The influence of obesity on inflammation and clinical symptoms in asthma

Gruchała-Niedoszytko M[1,2]*, Małgorzewicz S[2], Niedoszytko M[1], Gnacińska M[3], Jassem E[1]

1 Department of Allergology, Medical University of Gdansk, Gdansk, Poland
2 Department of Clinical Nutrition, Medical University of Gdansk, Gdansk, Poland
3 Department of Endocrinology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland

* CORRESPONDING AUTHOR:
Department of Clinical Nutrition
Medical University of Gdansk
Debinki 7,
80-210 Gdansk, Poland
Tel.: +48 58 349 2725,
Fax: +48 58 349 2723
e-mail: mg@gumed.edu.pl (Marta Gruchała-Niedoszytko)

ABSTRACT

Obesity and asthma are both important public health issues. Increasing number of studies suggest the association between obesity and asthma which may be causal or accidental. The studies on animal models show innate enhancement of airway hyper-responsiveness which suggest that chronic airway hyper-responsiveness may be related to chronic low-grade systemic inflammation occurring in obesity. These results are confirmed by studies on asthmatic patients which show that levels of inflammation markers were higher in obese asthma patients and are related to the parameters of obesity. However, adipokines secreted by adipose tissue have also been involved in the regulation of inflammation and allergic responses, and suggested to affect the risk of asthma, especially in obese female patients. The studies on the association between adiposity and atopy have conflicting results and the issue needs to be investigated in the future. Obesity also decreases lung volume and increases airway resistance inducing symptoms that could mimic asthma. Clinical studies suggest that asthma in obese subjects may differ from the classical phenotype of the disease. Obese patients referred for asthma exacerbation present a reduced response to standard asthma medications.

The review indicates that mechanical and inflammatory effects of obesity may explain the influence on asthma. Further studies on the association between adiposity and atopy on airway inflammation may confirm the active role of fat tissue, not only simple mechanical impairment of the thorax movement. Longitudinal studies are needed to understand the association between asthma, and obesity, which may open new therapeutic options for asthma treatment in obese patients.

Key words: asthma, obesity, inflammation, lung function

INTRODUCTION

Obesity and asthma are both important public health issues. Obesity is defined by body mass index (BMI) above 30 kg/m^2, which is highly correlated with body fat mass and is a useful measure in clinic and epidemiological studies. Obesity is a chronic disease and can affect almost every organ and tissue of the body. In the respiratory system, obesity is related to a wide range of disorders like asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, pulmonary embolism and aspiration pneumonia [1, 2].

REVIEW

Epidemiology

A global epidemic of obesity is observed nowadays. The WHO predicts that, by 2015 around 2.3 billion adults will be overweight (BMI>25) and more than 700 million will

be obese (BMI>30). In Europe, the prevalence of obesity has tripled in last two decades. Overweight and obesity are the most common chronic pediatric diseases in Europe. Childhood obesity is a strong risk factor for adult obesity and is associated with increased mortality and disability in adulthood [1, 2].

Parallel, the prevalence of asthma dramatically increased, with rates almost 2.5 times greater today as compared with 20 years ago [3]. An increasing number of studies suggest that there is an association between obesity and asthma which may be causal or accidental. Although the relationship between obesity and asthma still remains unclear, many authors suggest, that obesity is a risk factor for asthma and it is significantly associated with its prevalence, affecting the disease towards difficult-to-control phenotype with lower asthma –specific quality of life in both adults and children [4-11]. A recent study on patients with persistent asthma found, that obese individuals were significantly more likely than those with normal BMI to report (1) worse asthma-related quality of life, (2) worse asthma control, and (3) more asthma–related hospitalization, however, being overweight was not associated with adverse study outcomes [4]. There was a strong positive association between very low birth weight in children and, both, subsequent overweight and asthma at 12 years of age. The explanation for this association might be the early rapid weight gain of such infants [12]. The study by Rönmark et al. [13] showed that obesity increased 2.7-fold the risk of asthma and overweight 2.0-fold as compared with normal weight. In a Danish study, Thomsen et al. [14] reported that the occurrence of new cases of self-reported asthma (assessed by a questionnaire) during 8 years was 4.3% in subjects aged 20-40 years, with a linear relationship between baseline BMI and incidence of asthma in both men and women. Meta-analysis of these prospective epidemiological studies demonstrated a dose-dependent relationship between BMI and the incidence of asthma, with overweight increasing the risk of asthma by 38% (OR=1.38; CI 1.17 - 1.62) and obesity increasing the risk by 92% compared with normal weight (OR=.92; CI 1.43 - 259). McLachlan et al. [15], reported the significant association between body fat percentage and current asthma only in women. However in another study, no significant gender disparity in the obesity - asthma relation was found [16].

Pathology – molecular and animal models

The results of the epidemiological studies suggest a causal relationship between obesity and asthma, but do not explain the pathological mechanism of these relations. The mechanisms by which obesity may affect the airway inflammation and hypersensitivity or function of the lungs were studied in an animal model of obesity. The animal models of obesity in a mouse with genetic deficiencies in (1) leptin; a satiety hormone (*ob/ob* mouse) or (2) leptin receptor (*db/db* mouse) or (3) in carboxypeptidase E (an enzyme involved in processing prohormones and proneuropeptides involved in satiety and energy expenditure (*Cpe^fat* mouse)) show innate enhancement of airway hyper-responsiveness. The results suggest, that chronic airway hyper-responsiveness may be related to chronic low-grade systemic inflammation occurring in obesity. Furthermore, the airway responsiveness induced by ozone or ovalbumin sensitization is greater in obese than in lean wild-type mice [9, 17, 18]. It is not clear if the bronchial hyper-responsiveness occurring in the obese mice model is caused by the airway inflammation. Ozone exposure consistently increased lung inflammation in *db/db* obese mice and *Cpe^fat* mice in comparison to the lean mice [9, 18]. The significant increase in all BALF inflammatory parameters; IL-6, eotaxin, macrophage inflammatory protein -2 (MIP-2), soluble TNF receptor (sTNFR1), neutrophils in *db/db* mice vs. wild-type mice was found. Additionally, the serum level of IL-6, monocyte chemotactic protein-1 (MCP-1), total number of blood leukocytes were higher in *db/db* mice than in lean mice, although for IL-6 the difference did not reach statistical significance [18]. Similar data were observed in the study on *Cpe^fat* mice [9].

Johnston et al. [17] reported that ovalbumin sensitization enhances the airway hyper-responsiveness measured in methacholine challenge of the obese *ob/ob* mice in comparison with lean wild-type animals despite the absence of any differences in Th2 cytokine expression. Surprisingly, the migration of inflammatory cells to the lungs was even lower in obese animals. The number of inflammatory cells (eosinophils, lymphocytes, macrophages) in the bronchoalveolar lavage fluid following ovalbumin sensitization was significantly lower in obese compared with lean mice. There was no difference in the number of neutrophils in the bronchoalveolar lavage fluid between *ob/ob* and wild-type mice following ovalbumin sensitization. The data from bronchoalveolar fluid cells were confirmed by histopathology of the lung tissue which showed significantly higher inflammation score among wild-type versus *ob/ob* mice. Johnston et al. [17] measured the systemic inflammation analyzing the serum levels of eotaxin, soluble TNF receptors (sTNFR1, sTNFR2) and the total number of leukocytes. Eotaxin, sTNFR1, sTNFR2 were significantly increased in obese compared with lean mice. There were no differences in the total number of leukocytes between wild-type and *ob/ob* mice [17]. Preliminary data demonstrated that the neutralization of TNF-α with the anti-TNF-α antibody attenuates the innate airway hyper-responsiveness [19]. The studies on obese *ob/ob* mice exposed to ovalbumin suggest that obesity may affect in mechanical response on the airways and increase the systemic inflammatory markers but does not amplify the airway inflammation.

The different effects of obesity on airway inflammation observed in *Cpe^fat* mice (lack of carboxypeptidase E) and *db/db* mice (lack of the long form of leptin receptor (Ob-Rb)) but not Ob-Ra and *ob/ob* mice (lack of leptin) suggest

that leptin acting through Ob-Ra may modulate pulmonary inflammation.

Adipokines and asthma

The adipose tissue was recognized as an active endocrine organ that can affect the function of other organs and as an important source of several proinflammatory cytokines, chemokines, growth factors and adipokines like leptin, adiponectin and resistin [20]. Leptin and resistin are usually pro-inflammatory, while adiponectin has mainly anti-inflammatory properties [21]. Leptin levels increase in obesity [20] and leptin has therefore been suggested to belong to the factors explaining the relation between obesity and asthma. Some studies suggest that leptin affects asthma independently of BMI [22]. Some authors have found no differences in BMI between asthmatic and non-asthmatic individuals with high leptin levels. Adipocytes in white adipose tissue are the main source of leptin but adipocytes also secrete cytokines like TNF-α, IL-6, and IL-10. TNF-α stimulates the production of Th2 type cytokines. In summary, a common inflammatory pathway in both, obesity and asthma, is orchestrated by TNF. Also, the expression of leptin can be increased by TNF-α [23].

Adiponectin has been demonstrated to have anti-inflammatory properties and it is associated with lower risk for asthma in women regardless of BMI. Adiponectin and all of the known receptors for adiponectin (AdipoR1, AdipoR2, T-cadherin, and calreticulin) are expressed on multiple cell types in the lung [24]. Increasing BMI is associated with changes in the concentrations of airway adiponectin in asthmatics and healthy controls; however, these associations are not related to biomarkers of airway oxidation or inflammation [25]. Similarly to leptin, human data on the independent association between serum adiponectin concentrations and asthma are currently inconclusive [24]. Current studies show a protective association between serum adiponectin concentrations and risk for asthma, independent of BMI [24, 26]. These studies further suggest, that the protective association may be stronger in specific population subgroups, such as peripubertal girls and premenopausal women [24, 26]. On the other hand, Jartti et al. [27], in a large Finnish cohort study, did not show an independent association between serum adiponectin and asthma.

The role of resistin in obesity and also in asthma remains unclear. There are few publications on resistin in human asthma with conflicting results. Larochelle et al. [28] found higher resistin levels in asthmatics and the levels were increased with disease severity, while other authors [29] suggested that resistin may have a protective effect against asthma. Resistin expression is enhanced by inflammatory factors IL-1, IL-6 and TNF-α which are all known activators of NF-κB. In addition, pro-inflammatory effects of resistin are partly mediated through activation of the NF-κB pathway. Therefore, resistin may have a role as a factor or a predictor in steroid-responsive asthma [30].

Airway inflammation in obese asthmatics

In both, humans and mice, obesity is linked to chronic, low-grade systemic inflammation. Fat cells act as the endocrine cells and adipose tissue is a part of the endocrine system. The adipose tissue releases proinflammatory adipokines leading to inflammatory activation at sites distant to fat tissue [31]. These adipokines could also exacerbate asthma. Many adipokines including TNF-α , IL-6, plasminogen activator inhibitor 1, eotaxin, vascular endothelial growth factor (VEGF) and monocyte chemotactic protein (MCP)-1 have been associated with asthma and could play a role in the relationship between obesity and asthma. Adipose tissue produces adipokines such as leptin, adiponectin and resistin that might affect airway inflammation [10, 11]. Inflammation is present in both, asthma and obesity. It was hypothesized that in some cases a common inflammatory pathway may be found. Adipocytes may release proinflammatory hormones that in turn could contribute to the increase and severity of asthma. The levels of CRP and fibrinogen, two nonspecific markers of systemic inflammation, are higher in obese than non-obese asthmatic subjects [32, 33]. Interestingly, levels of CRP are inversely correlated with induced sputum eosinophils [32]. This suggests a possible influence of systemic inflammation on bronchial inflammation. Latest study evaluating the relationship between inflammatory cytokines and acute phase proteins in obesity and asthma confirm the above data. Interleukin 6, TNF-α, CRP, leptin levels were significantly higher in the obese asthmatics in comparison to the non-obese patients. The levels of inflammation markers were higher in obese asthma patients and were related to the parameters of obesity [22, 34, 35]. Additionally, the level of high-sensitivity C-reactive protein (HsCRP) is significantly higher during exacerbation than during the remission in asthmatic children. The decrease during remission was more prominent in children with low body mass index percentile. A reciprocal relationship was found between forced expiratory volume in 1 s and HsCRP [36]. However, Dixon et al. [35] did not find any association between CRP levels and asthma severity in obese asthmatic patients.

Obese asthma phenotype

Clinical studies suggest, that asthma in obese subjects may differ from the classical phenotype of the disease. Obese patients referred for asthma exacerbation present a reduced response to standard asthma medications [4, 32, 36-38]. Effective clinical care is complicated by heterogeneity in the physiologic and pathologic mechanisms associated with asthma and multidimensional nature of asthma. Haldar and Pavord et al. [39] performed cluster analysis for the identification of clinical asthma phenotypes. One of the severe asthma phenotypes characterized patients, predominantly females, without the eosinophilic airway inflammation [39]. Thus obesity might be associated with a phenotype of asthma that is more difficult to control with

weak response to anti-inflammatory treatment. The reported steroid resistance of asthma in obese patients may in part be explain by the non-eosinophilic airway inflammation seen with this phenotype. On the contrary, other study shows no significant differences between cell count in induced sputum (eosinophils, macrophages, lymphocytes, neutrophils) between obese and non-obese asthmatic patients [32, 34]. However, significant inverse correlation of the percentage of eosinophils in induced sputum with both, waist circumference and BMI, was found [32]. This may suggest a role of abdominal obesity in the inflammation of the airways. In agreement with the above data, van Veen et al. [33] found the negative association between sputum, both, eosinophils and neutrophils, and BMI among difficult to treat asthma patients. Another study including asthmatic and non-asthmatic patients did not present a correlation between BMI and any measure of cellular airway inflammation (total count, neutrophils, eosinophils, lymphocytes, macrophages) even after adjusting for the corticosteroid dose. The sputum lipid index, a surrogate marker for aspiration, was similar in obese and non-obese subjects [40]. The studies on the relationship between BMI and exhaled nitric oxide (eNO) - a measure of airway inflammation, present conflicting results. The study on healthy normal and overweight subjects described positive association between exhaled nitric oxide concentration and BMI and concluded that eNO could be considered a systemic inflammation link between airway inflammation and obesity [41]. A subsequent study by Kazaks et al. [42] including obese subjects, identified a positive correlation between BMI and exhaled NO in healthy individuals, but not in the patients with mild to moderate asthma, however, the authors did not find the association between obesity and elevated level of eNO among asthmatic patients. The authors concluded that the airway inflammation associated with asthma might be severe enough to mask the effect of obesity on exhaled nitric oxide. However, they did not control for inhaled and oral corticosteroid use that may also reduce airway inflammation. The measurement of body fat percentage using bioelectrical impedance analysis showed no association with eNO in asthmatic patients [15]. Another study showed a negative association between BMI and eNO in overweight and obese patients with asthma, independent of corticosteroid use [43]. The study [43] included patients with difficult to treat asthma and is in agreement with the above data. The body mass index was negatively associated with exhaled nitric oxide values even after adjusting for the corticosteroid dose [33].

It has been hypothesized that high levels of proinflammatory molecules released from adipose tissue into blood stream could influence airway inflammation thereby increasing the prevalence and the severity of asthma in obese patients. The findings of less severe airway inflammation in obese patients suggest that the mechanical effect of the amount of abdominal adipose tissue on the lung function and co-morbid factors could make them more symptomatic and difficult to treat. Presumably, mechanisms other than cellular and endothelial airway inflammation are involved in the relationship between asthma symptoms and obesity.

Obesity, atopy and hyperresponsiveness

Atopy is an important risk factor in the development of allergic asthma. Recent data indicate the relation of higher body mass index with increased prevalence of atopy [44]. Other studies describe a lack of relation between mean serum IgE level and blood eosinophil percentage with obesity in asthmatics [32, 33]. The airway responsiveness did not differ between these two groups neither [33]. There are, however, some opposite studies. Ciprandi et al. [8] found a clear relation between methacholine airway responsiveness and BMI among patients with asthma. BMI was significantly higher in patients with PD20 values <100 μg (mean BMI = 27.9) with respect to patients with PD20 values between 100 and 350 μg (mean BMI = 25.3). However, there was no association between the percentage of overweight/obese patients and mono- or polysensitization [8]. Additionally, in the latest study performed on asthmatic obese and non-obese patients, no association was found between positive skin prick test and obesity [45]. Regarding sex differences, the trend towards a positive association between body fat percentage and positive skin prick tests was found only in women [15]. In summary, the studies on the association between adiposity and atopy have conflicting results and the issue needs to be investigated in the future. Possible confirmation of the relationship between obesity and atopy may indicate the biologically active role of fat tissue rather than a mechanical one.

Obesity and lung function

Obesity decreases lung volume and increases airway resistance inducing symptoms that could mimic asthma. Subjects with obesity claim more wheeze and shortness of breath which may be due to the increased work of breathing and deconditioning [11]. In the obese, the functional residual capacity (FRC) is reduced because of the changes in the elastic properties of the chest wall. The lower functional residual capacity may unload the airway smooth muscle so that it shortens more, even when it is activated by normal parasympathetic tone or other bronchoconstriction factors [11, 43]. Small airway closure is an additional mechanical factor that may enhance the narrowing and airway hyperresponsiveness in obese subjects. It has been suggested, that the repeated opening and closing of peripheral airways may lead to rupture of alveolar attachments to bronchioles and over time perturbs smooth muscle function exacerbating the airway narrowing [11, 46]. Obesity is associated with both, reduced forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) [35]. Additionally, in women, a significant inverse association between the FEV1/ FVC ratio and body fat percentage was found, but by contrast to men lower body fat percentage was associated with airflow obstruction [15]. This finding

is similar to the observation by Sood et al. [24] who found that women not men had adjusted adiponectin concentration. Jones and Nzekwu [47] studied the lung function among individuals without lung disease. The results show that the expiratory reserve volume (ERV), vital capacity (VC), total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC) decline with increasing BMI, but the greatest impact was on ERV, as morbid obesity resulted in patients breathing near their residual volume. More importantly, they showed that the FEV1 to FVC ratio, which is the main information about presence of airflow obstruction, did not change with increasing BMI [47]. Similarly FVC and FEV1 decreased significantly and FEV1/ FVC ratio remained unchanged in simulated obesity in lean non-asthmatic subjects [48]. Furthermore, the latest study identified a significant decrease of ERV, FRC, TLC and RV in obese asthmatic subjects compared with non-obese. No changes were found in FEV1, FVC, FEV1/ FVC ratio [32,34]. Van Veen and Brinke et al. [33] found higher FEV1 in obese in comparison with non-obese patients with difficult to treat asthma. In patients with mild and moderate persistent asthma no differences in FEV1/ FVC ratio between obese and non-obese patients were found [35]. It seems that in obesity, the more typical spirometric result is restriction not obstruction. Studies on weight loss in humans have provided an experimental model to test the effects of weight loss on the lung function and airway inflammation. Eneli et al. [49] in a systemic review on weight loss and asthma, based on 15 relevant studies, noted an improvement in all studies in at least one asthma outcome (symptoms, use of medications, hospitalizations) after weight loss, regardless of the type of intervention (surgical vs. medical). In a 6-months medical weight loss study of 58 obese women, 24 of whom had asthma, weight loss improved FEV1 and FVC but did not affect the airway hyperresponsiveness [50]. Similar findings have been presented in a study of bariatric surgical patients with severe obesity. Patients who underwent the surgery, experienced improvements in both asthma symptoms and of approximately 5% in FEV1 and 8% in FVC. However, the exhaled nitric oxide concentration did not change after surgery [51]. These data suggest that weight loss does not affect airway inflammation and does not support the conclusion that obesity leads to airway allergic inflammation and asthma. The majority of the studies mentioned above were not randomized clinical trials. The Breathe Easier through Weight Loss Lifestyle Intervention (BE WELL) is planned to analyze if a 12 month weight loss intervention will improve the quality of life, lung function, medication use and health care utilization [52]. Interestingly, in another study it was found that the greatest rates of change in FRC and ERV occurred in the overweight when BMI values were under 30 what does not support the conclusion about mechanical effect of obesity on the lung function [47]. Probably, more factors which are commonly used for defining obesity, such as percentage of body fat, skin fold

thickness, waist circumference and waist to hip ratio, should be indicated as risk factors of the lung function impairment. BMI is a 'gold standard' to assess body composition and it correlates with total body fat content, but is not allowed to be used for overweight because of large muscle mass or those with high body fat levels and normal weight. More complex anthropometric measures that assess total body mass distribution and measures body fat mass and free fat mass should be studied. This misclassification of body fat could explain why the studies evaluating the association between BMI and airway inflammation provide conflicting findings.

Obesity is associated with a number of co-morbid factors, such as, chronic sinus disease, gastroesophageal reflux, respiratory infections, psychopathology and obstructive sleep apnea, which are well known factors influencing lack of asthma control [35].

CONCLUSIONS

Obesity has been described as a risk factor for asthma in a number of epidemiological studies. Mechanical and inflammatory effects of obesity may explain why obesity influences asthma. Obesity might induce systemic inflammation influencing pulmonary inflammatory mechanisms. Factors associated with obesity as a systemic inflammation may play a role in airway inflammation. The mechanisms for the association between asthma and obesity remain still unclear. Further studies on the association between adiposity and atopy or airway inflammation may confirm the biologically active role of fat tissue rather than simple mechanical mechanism. Longitudinal studies are needed to understand the pathophysiological association between asthma, obesity and adipokines, and may also open new therapeutic options for asthma treatment in obese patients.

REFERENCES

1.   World Health Organization. WHO European Ministerial Conference on Counteracting Obesity. Conference report [Internet]. Denmark: WHO; 2007 [cited 2011 Dec 18]. 33p. ISBN: 978 92 890 7281 6. Available from: http://www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/obesity/publications/pre-2009/who-european-ministerial-conference-on-counteracting-obesity.-conference-report

2.   World Health Organization. Overweight and obesity. Fact sheet no. 311 [Internet]. Geneva: WHO; 2006 [cited 2011 Dec 18]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html.

3.   Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveilance for asthma – United

Srates, 1980-1999. MMWR Surveill Summ. 2002 Mar 29;51(1):1-13.

4.   Mosen DM, Schatz M, Magid DJ, Camargo CA Jr. The relationship between obesity and asthma severity and control in adults. J Allergy Clin Immunol. 2008 Sep;122(3):507-11.

5.   Shimizu K, Konno S, Shimizu K, Isada A, Takahashi A, Hattori T, Maeda Y, Takahashi D, Takahashi K, Nakagawa T, Taniguchi M, Akiyama K, Akazawa A, Hizawa N, Nishimura M. Prevalence in adult asthma and allergic rhinitis in Kamishihoro town, Hokkaido – association with smoking habit and obesity. Arerugi. 2008 Jul;57(7):835-42.

6.   Colombo BM, Murdaca G, Ciprandi G, Sormani MP. Body mass index in Th1 and Th2 disease. Immunology Letters. 2008 Apr;117(1):119-20.

7.   Kusunoki T, Morimoto T, Nishikomori R, Heike T, Ito M, Hosoi S, Nakahata T. Obesity and the prevelance of allergic diseases in schoolchildren. Pediatr Allergy Immunol. 2008 Sep;19(6):527-34.

8.   Ciprandi G, Pistorio A, Tosca M, Ferraro MR, Cirillo I. Body mass index, respiratory function and bronchial hyperreactivity in allergic rhinitis and asthma. Respiratory Medicine. 2008 Feb;103(2):1-7.

9.   Johnston RA, Theman TA, Shore SA. Augmented responses to ozone in obese carboxypeptidase E- deficient mice. Am J Physiol Regul Integr Comp Physiol. 2006 Jan;290(1):126-33.

10.   McClean KM, Kee F, Young IS, Elborn JS. Obesity and the lung: Epidemiology. Thorax 2008 Jul;63(7):649-54.

11.   Shore SA. Obesity and asthma. J Allergy Clin Immunol. 2008 May;121(5):1087-93.

12.   Mai XM, Gäddlin PO, Nilsson L, Leijon I. Early rapid weight gain and current overweight in relation to asthma in adolescents born with very low birth weight. Pediatr Allergy Immunol. 2005 Aug;16(5):380-5.

13.   Rönmark E, Andersson C, Nyström L, Forsberg B, Järvholm B, Lundbäck B. Obesity increases the risk of incident asthma among adults. Eur Respir J. 2005 Feb;25(2):283-8.

14.   Thomsen SF, Ulrik CS, Kyvik KO. The incidence of asthma in young adults. Chest. 2005 Jun;127(6):1928-34.

15.   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.

16.   Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007 Apr;175(7):661-6.

17.   Johnston RA, Zhu M, Rivera-Sanchez M. Allergic airway responses in obese mice. Am J Respir Crit Care Med. 2007 Oct;176 (7):650-8.

18.   Lu FL, Johnston RA, Flynt L. Increased pulmonary responses to acute ozone exposure in obese db/db mice. Am J Physiol Lung Cell Mol Physiol. 2006 May;290(5):856-65.

19.   Lang JE, Wiliams ES, Shore SA. TNFα contributes to innate airway hyperresponsiveness in murine obesity. Am J Respir Crit Care Med 2007. May;175(5):912-9.

20.   Gnacińska M, Małgorzewicz S, Stojek M, Łysiak-Szydłowska W, Sworczak K. Role of adipokines in complications related to obesity: a review. Adv Med Sci. 2009;54(2):150-7.

21.   Fantuzzi G. Adipose tissue, adipokines, and in- flammation. J Allergy Clin Immunol. 2005 May, 115(5):911-9.

22.   Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyper responsiveness. J Allergy Clin Immunol. 2005 May;115(5):925-7.

23.   Leivo-Korpela S, Lehtimäki L, Vuolteenaho K, Nieminen R, Kankaanranta H, Saarelainen S, Moilanen E. Adipokine resistin predicts anti-inflammatory effect of glucocorticoids in asthma. J Inflamm (Lond). 2011 May 26;8:12.

24.   Sood A, Cui X, Qualls C, Beckett WS, Gross MD, Steffes MW, Smith LJ, Jacobs DR Jr. Association between asthma and serum adiponectin concentration in women. Thorax. 2008 Oct; 63(10):877–82.

25.   Holguin F, Rojas M, Brown LA, Fitzpatrick AM. Airway and plasma leptin and adiponectin in lean and obese asthmatics and controls. J Asthma. 2011 Apr;48(3):217-23.

26.   Nagel G, Koenig W, Rapp K, Wabitsch M, Zoellner I, Weiland SK. Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. Pediatr Allergy Immunol. 2009 Feb;20(1): 81–8.

27.   Jartti T, Saarikoski L, Jartti L, Lisinen I, Jula A, Huupponen R, Viikari J, Raitakari OT. Obesity, adipokines and asthma. Allergy. 2009 May;64(5):770–7.

28.   Larochelle J, Freiler J, Dice J, Hagan L. Plasma resistin levels in asthmatics as a marker of disease state. J Asthma. 2007 Sep;44(7):509-13.

29.   Kim KW, Shin YH, Lee KE, Kim ES, Sohn MH, Kim KE. Relationship between adipokines and manifestations of childhood asthma. Pediatr Allergy Immunol. 2008 Sep;19 (6):535-40.

30.   Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem Biophys Res Commun. 2005 Sep;334(4):1092-101.

31.   Alvarez-Liamas G, Szalowska E, de Vries MP, Weening D, Landman K, Hoek A, Wolffenbuttel BHR, Roelofsen H, Vonk RJ. Charakterization of the human visceral adipose tissue secretome. Molecular and Cellular Proteomics. 2007 Apr;64(4):589-600.

32.   Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? Chest. 2008 Aug;134(2):317-23.

33.   van Veen IH, Brinke A, Sterk PJ, Rabe KF. Airway inflammation in obese and nonobese patients with difficult to treat asthma. Allergy. 2008 May;63(5):570-4.

34. Sutherland TJ, Cowan JO, Young S, Gouldin A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma. Am J Respir Crit Care Med. 2008 Sep;178(5):469-75.

35. Dixon EA, ShadeDM, Cohen RI, Skloot GS, Holbrook JT, Smith LJ, Lima JJ, Allayee H, Irvin ChG, Wise RA. Effect of obesity on clinical presentation and response to treatment in asthma. Journal of Asthma. 2006 Sep;43(7):553-8.

36. Soferman R, Glatstein M, Sivan Y, Weisman Y. HsCRP levels: measurement of airway inflammation in asthmatic children. Pediatr Int. 2008 Feb;50(1):12-6.

37. Segura MN, Murillo GE, Rojas-Dotor S, Rico G, Martinez HL, Sandoval SC. Inflamatory markers associated with asthma and body mass index. Rev Alerg Mex. 2007 Nov-Dec;54(6):196-200.

38. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DYM. Body Mass and Glucocorticoid response in asthma. Am J Respir Crit Care Med. 2008 Oct;178(7):682-7.

39. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brithling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008 Aug;178(3):218-24.

40. Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K. Effect of obesity on airway inflammation:cross-sectional analysis of body mass index and sputum cell counts. Clinical and Experimental Allergy. 2007 Jul;37(7):1049-54.

41. De Winter-de Groot KM, Van der Ent CK, Prins I, Tersmette JM, Uiterwaal CS. Exhaled nitric oxide: missing link between asthma and obesity? J Allergy Clin Immunol. 2005 Feb;115(2):419-20.

42. 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 allery and Clin Immunol. 2005 Oct;116(4):929-30.

43. Barros R, Moreira A, Fonseca J, Moreira P, Fernandes L, de Oliveira JF, Delgado L Castel- Branco MG. Obesity and airway inflammation in asthma. J Allergy Clin Immunol. 2006 Jun;117(6):1501-2.

44. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Factors related to alergic sensitization to aeroallergens in a cross-sectional study in adults: The Copenhagen Alergy Study. Clin Exp Allergy. 2001 Dec;31(9):1409-17.

45. Canoz M, Erdenen F, Uzun H, Muderrisoglu C, Aydin S. The relationship of inflammatory cytokines with asthma and obesity. Clin Invest Med. 2008 Dec;1(6):31-6.

46. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. Thorax. 2008 Nov;63(11):1018-23.

47. Jones RL, Nzekwu MM. The effects of the body mass index on lung volumes. Chest. 2006 Sep;130(3):827-35.

48. Wang L, Cerny FJ, Kufel TJ, Grant BJB. Simulated obesity-related changes in lung volume increases airway responsiveness in lean nonasthmatic subjects. Chest. 2008 Sep;130(3);834-84.

49. Eneli IU, Skybo T, Camargo Jr CA. Weight loss and asthma: a systemic review. Thorax. 2008 Aug;63(8):671-6.

50. Aaron SD, Ferguson D, Dent R. Effect of weight reduction on respiratory function and airway reactivity in obese women. Chest. 2004 Jun;125(6):2046-52.

51. Maniscalco M, Zedda A, Faraone S. Weight loss and asthma control in severely obese asthmatic females. Respir Med. 2008 Jan;102(1):102-8.

52. Ma J, Strub P, Camargo CA Jr, Xiao L, Ayala E, Gardner CD, Buist AS, Haskell WL, Lavori PW, Wilson SR. The Breathe Easier through Weight Loss Lifestyle (BE WELL) Intervention: a randomized controlled trial. BMC Pulm Med. 2010 Mar 24;10:16.