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Is There a Link Between Obesity and Asthma?

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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.[1] The prevalence of asthma is higher in obese than in lean adults[1,2] and obesity increases the incidence of asthma by 2.0- and 2.3-fold in children and adults, respectively.[2,3] Moreover, significant dose-dependent effects of elevated body mass index on asthma are observed.[1,2]

Obese asthmatic patients are often described as severe and poorly controlled[4,5] perhaps because they are less responsive to corticosteroids and exhibit a different (*e.g.*, less atopic) inflammatory phenotype.[6] Obesity is associated with chronic low-grade systemic inflammation that is thought to enhance systemic complications.[7] 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.[8] 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 impact 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.[9-11] Leptin and leptin receptors are expressed by human lung cells, including epithelial cells, type II pneumocytes, and macrophages.[12-14] 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.[15] 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.[16-19] Although data are lacking on the di-

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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,[20,21] and enhancement of airway hyperresponsiveness (AHR) including exercise-induced bronchoconstriction.[21,22] 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.[23] In contrast, a controlled observational study failed to show a significant obesity-by-asthma interaction although systemic inflammatory markers were higher in obese subjects.[24] 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.[25] A similar trend in women was shown in a second longitudinal study.[19]

Hersoug *et al.*[26] 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-α 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-α as well as nuclear factor-κB, and upregulates anti-inflammatory cytokines such as IL-10 and the IL-1 receptor antagonist.[27-31] Levels of adiponectin are reduced in obese subjects even though visceral adipose tissue is its main source.[32,33] This paradox may be explained by findings that macrophages produce IL-6 and TNF-α in adipose tissue which may directly inhibit the production of adiponectin.[34] Adiponectin and all binding receptors for adiponectin such as AdipoR1, AdipoR2, T-cadherin, and calreticulin are expressed on airway epithelial cells in the lung.[35]

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.[36] 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.[37]

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.[23]

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.[38] 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.[39] 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.[40] 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.*[41] 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.[42-47] Indeed, eosinophil numbers in BAL fluid or induced sputum were often lower in obese compared to non-obese subjects.[48-50] 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.[50] 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.[49] 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.[47] 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.*[45] 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 asthmatic patients may have a somewhat attenuated response to treatment with corticosteroids, findings consistent with the suggested severity of asthma in obese subjects.[5,51-53] 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.[44]

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-α, IL-1, IL-6, IL-8) that are crucial to innate immune responses against pathogens.[54-56] Classical activation is inhibited by Th2 cytokines which trigger "alternative" or "M2" program macrophages.[54-56] 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.[57] Inflammation in refractory asthma has also been associated with Th1 cytokines,[58,59] and M1 skewing of blood monocytes and alveolar macrophages has been documented in glucocorticoid-insensitive asthma.[60,61] Reduced clearance of dying cells by airway macrophages, efferocytosis, has been associated with more severe, glucocorticoid-insensitive asthma in obese asthmatics.[62] 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.[63]

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,[64] while subcutaneous fat on the limbs appears less metabolically active.[65] In addition, visceral adipose tissue may be a more important source of adiponectin; subcutaneous fat may be the primary source of leptin.[66,67]

The hypothesis that different types of adipose tissue have different influences on the obesity-asthma link was tested in a population-based cohort.[68] 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.*[69] 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.[70] 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.[71] 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

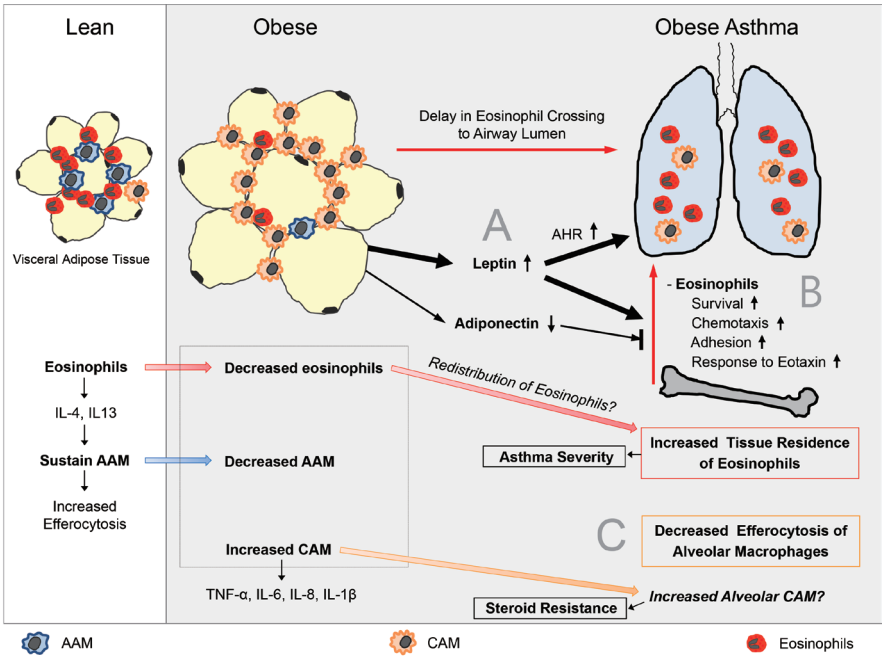

Figure. Schematic representation of links between obesity and asthma. (A) Adipokines (leptin and adiponectin) can regulate survival, chemotaxis, and adhesion of eosinophils and modulate activation of macrophages in tissue. (B) Migration of eosinophils from adipose tissue to the lungs of obese subjects 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.

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

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