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## Obesity-driven airway eosinophilia and neutrophilia in asthma

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### ABSTRACT

**Objective:** Asthma patients with comorbid obesity tend to have more severe, difficult-to-control asthma than lean asthma patients. This increase in asthma severity may be due, in part, to obesity-related adipokines, such as leptin, which contribute to airway hyperresponsiveness, sustained subclinical chronic inflammation, and treatment resistance. This narrative literature review aims to elucidate the differences in airway eosinophilia and neutrophilia profiles between asthma patients with and without obesity.

**Methods:** A PubMed search of full journal articles published between 1992 and 2024 was performed in April 2024 using the terms “asthma”, “tissue eosinophilia” and “obesity” combined with the Boolean operator “AND”. Articles detailing airway tissue eosinophilia and neutrophilia in asthma patients or mice were included. Only articles in English were included.

**Results:** To date, several studies have reported increased airway tissue eosinophilia in obese mouse asthma models (four studies) and in asthma patients with obesity (three studies). Airway tissue eosinophilia in asthma patients with obesity is driven by altered and elevated levels of adipokines, pro-inflammatory cytokines, and eosinophil-stimulating chemokines such as eotaxin. Leptin and eotaxin levels are increased in asthma with obesity and contribute to enhanced eosinophil recruitment, migration, adhesion to airway smooth muscles and fibroblasts, and reduced apoptosis.

**Conclusions:** Airway tissue eosinophilia is an important feature of obesity-associated asthma. Airway tissue eosinophilia is mainly driven by obesity-related homeostatic changes. These increased airway tissue eosinophils contribute to a more severe disease.

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Asthma; obesity; airway eosinophilia; cytokines

## Introduction

Asthma is the most common chronic lung disease in the United States, affecting approximately 8% of the population (1,2). Asthma is characterized by the inflammation and narrowing of small airways which causes cough, wheezing, shortness of breath and chest tightness (2). Cluster of differentiation 4-positive (CD4<sup>+</sup>) T-cells subsets, particularly T-helper 2 cells (TH2), plays a central role in the pathogenesis of asthma. TH2 cell activation leads to the secretion of inflammatory cytokines, notably interleukins-4, -5 and -13 (IL-4, IL-5 and IL-13) which participate in the recruitment of eosinophils, resulting in eosinophilic airway inflammation (3). Current asthma classifications distinguish between the predominantly eosinophil-driven inflammation subtype, defined as type-2 high (T2), and the non-eosinophilic subtype defined as non-type-2 (non-T2) (4). Non-T2 asthma

is characterized by the absence of eosinophilic inflammation. A feature of non-T2 asthma may include activation of T-helper 1 (TH1) and/or T-helper 17 (TH17) cells, and the subsequent recruitment of neutrophils in response to cytokines produced by the cell subsets. Non-T2 asthma is also sometimes characterized as paucigranulocytic (the absence of both eosinophilic and neutrophilic inflammation in the airways). Non-T2 asthma, by virtue of the lack of eosinophilic inflammation, is relatively unresponsive to corticosteroids (3).

Obesity, defined as a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, is recognized as a major risk factor for asthma (5). In the United States, the prevalence of asthma in lean adults is 7.1% versus 11.1% in adults with obesity, with 250,000 new asthma cases per year in the US related to obesity (5). Asthma patients with comorbid obesity tend to have more severe, difficult-to-control asthma (6), with increased daily

symptoms and poorer quality of life compared to lean asthma patients (7). Patients with obesity are less likely to achieve adequate control of their asthma with inhaled corticosteroids (ICSs) or with ICS in combination with a long acting beta agonist (LABA), due to increased production of inflammatory cytokines in obesity which decreases response to corticosteroids (8). Therefore, asthma with comorbid obesity was initially identified as a unique asthma phenotype. Asthma with comorbid obesity was found to be more prevalent in females with a late age of asthma onset (asthma onset  $\geq 12$  years of age) and absence of eosinophilic airway inflammation (Leicester classification) (9). The Severe Asthma Research Program (SARP) identified obesity-associated asthma as more prevalent in older women with late-onset non-atopic asthma, moderate reductions in forced expiratory volume in 1 s ( $FEV_1$ ), and recurrent oral corticosteroid use to treat exacerbations (10). However, more recent studies have identified two obesity-associated asthma phenotypes based on the immunologic signature. Early-onset (age of asthma onset  $< 12$  years of age) asthma with comorbid obesity is characterized by atopy, T2-driven, eosinophil-predominant airway inflammation. On the other hand, late-onset obesity-associated asthma predominates in females and is characterized by non-eosinophilic inflammation (11).

Increased obesity-related adipokines (cell signaling mediators released from adipose cells), such as leptin, contribute to airway hyperresponsiveness (AHR) and subclinical chronic inflammation, which is detectable in the blood of patients with obesity. This persistent systemic inflammation contributes to increased airway inflammation, asthma exacerbation frequency and reduced lung function (12). Adipokines play a central role in asthma pathogenesis and maintenance in patients with obesity. High leptin levels in obesity are associated with a decreased  $FEV_1$ , forced vital capacity (FVC) and ratio of  $FEV_1$  and FVC ( $FEV_1/FVC$ ) (13,14). Moreover, airway reactivity is related to the adipose tissue expression of leptin (15). As such, adipose tissue contributes to the maintenance of chronic inflammation through the secretion of adipokines and pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ). In contrast to lean patients with asthma, patients with asthma and comorbid obesity tend to have increased TH1 and TH17 cells in their airways at the expense of TH2 cells (16). Therefore, obesity-related asthma appears to be a more severe phenotype, associated with increased frequency of severe exacerbations requiring systemic corticosteroid and mechanical ventilation support (17). Eosinophils

have been studied in the setting of asthma as a potential treatment target. However, airway eosinophilia profiles differ in lean asthma patients compared to those with obesity. This narrative literature review aims to expose the differences in airway eosinophilia profiles in asthma patients with and without obesity.

## Methods

A PubMed search was performed in April 2024 using the terms “asthma”, “tissue eosinophilia” and “obesity” combined with the Boolean operator “AND”. The narrative literature search encompassed journal publication dates of 1992–2024. Full articles in English were included, with only abstracts and non-English articles excluded.

## Results and discussion

### *Airway inflammation in asthma patients with obesity*

#### *Eosinophils*

Asthma is a state of chronic airway inflammation, driven by CD4<sup>+</sup> TH2 cells. These cells secrete IL-5, which induces eosinophil recruitment by the airways. Recruited eosinophils produce IL-4 and IL-13 that contribute to airway smooth muscle (ASM) reactivity (18). In addition, eosinophils release inflammatory mediators such as eosinophil cationic protein, in part responsible for airway inflammation (19). Eosinophilic inflammation is defined by a count of greater than 2–3% sputum eosinophils (20). However, three studies have not found any correlation between obesity-associated asthma and sputum eosinophilic inflammation (21–23). Asthma patients with obesity exhibit altered T2 inflammation biomarkers such as decreased exhaled nitric oxide (NO), sputum eosinophils, and circulating eosinophils compared to lean asthma patients (11). Notably, Desai et al. demonstrated no correlation between sputum eosinophil counts and BMI in asthma patients (24). Furthermore, standard T2 inflammation markers – blood eosinophil counts, immunoglobulin E levels, and fractional exhaled nitric oxide (FeNO) – are reduced in individuals with asthma and concurrent obesity (25,26). Overweight asthma patients (BMI  $\geq 25$  kg/m<sup>2</sup> and  $< 30$  kg/m<sup>2</sup>) generally exhibit lower blood eosinophil counts compared to non-overweight counterparts, although blood eosinophil levels typically mirror sputum eosinophilia, indicative of eosinophilic airway inflammation (27).

On the other hand, eosinophilic airway inflammation is a feature of some patients with asthma and

comorbid obesity. In a cohort of Caucasian children aged 7–12 years of age, atopy correlated with increased BMI (28). However, when assessing the effect of asthma age of onset on the correlation between atopy and BMI, Holguin et al. found that, in a cohort of severe asthma patients, early-onset asthma patients with obesity, which comprised 38% of the cohort, had higher titers of IgE and more frequent atopic phenotypes than late-onset asthma patients with obesity (6). Therefore, airway eosinophilia is a feature of early-onset allergic asthma regardless of body mass.

### **Neutrophils**

Obesity-related asthma can also manifest as a non-allergic asthma phenotype that is characterized by low levels of airway eosinophils and increased levels of airway neutrophils (29). Neutrophilic asthma is defined by greater than 40–71% sputum neutrophils (20). In female asthma patients with obesity, sputum neutrophils are often increased and positively associated with BMI (30). BMI is positively correlated with blood neutrophil counts in females with asthma, but not in males with asthma (30). Asthma patients with obesity have higher blood and sputum neutrophil counts than lean asthma patients, but similar eosinophil counts (30). In addition, corticosteroids were associated with a significantly lesser increase of blood neutrophils in asthma patients with obesity versus lean patients, with no effect on eosinophils (30). In asthma patients with obesity undergoing bariatric surgery, airway neutrophilia decreases as a result of weight loss (19). Unlike allergic asthma, neutrophilic asthma is mainly driven by the TH1 and TH17 lymphocyte subsets, with interleukin-17 (IL-17) contributing to neutrophil recruitment in the lungs (31). Patients with obesity-associated asthma have increased levels of IL-17A and IL-17F in their airways, which is linked to asthma severity and steroid resistance (32). In obese mice, production of IL-17A is greatly increased in the lungs (33). Inversely, *Il17*-deficient obese mice did not develop obesity-associated AHR. IL-17A is produced by type 3 innate lymphoid cells (ILC3s). ILC3 clonal expansion is primarily driven by IL-1 $\beta$ , which also contributes to obesity-induced AHR (33). In human studies, circulating IL-17A levels are increased in women with obesity (34), and this increase in IL-17A may be driven by increased serum levels of leptin (35). Therefore, in asthma patients with obesity, neutrophilic inflammation characterized by increased BALF neutrophils appears to be driven by elevated IL-17 levels.

### **Mixed granulocytes**

Mixed granulocytic asthma is characterized by increase of both sputum eosinophils and neutrophil counts and is a severe phenotype of asthma (36). In obese mice with allergen-induced mixed granulocytic airway disease, increased macrophage accumulation in the lungs and bronchoalveolar lavage fluid (BALF) was observed, and these levels were resistant to dexamethasone compared to allergen-challenged lean mice (36,37). Patients with mixed granulocytic inflammation asthma are predominantly males, with a higher prevalence of obesity (38).

### **Tissue eosinophilia in asthma patients with obesity**

Asthma patients with T2 inflammation have significantly higher total airway wall, subepithelial and intraepithelial eosinophils. Lean asthma patients have higher density of eosinophils in the airway epithelium compared to non-asthma individuals, but no difference in subepithelial density (39). In normal circumstances, the airway epithelium allows leucocyte migration from the basal to the apical direction. In asthma patients with obesity, airway lumen eosinophilia is not increased as opposed to the observed increase in submucosal eosinophils (40). While airway intraepithelial eosinophilia was only associated with increased IL-5 and *IL5* mRNA in the sputum, submucosal eosinophilia was associated with increased IL-4, IL-5 and IL-13 in the sputum (39). Airway tissue eosinophil count is correlated with tissue biomarkers such as periostin, eotaxin-3 (encoded by *CCL26*) and thickening of the basement membrane with deposition of extracellular matrix proteins such as laminin and tenascin. In asthma, eosinophils bind to the extracellular membrane components, contributing to the thickening of the basement membrane through the release of transforming growth factor beta (TGF- $\beta$ ) and proteases (41). However, while increased *CCL26* levels, induced by IL-13 secretion by bronchial epithelial cells, is associated with a more severe asthma phenotype, *CCL26* levels did not correlate with tissue eosinophil count (42). Herder et al. showed that eotaxin, which is a marker of T2 activity, was the only biomarker that correlated with serum adiponectin levels (43). No correlation between sputum eosinophils and submucosal eosinophil counts in lean people with asthma has been reported (44–46), but a correlation between BALF and submucosal eosinophils was observed (46).

Three studies to date have observed increased airway tissue eosinophilia in asthma patients with obesity compared to lean asthma patients (Table 1). In severe asthma patients with obesity and elevated sputum IL-5, airway submucosal eosinophil counts were significantly higher than those in lean individuals with asthma. Indeed, Desai et al., found a positive correlation between the airway submucosal eosinophil number and BMI in patients with severe asthma and comorbid obesity (24). However, no differences were observed in sputum eosinophil and neutrophil counts in severe asthma when comparing lean, overweight and patients with obesity (24).

In patients with predominantly mild-to-moderate asthma, patients with obesity also had a significantly higher number of airway submucosal eosinophils and a lower number of sputum eosinophils compared with non-obese patients. Additionally, in patients with obesity, a significant positive association was found between the numbers of airway submucosal eosinophils and blood eosinophils, and between blood eosinophils and sputum eosinophils. Yet, no correlation was found between the count of airway submucosal eosinophils and sputum eosinophils in individuals with obesity. This study by van der Wiel et al. found that airway submucosal eosinophils were associated with a high BMI as well as a never-smoking status or fewer pack-year smoking history (47).

Using single photon emission computed tomography, Farahi et al. characterized pulmonary eosinophil uptake in asthma patients with obesity versus non-obese asthma patients and showed an enhanced pulmonary uptake of eosinophils in patients with obesity. However, this increase in eosinophil uptake was not caused by early retention since patients with obesity had a faster first pass mean transit time as

opposed to lean patients. Post-injection tissue eosinophil values were similar between both groups (48).

In contrast to those studies mentioned above, a single study reported that at 12 months following bariatric surgery, no change was observed in airway submucosal eosinophil counts in either asthma or non-asthma patients with obesity (49). The findings of this study suggest that the mechanisms directing airway tissue eosinophilia in asthma with comorbid obesity may be heterogeneous and more research is needed to understand the influence of weight loss on the processes governing airway tissue eosinophil retention, trafficking, and survival.

Composition of airway cytokines involved in eosinophil recruitment and activity also varies in asthma, with no difference in sputum *IL4* and *IL13* mRNA between asthma patients with and without obesity. However, sputum *IL5*, *IL17A* and interleukin-25 (*IL25*) mRNA are significantly higher in individuals with asthma and obesity. A positive correlation was found between sputum *IL5* RNA and BMI which may contribute to airway tissue eosinophilia (50). The significance of increased airway submucosal eosinophils was demonstrated by Wilson et al. who showed that an increased number of airway submucosal eosinophils are associated with an increased risk of epithelial damage. Airway submucosal eosinophils were also found to be markers of ASM infiltration by eosinophils and T lymphocytes (51). Therefore, at least three studies have found that asthma patients with obesity have increased airway tissue eosinophilia and higher levels of sputum IL-5, IL17A, and IL25 mRNA, correlating positively with BMI, while no significant differences have been observed in sputum eosinophil and neutrophil counts among lean, overweight, and obese asthma patients.

**Table 1.** Summary of studies on tissue eosinophilia in obese patients with asthma.

Study	Asthma severity	Obesity + asthma cohort		Comparator cohort		Correlations
		Number of patients	Median Submucosal eosinophils (cells/mm <sup>2</sup> )	Number of patients	Median Submucosal eosinophils (cells/mm <sup>2</sup> )	
Desai et al. (24)	Severe	55	19.4	48 overweight 28 lean 19 HC	8.8 8.2 4.6	Elevated sputum IL-5, low sputum eosinophils
van der Wiel et al. (47)	Mild-to-moderate	32	38	115 non-obese	19	Blood eosinophils ( $r = 0.515$ , $p = .01$ )
Farahi et al. (48)	Mostly severe	28	16.23	33 non-obese	8.58	Increased eosinophil migration to the lungs
Huisstede et al. (49)	Mild-to-moderate	8 obese asthma + BS (12 months follow-up)	3.0 at baseline 1.4 at 12-months after BS <sup>a</sup>	14 obese w/o asthma + BS (12 months follow-up)	1.3 at baseline 2.5 at 12-months after BS	No correlations

HC: healthy controls; w/o: without; BS: bariatric surgery.

<sup>a</sup>These patients served as their own controls compared to baseline;  $p = .889$ .

### Animal models of obesity and airway disease and lung tissue eosinophilia

Tissue eosinophilia in obese mice asthma models has been extensively studied (Table 2). In mouse models, obesity achieved by a high-fat diet (HFD) is associated with increased airway wall eosinophils whereas lean mice administered a low-fat diet (LFD) have increased eosinophils in BALF (52). In AKR mice fed a HFD and sensitized to ovalbumin (OVA), obesity increases susceptibility to allergic sensitization as compared to LFD-fed mice. High circulating levels of IL-5 were observed after OVA sensitization, with higher levels found in HFD-fed mice compared to LFD-fed mice. Consequently, increased eosinophilia was observed in the peribronchial and perivascular spaces of the lungs of HFD-fed mice compared to LFD-fed mice, with a clear correlation between pulmonary eosinophil count and body weight (53). When comparing BALF from both LFD- and HFD-fed mice with asthma, LFD-fed mice exhibited increased numbers of inflammatory cells including lymphocytes, eosinophils, and neutrophils. However, HFD-fed mice had higher eosinophil counts in BALF with a high number of lung eosinophils on histology compared to LFD-fed mice (54). In mouse studies, eotaxin (CCL11), an eosinophil chemoattractant, is increased in house dust mite (HDM) allergen-induced allergic airway disease in mice fed a HFD. Despite this increase in eotaxin, BAL fluid eosinophil levels were similar to LFD-fed mice. Yet, peribronchiolar eosinophils, eosinophil peroxidase protein level and lung tissue IL-5 were increased in HFD-fed mice. LFD-fed mice had higher levels of IL-33 and IL-1 $\beta$  in BALF (55).

Moreover, HFD-fed mice are characterized by increased serum leptin levels but decreased serum adiponectin levels. In mouse models, leptin, which is increased in obesity, increases airway reactivity and induces the development non-T2 asthma (56,57). Leptin is secreted by adipocytes, and its levels are

proportional to body fat mass (29). Conversely, weight loss strategies such as bariatric surgery, have been proven to decrease asthma burden and airway inflammation, in part, due to the decrease in systemic leptin concentration (58). Therefore, in patients with obesity, leptin contributes to the development of asthma.

OVA challenge in obese mice results in bone marrow stimulation and eosinophil hyperproduction and accumulation in the bone marrow and airway connective tissue. Obese sensitized mice have significantly greater peribronchiolar eosinophil inflow in at 48 h (approximately 5.3-fold) and 72 h (approximately 2.7-fold) in response to the OVA challenge than lean sensitized mice. BALF of obese OVA sensitized and challenged mice was characterized by increased levels of IL-5, eotaxin, TNF- $\alpha$  and interleukin-10 (IL-10), and a decreased number of eosinophils. Obesity was associated with delayed eosinophil transit through the airway epithelium and into the lumen. In fact, in comparison to the lean mice, obese mice BALF had a substantially reduced eosinophil counts 24 and 48 h after the OVA challenge ( $p < .05$ ). Conversely, after 72 h, the number of eosinophils in the BAL fluid of obese mice was approximately 65% greater ( $p < .05$ ) than that of the lean animals (59). Obese OVA sensitized and challenged mice had increased epithelial cell detachment, eosinophil and neutrophil infiltration, subepithelial fibrosis, elastic fiber fragmentation and mucous cell hyperplasia than control lean mice (60). Furthermore, in lean guinea pigs, eosinophil migration into the airway lumen occurs within 10 min of allergen exposure. This migration results in up to 63% and 73% decrease in tissue eosinophils, and clearance into the airway lumen after 30 and 60 min, respectively (61). Therefore, in animal models of obesity-associated allergen-induced airways disease, increased tissue eosinophilia and decreased BAL fluid eosinophils point to impaired transepithelial migration of eosinophils due to obesity-related alterations of airways tissue and sustained inflammation which favor eosinophil retention within the airway walls.

**Table 2.** Summary of studies on tissue eosinophilia in obese mice with asthma.

Study	Mice type	Obese asthma model	Control	Change in tissue eosinophils
Pinkerton et al. (52)	BALB/c	HFD-OVA	Control Chow	Increased
Dietze et al. (53)	AKR mice	HFD-OVA	LFD-OVA	Increased <sup>a</sup>
Everaere et al. (54)	C57BL/6J	HFD-HDM	LFD-HDM	Increased
Chandrasekaran et al. (55)	C57BL/6NJ	HFD-HDM	LFD-HDM	Increased

HFD: high-fat diet; LFD: low-fat diet; OVA: ovalbumin; HDM: house dust mite.

<sup>a</sup>Peribronchial and perivascular spaces.

### Potential effects of therapies on tissue eosinophilia

Mepolizumab, a monoclonal anti-IL-5 antibody, is associated with a significant decrease in bone marrow and peripheral blood eosinophils as well as a decrease in BALF eosinophils, compared to placebo at 4 weeks after the initial dose. In addition, mepolizumab reduced bronchial submucosal eosinophil counts by 55%. However, despite the decrease in numbers of eosinophils in the airway tissue, no reduction was

seen with regards to the eosinophil major basic protein staining intensity in the airway with treatment when compared to the placebo. Therefore, despite treatment, evidence of residual airway eosinophils with ongoing degranulation was observed (62). A possible explanation for this observation could be that cytokines other than IL-5 drive the development and sustainability of eosinophils in the tissue, such as interleukin-3 (IL-3) and GM-CSF (63). Also, the increased concentration of IL-5 in asthma causes a downregulation of its receptors on eosinophils making these cells less dependent on IL-5 for survival (62). Interestingly, however, increased IL-5 levels and tissue eosinophils in asthma patients with obesity, did not predict response to anti-IL-5 therapies (64).

In lean mice, after OVA challenge, an increase in lung tissue eosinophilia was noted and was followed by the development of airway eosinophilia. With continued daily budesonide treatment, lung tissue eosinophilia development was inhibited. Yet, this treatment resulted in increased airway eosinophils, enhancing eosinophils clearance through the lungs (65). Corticosteroids facilitate eosinophil migration from tissue to the lumen, without increasing their apoptosis, or affecting their entry into the lumen (66). However, in obese, HDM allergen-challenged mice with asthma, dexamethasone failed to control the symptoms and reduce the number of total cells found in BALF in comparison with lean, HDM allergen-challenged mice (37). Tissue eosinophils that infiltrate the airways can adhere to cells in the airway epithelium. The adherence is further amplified by INF- $\gamma$  and TNF- $\alpha$ , the latter acting through the upregulation of intercellular adhesion molecule 1 (ICAM-1). Yet, ICAM-1 inhibition does not block eosinophil adhesion. Dexamethasone, on the other hand, suppresses eosinophil adhesion to bronchial epithelial cells (67).

### **Potential mechanisms of eosinophil retention in the airway tissue**

#### **Adipokines: adiponectin and leptin**

In adiponectin (*Adipoq*)-deficient mice, allergic airways disease induced by OVA administration resulted in marked eosinophilic airway inflammation and perivascular eosinophils accumulation, compared to wild-type mice. Eosinophils were increased fivefold in the BAL fluid of *Adipoq*-deficient mice, as compared to wildtype. In *Adipoq*-deficient mice, *Ccl11* (eotaxin-1) and *Ccl24* (eotaxin-2) mRNAs encoding proteins that participate in cellular recruitment, were increased, whereas *Ccl8*, *Ifng*, *Il4*, *Il5*, *Il13*, *Il6*, and *Tnfa* mRNAs

did not differ between *Adipoq*-deficient mice and wildtype mice (68). Additionally, leptin upregulates ICAM-1 and integrin beta chain-2 (CD18), which play a role in the recruitment of eosinophils and their migration to inflammatory sites and suppresses intercellular adhesion molecule 3 (ICAM-3) and L-selectin without affecting CC motif chemokine receptor 3 (CCR3). These changes induce tissue eosinophilia in the lungs and airways by enhancing eosinophil migration and adhesion to the tissues. Leptin inhibition reverses leptin-mediated eosinophil survival and cell surface adhesion to tissue (69). Conus et al. demonstrated that human eosinophils express leptin receptors on their surface and these receptors delay eosinophil apoptosis in a concentration dependent manner. Leptin acts by delaying Bax cleavage and mitochondrial cytochrome C release in eosinophils (70). However, high-fat diet was shown to attenuate mouse lung eosinophilia, eotaxin and interleukin-15 (IL-15) in non-obese mice with mild to moderate allergic airway inflammation. These mice were heavier than those on control diet but were not obese, they were classified as pre-obese (71). In mice treated with adiponectin, airway responsiveness to intravenous methacholine, T2 cytokine levels, and BAL fluid cells were reduced after OVA exposure compared to control treatment. Similarly, a 30% fall in blood adiponectin levels was noted after the OVA challenge, due to a decrease in *Adipoq* mRNA expression in adipose tissue. Therefore, adiponectin appears to play a role in attenuating allergic airway inflammation and AHR, and blood adiponectin levels are lowered during pulmonary allergic responses (72).

#### **Eotaxin**

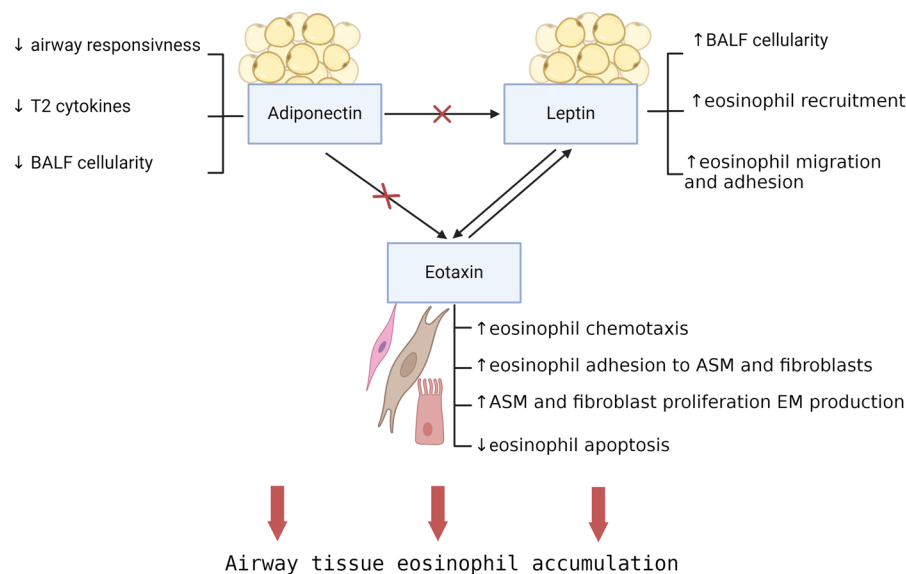
Eotaxin, is a chemokine with a high affinity for CCR3 that triggers eosinophilic chemotaxis. Eotaxin levels increase with obesity, and eotaxin mRNA is increased in the adipose tissue of obese mice (73). Johnston et al. demonstrated that *ob/ob* mice had significantly higher eotaxin-1 levels but lower eosinophil counts in BAL fluid compared to wild-type, which suggests a potential role for leptin in eosinophil accumulation (57). However, adiponectin reduces eotaxin-induced eosinophil functions, without modifying cellular lifespan, by decreasing calcium signaling. Therefore, increasing circulating adiponectin might be another treatment modality in asthma in general and in asthma with comorbid obesity in particular (74). Similarly, leptin can cause eosinophil migration in a dose-dependent manner, and leptin enhances chemotaxis response to eotaxin (69,70).

In asthma patients with obesity, eotaxin induces increased eosinophil chemotaxis in comparison with non-obese asthma individuals. Adhesion molecules such as ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) are important mediators of adhesion, with enhanced adhesion seen in patients with obesity (75). In the airway tissue, eosinophils strongly express  $\alpha_4\beta_1$  integrin and  $\alpha_M\beta_2$  integrin, which bind to VCAM-1 and ICAM-1 as well as other constituents of the extracellular membrane such as laminin, fibrin/fibrinogen and vitronectin (76). Delayed eosinophil migration through the airway and into the lumen could be explained, in part, by increased eosinophil adhesion to ASM cells or pulmonary fibroblasts and prolonged viability. Additionally, eosinophil adhesion to airway pulmonary structural cells enhances eosinophil viability. Eosinophils stimulate ASM, fibroblast proliferation and production of extracellular matrix components (77). Airway eosinophilia leads to more frequent exacerbations, which enhances airway remodeling (77). Thus, accumulation of eosinophils in the airway through adhesion to stromal cells increases the risk of airway remodeling and fixed airway obstruction in asthma. As obesity also contributes to fixed airway obstruction in asthma (78), airway tissue

eosinophilia may amplify airway remodeling in asthma patients with obesity. These potential mechanisms are summarized in Figure 1.

### Conclusions and future directions

To conclude this narrative literature review, airway tissue eosinophils appear to be an important feature of obesity-associated asthma. The available data suggest that the presence of eosinophils in the airway tissue is mainly driven by obesity-related homeostatic changes. The sustained chronic inflammation state promoted by leptin and adiponectin dysregulation may impede proper eosinophil migration through the airway tissue, leading to eosinophil accumulation in the airway wall. These stagnant eosinophils contribute to a more severe symptomatology, with an increased frequency of exacerbation and most importantly, resistance to the current therapies available, among which are corticosteroids and biologic therapies targeting T2 inflammation. Additional studies are needed to better understand molecular mechanisms involved in the eosinophil entrapment in the airway walls as well as potential treatment options that would target these mechanisms. Given that obesity-associated asthma is



**Figure 1.** Processes contributing to airway tissue eosinophilia in asthma with comorbid obesity. In lean patients with asthma, circulating adiponectin (secreted by adipose tissue) suppresses the secretion of leptin, a pro-inflammatory adipokine, leading to decreased airway responsiveness and reduced secretion of T2 cytokines and bronchoalveolar fluid (BALF) cellularity. In contrast, individuals with asthma and comorbid obesity have an altered balance of adipokines, with reduced levels of adiponectin and elevated secretion of leptin. Leptin promotes eosinophil recruitment from the bone marrow and enhances eosinophil migration to the airways, as well as eosinophil adhesion to airway smooth muscles (ASMs) and fibroblasts, thereby increasing BALF cellularity. Leptin also induces and amplifies the secretion of the potent eosinophil chemoattractant, eotaxin, by airway structural cells. Eotaxin, in turn, sustains leptin secretion and further enhances eosinophil chemotaxis, adhesion to ASM and fibroblasts, and eosinophil-induced ASM and fibroblast proliferation and extracellular matrix production. Additionally, eotaxin prevents eosinophil apoptosis. All of these processes may contribute to accumulation of eosinophils in airway tissue of patients with asthma and obesity.

a major problem, efforts should focus on finding suitable treatment options that would minimize airway remodeling associated with obesity and promote eosinophil clearance from within the airway wall.

### Author contributions

Study concept and design: JLI and JZ; drafting of the manuscript: JZ; critical revision of the manuscript: LGQ and JLI; and study supervision: JLI.

### Declaration of interest

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