determinants of human obesity. Polymorphism of the PRKCA gene contributes to increased adipose tissue accumulation as well as to asthma pathogenesis by different mechanisms including airway inflammation, mucus production, airway remodelling and leukotriene signalling [28].

In summary, the nature of the asthma-obesity relationship is very complex and involves several mechanisms, of which major roles are played by bronchial smooth muscle cells dysfunction, inflammatory mediators and oxidative stress, dietary and genetic factors.

References

1. Sood A. Pulmonary Physiology and Pathophysiology in Obesity. J Appl Physiol 2010; 108: 744–753.
2. Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol 2005; 115: 897–909.
3. Cetlin AA, Gutierrez MR, Bettiol H, Barbieri MA, Vianna EO. Influence of asthma definition on the asthma-obesity relationship. BMC Public Health 2012; 12: 844–853.
4. Black MH, Smith N, Porter AH, Jacobsen SJ, Koebnick C. Higher Prevalence of Obesity Among Children With Asthma. Obesity 2012; 20: 1041–1047.
5. Crapo RO, Casaburi R, Coates AL et al. Guidelines for methacholine and exercise challenge testing-1999. Am J Respir Crit Care Med 2000; 161: 309–329.
6. Vangeepuram N, Teitelbaum SL, Galvez MP, Brenner B, Doucette J, Wolff MS. Measures of Obesity Associated with Asthma Diagnosis in Ethnic Minority Children. J Obesity 2011; doi: 10.1155/2011/517417.
7. 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.
8. Ford ES, Mannino DM, Redd SC, Mokdad AH, Mott JA. Body mass index and asthma incidence among USA adults. Eur Respir J 2004; 24: 740–744.
9. 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: 2046–2052.
10. Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. Thorax 2003; 58: 1031–1035.
11. Sood A, Verhulst S, Varma A, Eagleton L, Henkle J, Hopkins-Price P. Association of excess weight and degree of airway responsiveness in asthmatics and non-asthmatics. J Asthma 2006; 43: 1–6.
12. Kazaks A, Uriu-Adams JY, Stern JS, Albertson TE. No significant relationship between exhaled nitric oxide and body mass index in people with asthma. J Allergy Clin Immunol 2005; 116: 929–930.

13. Holguin FE, Bleecker R, Busse WW et al. Obesity and asthma, an association modified by age of asthma Onset. J Allergy Clin Immunol 2011; 127: 1486–1493.

14. Bergmann K, Sypniewska G. Is there an association of allergy and cardiovascular disease. Biochem Med 2011; 21: 210–218.

15. Amrani Y, Panettieri RA Jr. Cytokines induce airway smooth muscle cell hyperresponsiveness to contractile agonists. Thorax 1998; 53: 713–716.

16. Lang JE. Obesity, nutrition, and asthma in children. Ped Allergy Immunol Pulmunol 2012; 25: 64–75.

17. Ma Z, Paek D, Oh CK. Plasminogen activator inhibitor-1 and asthma: role in the pathogenesis and molecular regulation. Clin Exp Allergy 2009 39: 1136–1144.

18. Mul JD, Yi CX, van den Berg SAA et al. Am J Physiol Endocrinol Metab 2010; 298: E477–E488.

19. Hamamoto A, Horikawa M, Saho T, Saito Y. Mutation of Phe318 within the NPxxY(x)(5,6)F motif in melanin-concentrating hormone receptor 1 results in an efficient signaling activity. Front Endocrinol (Lausanne). 2012;3:147. doi: 10.3389/fendo.2012.00147.

20. Yuksel H, Sogut A, Yilmaz O, Onur E, Dinc G. Role of adipokines and hormones of obesity in childhood asthma. Allergy Asthma Immunol Res 2012; 4: 98–103.

21. Bruno A, Pace E, Chanez P et al. Leptin and leptin receptor expression in asthma. J Allergy Clin Immunol 2009; 124: 230–237.

22. Taleb S, Herbin O, Ait-Oufella H et al. Defective leptin/leptin receptor signaling improves regulatory T cell immune response and protects mice from atherosclerosis. Arterioscler Thromb Vasc Biol 2007; 27: 2691–2698.

23. Shin JH, Kim JH, Lee WY, Shim JY. The expression of adiponectin receptors and the effects of adiponectin and leptin on airway smooth muscle cells. Yonsei Med J 2008; 49: 804–810.

24. Medoff BD, Okamoto Y, Leyton P et al. Adiponectin-deficiency increases allergic airway inflammation and pulmonary vascular remodeling. Am J Respir Cell Mol Biol 2009; 41: 397–406.

25. Searing DA, Zhang Y, Murphy JR, Hauk Elena Goleva E, Leung DY. Decreased serum vitamin D levels in children with astma are associated with increased corticosteroid use. J Allergy Clin Immunol 2010; 125: 995–1000.

26. Ginde AA, Sutherland ER. Vitamin D in asthma: panacea or truepromise? J Allergy Clin Immunol 2010; 126: 59–60.

27. Brem JM, Celedo JC, Soto-Quiros ME et al. Serum Vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med 2009; 179: 765–771.

28. Murphy A, Tantisira KG, Soto-Quiros ME et al. PRKCA: a positional candidate gene for body mass index and asthma. Am J Hum Genet 2009; 85: 87–96.