



# Is There a Link Between Obesity and Asthma?

Sang-Ha Kim,<sup>1,3</sup> E. Rand Sutherland,<sup>2</sup> Erwin W. Gelfand<sup>1\*</sup>

Departments of Pediatrics<sup>1</sup> and Medicine<sup>2</sup>, National Jewish Health, Denver, Colorado, USA

<sup>3</sup>Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Increasing epidemiological data identify a link between obesity and asthma incidence and severity. Based on experimental data, it is possible that shared inflammatory mechanisms play a role in determining this linkage. Although controversial, the role of adipokines may be central to this association and the maintenance of the asthma phenotype. While leptin and adiponectin have a causal link to experimental asthma in mice, data in humans are less conclusive. Recent studies demonstrate that adipokines can regulate the survival and function of eosinophils and that these factors can affect eosinophil trafficking from the bone marrow to the airways. In addition, efferocytosis, the clearance of dead cells, by airway macrophages or blood monocytes appears impaired in obese asthmatics and is inversely correlated with glucocorticoid responsiveness. This review examines the potential mechanisms linking obesity to asthma.

**Key Words:** Obesity; asthma; adipokines; eosinophils; macrophages; adipose tissue

## INTRODUCTION

Obesity is an important risk factor in the development of asthma.<sup>1</sup> The prevalence of asthma is higher in obese than in lean adults<sup>1,2</sup> and obesity increases the incidence of asthma by 2.0- and 2.3-fold in children and adults, respectively.<sup>2,3</sup> Moreover, significant dose-dependent effects of elevated body mass index on asthma are observed.<sup>1,2</sup>

Obese asthmatic patients are often described as severe and poorly controlled<sup>4,5</sup> perhaps because they are less responsive to corticosteroids and exhibit a different (*e.g.*, less atopic) inflammatory phenotype.<sup>6</sup> Obesity is associated with chronic low-grade systemic inflammation that is thought to enhance systemic complications.<sup>7</sup> It is known that adipose tissue can regulate systemic inflammation through the production of a variety of adipokines which may link the two disorders mechanistically.<sup>8</sup> Such observations, made in a number of epidemiological studies, imply that obesity increases the risk of developing asthma and implicates immunological mechanisms relevant to both disorders. In addition to increasing the risk of developing asthma, these pathways may also converge to enhance airway inflammation, thus skewing asthma towards a more difficult-to-control phenotype.

Despite these emerging data derived from epidemiological, clinical, and translational science, many aspects of the asthma-obesity association remain unclear. This review focuses on the relationship between obesity and airway inflammation, the im-

pact of obesity as a modifier of risks and response to treatment, and the mechanistic roles of adipokines and adipose tissue.

## Adipokines and airway inflammation

### Leptin

Leptin is synthesized and secreted mainly by adipose tissue and levels increase in line with obesity.<sup>9-11</sup> Leptin and leptin receptors are expressed by human lung cells, including epithelial cells, type II pneumocytes, and macrophages.<sup>12-14</sup> Leptin has proinflammatory systemic activities that may contribute, at least in part, to bronchial asthma.

In experimental models in mice, leptin is causally associated with asthma. Shore *et al.* demonstrated that administration of exogenous leptin to BALB/cJ mice augmented airway responsiveness following ovalbumin challenge.<sup>15</sup> However, human data correlating serum leptin levels with asthma risk are lacking. In studies supporting a role for systemic leptin levels on asthma prevalence in humans, the association between serum leptin levels and asthma prevalence appeared stronger in specific populations such as prepubertal boys, prepubertal girls, and premenopausal women.<sup>16-19</sup> Although data are lacking on the di-

**Correspondence to:** Erwin W. Gelfand, MD, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA.

Tel: +1 303 398 1196; Fax: +1 303 270 2105; E-mail: [gelfande@njhealth.org](mailto:gelfande@njhealth.org)

Received: November 12, 2013; Accepted: December 10, 2013

• There are no financial or other issues that might lead to conflict of interest.

rect role of leptin on airway inflammation in obese asthmatic patients, several studies suggest that systemic leptin is associated with severity of symptoms, impairment of lung function,<sup>20,21</sup> and enhancement of airway hyperresponsiveness (AHR) including exercise-induced bronchoconstriction.<sup>21,22</sup> A case-control study demonstrated that body mass index was highly associated with greater levels of urinary cysteinyl leukotrienes and levels of leptin were positively associated with urinary cysteinyl leukotriene levels.<sup>23</sup> In contrast, a controlled observational study failed to show a significant obesity-by-asthma interaction although systemic inflammatory markers were higher in obese subjects.<sup>24</sup> Longitudinal analysis of a large population-based cohort followed over 25 years demonstrated that body mass index is a stronger predictor of incident asthma than the metabolic syndrome, especially in women.<sup>25</sup> A similar trend in women was shown in a second longitudinal study.<sup>19</sup>

Hersoug *et al.*<sup>26</sup> hypothesized that changes in adipokines and proinflammatory cytokines secreted by adipose tissue result in increased risk of an allergic disease such as asthma, by decreasing development of immunologic tolerance. This review showed that leptin, IL-6, and TNF- $\alpha$  decrease the activity of regulatory T-lymphocytes while adiponectin induces IL-10 expression and production in human macrophages and adipocytes. Obesity *per se* may skew immune status towards a Th2 phenotype, increasing the risk of developing an allergic disease. Currently, there are no precise data to support or refute this hypothesis.

#### *Adiponectin*

Adiponectin is predominantly an anti-inflammatory adipokine that down-regulates proinflammatory cytokines, such as IL-6 and TNF- $\alpha$  as well as nuclear factor- $\kappa$ B, and upregulates anti-inflammatory cytokines such as IL-10 and the IL-1 receptor antagonist.<sup>27-31</sup> Levels of adiponectin are reduced in obese subjects even though visceral adipose tissue is its main source.<sup>32,33</sup> This paradox may be explained by findings that macrophages produce IL-6 and TNF- $\alpha$  in adipose tissue which may directly inhibit the production of adiponectin.<sup>34</sup> Adiponectin and all binding receptors for adiponectin such as AdipoR1, AdipoR2, T-cadherin, and calreticulin are expressed on airway epithelial cells in the lung.<sup>35</sup>

Adipokine levels are associated with asthma in mice. Exogenous adiponectin administration inhibited ovalbumin-induced AHR and airway inflammation while reducing total cell counts and eosinophil numbers.<sup>36</sup> Additionally, this study demonstrated that allergen challenge reduced the expression of adiponectin in adipose tissue and adiponectin receptor expression in the lung. These results were supported by another study using a chronic experimental asthma model in mice which demonstrated that allergic airway inflammation was increased in adiponectin-deficient mice compared with wild-type mice. These mice showed a greater accumulation of eosinophils and monocytes in the airways.<sup>37</sup>

Human data are limited however, and, unlike the studies in mice, are somewhat equivocal when associating levels of serum adiponectin with asthma. As with the studies on leptin, there are no conclusive data showing that serum adiponectin concentrations are associated with lower levels of urinary cysteinyl leukotrienes.<sup>23</sup>

#### **Systemic and airway inflammatory cells**

##### *Effects on survival and function of eosinophils*

Eosinophils are the predominant effector cells in allergic inflammatory diseases and tissue eosinophilia is a hallmark of bronchial asthma. IL-5 plays a critical role in eosinophil survival and chemokines and chemokine receptors such as eotaxin (CCL11), CCR-3, and ICAM-1 are important for the recruitment of eosinophils to the lung. The specific activity of eotaxin is mediated through CCR-3, expressed mainly on the surface of eosinophils. Circulating eosinophils cross the endothelium into lung tissues through interactions between eosinophil adhesion molecules and endothelial adhesion receptors such as ICAM-1 and VCAM-1.

In light of the purported association between obesity and asthma, several recent studies suggested that adipokines can affect the survival and function of eosinophils, focusing on chemotactic responses and adhesion activities in the pathogenesis of asthma. Leptin directly activates eosinophils and delays spontaneous apoptosis of mature eosinophils using surface receptors expressed on human eosinophils.<sup>38</sup> Leptin thus may serve as an important eosinophil survival factor through anti-apoptotic activity.

A cross-sectional study in children and adolescents showed that eosinophil chemotaxis and adhesion activities were enhanced in asthmatic obese patients compared with asthmatic non-obese, non-asthmatic obese, and non-obese individuals when eosinophils were stimulated with eotaxin, platelet-activating factor or RANTES in a microchemotaxis chamber and cultured on fibronectin-coated plates.<sup>39</sup> Serum leptin levels were higher in the obese compared to non-obese subjects. *In vitro* studies using purified peripheral blood eosinophils from subjects with mild eosinophilia showed that eosinophils, pretreated with leptin, augmented chemotactic responses to eotaxin.<sup>40</sup> Studies such as these support the notion of functional links between eosinophilic activity and chemotaxis and serum leptin levels. These findings provide a mechanistic link suggesting that leptin is involved in enhanced eosinophil accumulation into the airways of obese patients.

In contrast to leptin, Yamamoto *et al.*<sup>41</sup> demonstrated that the adiponectin receptors AdipoR1 and AdipoR2 were expressed on human peripheral blood eosinophils but that adiponectin, in a dose-dependent manner, attenuated eotaxin-induced eosinophil adhesion activity. However, no effects were observed on the survival of eosinophils.

### *Delay in eosinophil crossing to the airway lumen*

Most studies have failed to show differences in peripheral blood, sputum, or bronchoalveolar lavage (BAL) fluid eosinophil numbers comparing obese to non-obese asthmatics.<sup>42-47</sup> Indeed, eosinophil numbers in BAL fluid or induced sputum were often lower in obese compared to non-obese subjects.<sup>48-50</sup> Interestingly, obesity may affect eosinophil trafficking from the bone marrow to lung tissue and interfere with transit to the airways in mice with experimental asthma.<sup>50</sup> In this study, mice were fed a high-fat diet and eosinophil counts, Th1 and Th2 cytokines, and chemokines in bone marrow, lung tissue, and BAL fluid after sensitization and challenge with ovalbumin were monitored. The results showed that total leukocyte and eosinophil counts in BAL fluid were significantly lower in the obese compared to the lean mice but that the total number of leukocytes and eosinophils in lung tissue surrounding the bronchial and bronchiolar segments were largely higher in the obese mice than in the lean group; levels of IL-5 and eotaxin were higher in obese mice; the numbers of mature and immature eosinophils in bone marrow were higher in the obese mice. To define potential effects of high-fat intake on immune alterations in allergic asthma, lung eosinophilia and IL-5 levels in BAL fluid were examined in sensitized and challenged mice. These responses were reduced in non-obese mice maintained on a high-fat diet compared to control mice fed an isocaloric control diet.<sup>49</sup> These results were paralleled by decreased eotaxin levels in serum and BAL fluid of mice fed the high-fat diet. In contrast, splenocytes from mice fed the high-fat diet released significantly higher levels of MCP-1, indicating that the high-fat diet in a pre-obese state may itself affect the mobilization of eosinophils in response to allergen exposure.

In a study of 131 patients with severe asthma, airway submucosal eosinophil numbers were shown to be higher in obese subjects with severe asthma compared to a lean group, but there was no association between the numbers of eosinophils in sputum or peripheral blood and body mass indices.<sup>47</sup> These results suggested that diet-induced obesity promotes eosinophil trafficking from bone marrow to lung but appears to delay their transiting through the epithelium into the airways. It is possible that recruited eosinophils are resident for longer periods in lung peribronchial and peribronchiolar segments, aided by the overproduction of cytokines and chemokines.

### *Effects on neutrophils*

Telenga *et al.*<sup>45</sup> identified significant differences in the severity of asthma between obese and non-obese patients using pooled asthma cohorts and showed that neutrophil counts in the peripheral blood and percentages of sputum neutrophils were higher in obese compared to non-obese asthmatics. Improvement in lung function and lowering of sputum eosinophils following a 2-week course of corticosteroids was significantly lower in obese asthmatics. These results indicated that obese asth-

matic patients may have a somewhat attenuated response to treatment with corticosteroids, findings consistent with the suggested severity of asthma in obese subjects.<sup>51-53</sup> Of note, the increased neutrophilic inflammation was only observed in females. An increase in the percentages of neutrophils in sputum was also shown to positively correlate with body mass indices in female asthmatics and the prevalence of neutrophilic asthma was significantly greater in obese compared with non-obese female asthmatics.<sup>44</sup>

### *Dysfunctional activation of airway macrophages towards inflammation*

The phenotype of blood monocytes and tissue macrophages in obesity is consistent with "classical" or "M1" activation, in which there is expression of inflammatory mediators (*e.g.*, TNF- $\alpha$ , IL-1, IL-6, IL-8) that are crucial to innate immune responses against pathogens.<sup>54-56</sup> Classical activation is inhibited by Th2 cytokines which trigger "alternative" or "M2" program macrophages.<sup>54-56</sup> Additionally, the same mechanisms which lead to classically activated macrophages may lead them to become deficient in recognition and engulfment of apoptotic cells, impairing resolution of airway inflammation.<sup>57</sup> Inflammation in refractory asthma has also been associated with Th1 cytokines,<sup>58,59</sup> and M1 skewing of blood monocytes and alveolar macrophages has been documented in glucocorticoid-insensitive asthma.<sup>60,61</sup> Reduced clearance of dying cells by airway macrophages, efferocytosis, has been associated with more severe, glucocorticoid-insensitive asthma in obese asthmatics.<sup>62</sup> Impairment of macrophage efferocytosis in the airways was 40% higher in obese patients. Dysfunction of efferocytosis in blood monocytes was similarly higher in obese asthmatic patients. Moreover, efferocytosis in airway macrophages was inversely correlated with glucocorticoid response. Thus, impairment of efferocytosis by macrophages and monocytes was associated with obese asthmatic patients and this dysfunction of macrophages was associated with insensitivity to glucocorticoids. A possible associated connection was that leptin levels in BAL fluid were significantly higher in obese asthmatics and that airway macrophages from obese asthmatics were most sensitive to production of proinflammatory cytokines in response to leptin in *ex vivo* studies.<sup>63</sup>

Taken together, these reports identify an important paradox. The findings indicate that inflammatory and functional phenotypes of airway macrophages differ in obese and non-obese asthmatics, and that these differences may be associated with important clinical variables, including response to steroids, the most widely used drugs in the treatment of persistent asthma.

### **Adipose tissue**

What remains to be defined is how adipose tissue is indeed linked to asthma, especially when considering potential differences in adipose tissue at different sites. Adipose tissue can be

classified by its distribution, visceral, subcutaneous on the trunk, subcutaneous on the limbs, or ectopic. Visceral adipose tissue on the trunk is highly metabolically active,<sup>64</sup> while subcutaneous fat on the limbs appears less metabolically active.<sup>65</sup> In addition, visceral adipose tissue may be a more important source of adiponectin; subcutaneous fat may be the primary source of leptin.<sup>66,67</sup>

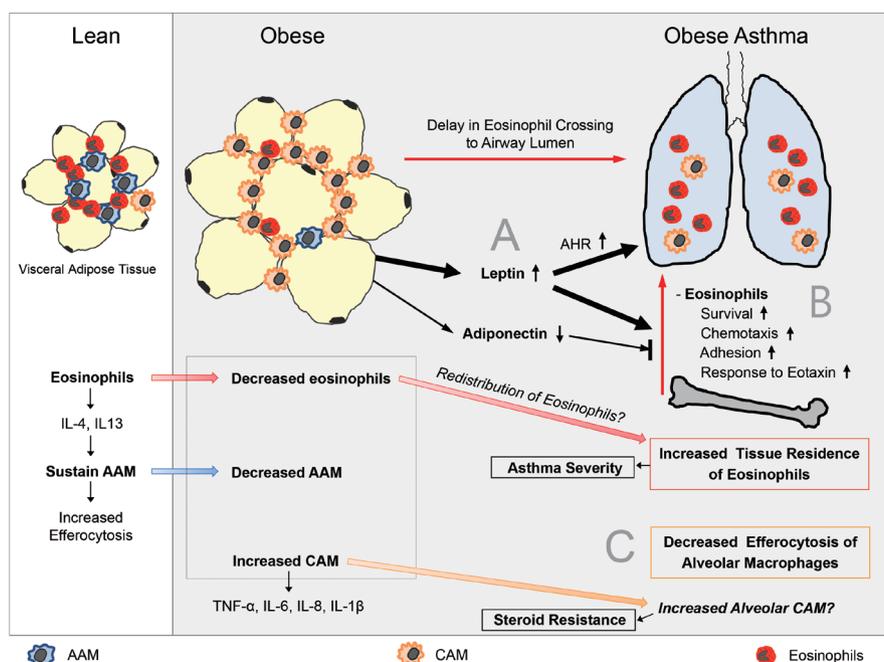
The hypothesis that different types of adipose tissue have different influences on the obesity-asthma link was tested in a population-based cohort.<sup>68</sup> The data showed that all types of adiposity and adiposity measures were associated with a higher risk of asthma, but this association was only demonstrated in non-atopic subjects. Recently, Sideleva *et al.*<sup>69</sup> examined the presence of inflammatory changes in adipose tissue and changes in the airways of obese asthmatics and obese controls. They showed that leptin expression and macrophage markers (CD68) were increased but the expression of adiponectin was decreased in visceral adipose tissue from asthmatics. In addition, airway epithelial cells from asthmatic patients had significantly higher expression levels of receptors for leptin and adiponectin. Interestingly, leptin expression in visceral adipose tissue was significantly correlated with AHR. They suggested that inflammation in visceral fat and the release of adipokines from visceral adipose tissue directly affected airway responsiveness, and, by association, the pathogenesis of asthma in obese individuals.

In visceral adipose tissue, eosinophils were shown to maintain alternatively activated macrophages in conjunction with glucose homeostasis.<sup>70</sup> Eosinophil migration into adipose tissue from lung and spleen was mediated by integrins and required IL-4 or IL-13 for reconstitution of alternatively activated macrophages. In addition, eosinophil counts in adipose tissue

were decreased in mice fed a high-fat diet and negatively correlated with body weight. Eosinophils were not reduced in lung, spleen, or bone marrow. The group subsequently showed that innate lymphoid type 2 cells, a recently characterized population of innate immune effector cells, have a role in sustaining eosinophilia and alternatively activated macrophages in adipose tissue.<sup>71</sup> Innate lymphoid type 2 cells expressing IL-5 and IL-13 were demonstrated in visceral adipose tissue.

## SUMMARY

It appears that the linking of obesity to asthma prevalence, severity, and response to conventional therapies, is only in its infancy, with associations that vary in strength across studies and discordant results between mouse and man. This does not suggest that the correlations do not exist or are unimportant, but highlights the need for more focused studies. Adding to the complexity is the growing recognition that asthma in obese patients is heterogeneous and dynamic, with many inter- and intra-patient variables. Even the investigations on the impact of weight loss on asthma reduction need careful scrutiny, especially beyond short-term evaluations. Studies have demonstrated that adipokines can regulate survival and recruitment of eosinophils and affect eosinophil localization with accumulation of eosinophils in peribronchial lung tissue but not in the airway lumen. In addition, impairment of efferocytosis by macrophages in obese asthmatics and immunological changes in adipose tissue may together play an important role in the mechanistic association of obesity with asthma. With the progress in research in obesity and the recognition of the role of site-specific adipose tissue alterations in immune-inflammatory pathways involving



**Figure.** Schematic representation of links between obesity and asthma. (A) Adipokines (leptin and adiponectin) can regulate survival, chemotaxis, and adhesion of eosinophils and modulate activation of macrophages in tissue. (B) Migration of eosinophils from adipose tissue to the lungs of obese subjects is suggested by findings of decreased eosinophil numbers in adipose tissue and increases in lung tissue. Adipokines may result in delayed transit to the airway lumen, resulting in the selective accumulation of eosinophils in peribronchial lung tissue. (C) Immunological changes in activated macrophages of obese individuals may play an important role in systemic and airway inflammation, perhaps explaining the association and even the cause of a glucocorticoid-insensitive asthma phenotype. AAM, alternatively activated macrophages; CAM, classically activated macrophages; AHR, airway hyperreactivity.

eosinophils, activated macrophages and innate lymphoid cells, advancements in understanding associations of obesity with asthma are becoming more fruitful (Figure).

## REFERENCES

- 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.
- Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obes Rev* 2013;14:222-31.
- 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;25:282-8.
- 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;122:507-11.e6.
- Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008;178:682-7.
- Camargo CA Jr, Sutherland ER, Bailey W, Castro M, Yancey SW, Emmett AH, Stempel DA. Effect of increased body mass index on asthma risk, impairment and response to asthma controller therapy in African Americans. *Curr Med Res Opin* 2010;26:1629-35.
- Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest* 2011;121:2111-7.
- Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005;115:911-9.
- Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, Nishimura H, Yoshimasa Y, Tanaka I, Mori T, Nakao K. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. *Nat Med* 1997;3:1029-33.
- Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, Lewin MJ. The stomach is a source of leptin. *Nature* 1998;394:790-3.
- Ruhl CE, Everhart JE. Leptin concentrations in the United States: relations with demographic and anthropometric measures. *Am J Clin Nutr* 2001;74:295-301.
- Bruno A, Pace E, Chanez P, Gras D, Vachier I, Chiappara G, La Guardia M, Gerbino S, Profita M, Gjomarkaj M. Leptin and leptin receptor expression in asthma. *J Allergy Clin Immunol* 2009;124:230-7, 237.e1-4.
- Vernooy JH, Drummen NE, van Suylen RJ, Cloots RH, Möller GM, Bracke KR, Zuyderduyn S, Dentener MA, Brusselle GG, Hiemstra PS, Wouters EF. Enhanced pulmonary leptin expression in patients with severe COPD and asymptomatic smokers. *Thorax* 2009;64:26-32.
- Bergen HT, Cherlet TC, Manuel P, Scott JE. Identification of leptin receptors in lung and isolated fetal type II cells. *Am J Respir Cell Mol Biol* 2002;27:71-7.
- 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.
- Guler N, Kırerlerli E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol* 2004;114:254-9.
- 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;20:81-8.
- Sood A, Ford ES, Camargo CA Jr. Association between leptin and asthma in adults. *Thorax* 2006;61:300-5.
- Sood A, Dawson BK, Eid W, Eagleton LE, Henkle JQ, Hopkins-Price P. Obesity is associated with bronchial hyper-responsiveness in women. *J Asthma* 2005;42:847-52.
- 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;8:12.
- Leão da Silva P, de Mello MT, Cheik NC, Sanches PL, Munhoz da Silveira Campos R, Carnier J, Inoue D, do Nascimento CM, Oyama LM, Tock L, Tufik S, Dâmaso AR. Reduction in the leptin concentration as a predictor of improvement in lung function in obese adolescents. *Obes Facts* 2012;5:806-20.
- Baek HS, Kim YD, Shin JH, Kim JH, Oh JW, Lee HB. Serum leptin and adiponectin levels correlate with exercise-induced bronchoconstriction in children with asthma. *Ann Allergy Asthma Immunol* 2011;107:14-21.
- Giouleka P, Papatheodorou G, Lyberopoulos P, Karakatsani A, Alchanatis M, Roussos C, Papiris S, Loukides S. Body mass index is associated with leukotriene inflammation in asthmatics. *Eur J Clin Invest* 2011;41:30-8.
- Sutherland TJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008;178:469-75.
- Assad N, Qualls C, Smith LJ, Arynchyn A, Thyagarajan B, Schuyler M, Jacobs DR Jr, Sood A. Body mass index is a stronger predictor than the metabolic syndrome for future asthma in women. The longitudinal CARDIA study. *Am J Respir Crit Care Med* 2013;188:319-26.
- Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *Allergy* 2007;62:1205-13.
- Ajuwon KM, Spurlock ME. Adiponectin inhibits LPS-induced NF-kappaB activation and IL-6 production and increases PPARgamma2 expression in adipocytes. *Am J Physiol Regul Integr Comp Physiol* 2005;288:R1220-5.
- Masaki T, Chiba S, Tatsukawa H, Yasuda T, Noguchi H, Seike M, Yoshimatsu H. Adiponectin protects LPS-induced liver injury through modulation of TNF-alpha in KK-Ay obese mice. *Hepatology* 2004;40:177-84.
- Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. *Biochem Biophys Res Commun* 2004;316:924-9.
- Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, Maeda K, Nagaretani H, Kishida K, Maeda N, Nagasawa A, Funahashi T, Matsuzawa Y. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. *Circulation* 2004;109:2046-9.
- Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochem Biophys Res Commun* 2004;323:630-5.
- Steffes MW, Gross MD, Schreiner PJ, Yu X, Hilner JE, Gingerich R, Jacobs DR Jr. Serum adiponectin in young adults--interactions with

- central adiposity, circulating levels of glucose, and insulin resistance: the CARDIA study. *Ann Epidemiol* 2004;14:492-8.
33. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;257:79-83.
  34. Bruun JM, Lihn AS, Verdich C, Pedersen SB, Toubro S, Astrup A, Richelsen B. Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. *Am J Physiol Endocrinol Metab* 2003;285:E527-33.
  35. Miller M, Cho JY, Pham A, Ramsdell J, Broide DH. Adiponectin and functional adiponectin receptor 1 are expressed by airway epithelial cells in chronic obstructive pulmonary disease. *J Immunol* 2009;182:684-91.
  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. Medoff BD, Okamoto Y, Leyton P, Weng M, Sandall BP, Raheer MJ, Kihara S, Bloch KD, Libby P, Luster AD. Adiponectin deficiency increases allergic airway inflammation and pulmonary vascular remodeling. *Am J Respir Cell Mol Biol* 2009;41:397-406.
  38. Conus S, Bruno A, Simon HU. Leptin is an eosinophil survival factor. *J Allergy Clin Immunol* 2005;116:1228-34.
  39. Grotta MB, Squebola-Cola DM, Toro AA, Ribeiro MA, Mazon SB, Ribeiro JD, Antunes E. Obesity increases eosinophil activity in asthmatic children and adolescents. *BMC Pulm Med* 2013;13:39.
  40. Kato H, Ueki S, Kamada R, Kihara J, Yamauchi Y, Suzuki T, Takeda M, Itoga M, Chihara M, Ito W, Kayaba H, Chihara J. Leptin has a priming effect on eotaxin-induced human eosinophil chemotaxis. *Int Arch Allergy Immunol* 2011;155:335-44.
  41. Yamamoto R, Ueki S, Moritoki Y, Kobayashi Y, Oyamada H, Konno Y, Tamaki M, Itoga M, Takeda M, Ito W, Chihara J. Adiponectin attenuates human eosinophil adhesion and chemotaxis: implications in allergic inflammation. *J Asthma* 2013;50:828-35.
  42. Lessard A, Turcotte H, Cormier Y, Boulet LP. Obesity and asthma: a specific phenotype? *Chest* 2008;134:317-23.
  43. Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ, Kerckmar CM, Visness CM, Matsui EC, Steinbach SF, Szefler SJ, Sorkness CA, Morgan WJ, Teach SJ, Gan VN. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol* 2010;125:584-92.
  44. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. *Eur Respir J* 2011;38:594-602.
  45. Telenga ED, Tideman SW, Kerstjens HA, Hacken NH, Timens W, Postma DS, van den Berge M. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012;67:1060-8.
  46. Jensen ME, Gibson PG, Collins CE, Wood LG. Airway and systemic inflammation in obese children with asthma. *Eur Respir J* 2013;42:1012-9.
  47. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, Bafadhel M, Singapuri A, Siddiqui S, Woods J, Herath A, Anderson IK, Bradding P, Green R, Kulkarni N, Pavord I, Marshall RP, Sousa AR, May RD, Wardlaw AJ, Brightling CE. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. *Am J Respir Crit Care Med* 2013;188:657-63.
  48. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. *Allergy* 2008;63:570-4.
  49. de Vries A, Hazlewood L, Fitch PM, Seckl JR, Foster P, Howie SE. High-fat feeding redirects cytokine responses and decreases allergic airway eosinophilia. *Clin Exp Allergy* 2009;39:731-9.
  50. Calixto MC, Lintomen L, Schenka A, Saad MJ, Zanesco A, Antunes E. Obesity enhances eosinophilic inflammation in a murine model of allergic asthma. *Br J Pharmacol* 2010;159:617-25.
  51. 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.
  52. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 2007;101:2240-7.
  53. Sutherland ER, Lehman EB, Teodorescu M, Wechsler ME; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Body mass index and phenotype in subjects with mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2009;123:1328-34.e1.
  54. Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J Immunol* 2000;164:6166-73.
  55. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 2004;25:677-86.
  56. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat Rev Immunol* 2005;5:953-64.
  57. McPhillips K, Janssen WJ, Ghosh M, Byrne A, Gardai S, Remigio L, Bratton DL, Kang JL, Henson P. TNF-alpha inhibits macrophage clearance of apoptotic cells via cytosolic phospholipase A2 and oxidant-dependent mechanisms. *J Immunol* 2007;178:8117-26.
  58. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, Bradding P, Brightling CE, Wardlaw AJ, Pavord ID. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med* 2006;354:697-708.
  59. Truyen E, Coteur L, Dilissen E, Overbergh L, Dupont LJ, Ceuppens JL, Bullens DM. Evaluation of airway inflammation by quantitative Th1/Th2 cytokine mRNA measurement in sputum of asthma patients. *Thorax* 2006;61:202-8.
  60. Goleva E, Hauk PJ, Hall CE, Liu AH, Riches DW, Martin RJ, Leung DY. Corticosteroid-resistant asthma is associated with classical antimicrobial activation of airway macrophages. *J Allergy Clin Immunol* 2008;122:550-9.e3.
  61. Hakonarson H, Bjornsdottir US, Halapi E, Bradfield J, Zink F, Mouy M, Helgadottir H, Gudmundsdottir AS, Andrason H, Adalsteinsdottir AE, Kristjansson K, Birkenis I, Arnason T, Andresdottir M, Gislason D, Gislason T, Gulcher JR, Stefansson K. Profiling of genes expressed in peripheral blood mononuclear cells predicts glucocorticoid sensitivity in asthma patients. *Proc Natl Acad Sci U S A* 2005;102:14789-94.
  62. Fernandez-Boyanapalli R, Goleva E, Kolakowski C, Min E, Day B, Leung DY, Riches DW, Bratton DL, Sutherland ER. Obesity impairs apoptotic cell clearance in asthma. *J Allergy Clin Immunol* 2013;131:1041-7, 1047.e1-3.
  63. Lugogo NL, Hollingsworth JW, Howell DL, Que LG, Francisco D, Church TD, Potts-Kant EN, Ingram JL, Wang Y, Jung SH, Kraft M. Alveolar macrophages from overweight/obese subjects with asthma demonstrate a proinflammatory phenotype. *Am J Respir Crit Care Med* 2012;186:404-11.

64. Bergman RN, Kim SP, Hsu IR, Catalano KJ, Chiu JD, Kabir M, Richey JM, Ader M. Abdominal obesity: role in the pathophysiology of metabolic disease and cardiovascular risk. *Am J Med* 2007;120:S3-8.
65. Dulloo AG, Jacquet J, Solinas G, Montani JP, Schutz Y. Body composition phenotypes in pathways to obesity and the metabolic syndrome. *Int J Obes (Lond)* 2010;34 Suppl 2:S4-17.
66. Swarbrick MM, Havel PJ. Physiological, pharmacological, and nutritional regulation of circulating adiponectin concentrations in humans. *Metab Syndr Relat Disord* 2008;6:87-102.
67. Montague CT, Prins JB, Sanders L, Digby JE, O'Rahilly S. Depot- and sex-specific differences in human leptin mRNA expression: implications for the control of regional fat distribution. *Diabetes* 1997;46:342-7.
68. Fenger RV, Gonzalez-Quintela A, Vidal C, Gude F, Husemoen LL, Aadahl M, Berg ND, Linneberg A. Exploring the obesity-asthma link: do all types of adiposity increase the risk of asthma? *Clin Exp Allergy* 2012;42:1237-45.
69. Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, Dienz O, Irvin CG, Dixon AE. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med* 2012;186:598-605.
70. Wu D, Molofsky AB, Liang HE, Ricardo-Gonzalez RR, Jouihan HA, Bando JK, Chawla A, Locksley RM. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 2011;332:243-7.
71. Molofsky AB, Nussbaum JC, Liang HE, Van Dyken SJ, Cheng LE, Mohapatra A, Chawla A, Locksley RM. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J Exp Med* 2013;210:535-49.