Clinical Characteristics and Management Strategies for Adult Obese Asthma Patients

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Abstract: The rates of asthma and obesity are increasing concurrently in the United States. Epidemiologic studies demonstrate that the incidence of asthma increases with obesity. Furthermore, obese individuals have asthma that is more severe, harder to control, and resistant to standard medications. In fact, specific asthma-obesity phenotypes have been identified. Various pathophysiologic mechanisms, including mechanical, inflammatory, metabolic and microbiome-associated, are at play in promulgating the obese-asthma phenotypes. While standard asthma medications, such as inhaled corticosteroids and biologics, are currently used to treat obese asthmatics, they may have limited effectiveness. Targeting the underlying aberrant processes, such as addressing steroid resistance, microbiome, metabolic and weight loss approaches, may be helpful.

Keywords: asthma, obesity, body mass index, BMI

Introduction

The CDC reported an asthma prevalence of 8.0% in US adults based on the 2019 National Health Interview Survey (NHIS). Obesity is an important risk factor for asthma incidence and asthma morbidity in children and adults. In 2010, the obesity rate among adults with current asthma (38.8%) was significantly higher than the rate among adults without asthma (26.8%). Women have a higher asthma prevalence, and some studies indicate that the impact of obesity appears to be more profound in this population. Obese women have 6–7% higher prevalence of asthma than non-obese women. Obesity has been associated with the development of asthma, worsening asthma symptoms, and poor asthma control. Up to 60% of severe asthmatics are obese. This leads to increased medication use and hospitalizations.

A meta-analysis in 2007 of seven prospective studies involving more than 300,000 adults revealed that overweight and obese individuals have 50% increased risk of a new diagnosis of asthma. The odds ratio of incident asthma was 1.5 in overweight individuals with a body mass index (BMI) ≥25 and 1.9 in obese subjects (BMI > 30), compared to normal-weight individuals. Sex did not seem to be a significant modifier of overweight or obesity and asthma risk. The odds ratio of asthma over 1 year follow-up was 1.46 for males and 1.68 for women. The risk increases in non-allergic asthmatics. Effectively, 250,000 new cases of asthma per year in the United States are related to obesity.

The economic cost and overall morbidity of both asthma and obesity underlie the importance of understanding the asthma–obesity interaction. This review of the relationship between asthma and obesity describes clinical insights into the asthma-obesity phenotypes in adults, pathophysiology, effect of medical strategies and the role of surgical and non-surgical weight loss strategies.

Asthma Obesity Phenotypes

Obesity may have a role in the development, severity and control of asthma, but it remains to be established if obesity drives the development of asthma or is a confounder or comorbidity. Current understanding of asthma encompasses...
identification of multiple subgroups or phenotypes, based on clinical characteristics, triggers or general inflammatory processes and response to therapy. Several asthma-obese phenotypes in adults have been identified using unbiased analytical approaches. The origins of the asthma-obesity association and asthma-obesity phenotypes are complex and highly variable between individuals. Asthma associated with obesity may consist of a form of late-onset asthma induced by obesity or a form of early-onset asthma where pre-existing symptoms are aggravated by weight gain. There are differences between obese and non-obese asthmatics, but the studies also demonstrate that asthma phenotypes are heterogeneous among obese individuals, particularly regarding degree of control and response to inhaled corticosteroid (ICS) treatment.

Late-Onset Obese-Asthma Phenotype
Cluster analysis has identified a unique asthma-obesity phenotype predominantly in females with late age of onset and decreased Th2 inflammation that is refractory to conventional asthma treatment, particularly ICS. It is proposed to have little or no eosinophilic inflammation and is driven by changes in airway structure and function. Halder et al performed a cluster analysis in asthmatics followed in primary and secondary care settings. Patients followed in primary care had mild to moderate asthma. More females (81%) were found in the asthma-obesity group with later onset of asthma (mean age of onset 35.3 ± 19 yr.), less atopy and more neutrophilic inflammation compared to other groups. Fractional exhaled nitric oxide (FeNO) and percentage of sputum eosinophils were lower. Another obese cluster was found in the refractory/secondary care group, but with lower age of asthma onset (15.4±15.2 yr), more symptoms and more missed appointments. Analysis of patients in the NIH Severe Asthma Research Program (SARP) by Moore et al also identified an asthma-obesity cluster consisting mainly of older women (mean age, 50 years; range, 34–68 years) with the highest body mass index [BMI] (58% with BMI >30) and late-onset asthma (all older than 23 years of age), who were less likely to be atopic (64% with > one positive skin prick test). Despite a shorter reported duration of asthma, subjects in this cluster had decreased baseline pulmonary function (71% with FEV1 <80% predicted). These subjects reported complicated medical regimens, with more than half describing treatment with three or more asthma drugs (one of which was frequently high-dose ICS) and 17% received regular systemic corticosteroids. Despite this increased reliance on medications, they reported higher health-care utilization (especially the need for oral corticosteroid bursts) and daily asthma symptoms. Health-care utilization appeared out of proportion to the degree of airflow obstruction. The clinical characteristics of this group highlighted the relationship between obesity, level of asthma symptoms, and health-care utilization.

Early Onset Obese-Asthma Phenotype
Asthma complicated by obesity is usually early in onset with eosinophilic inflammation and high levels of serum IgE. Asthma control in these obese early-onset asthmatics from the SARP cohort was worse than in non-obese asthmatics, with a 3-fold increase in hospitalizations and a 6-fold increase in intensive care admissions compared to non-obese asthmatics. Obese early-onset asthmatics were more likely to have continuous wheeze, nocturnal asthma symptoms, lower asthma-related quality of life, and severe asthma compared to leaner early-onset asthmatics. This phenotype is associated with more severe airway obstruction and airway hyperresponsiveness compared to lean asthmatics with early-onset asthma. Increased eosinophilic inflammation, glucocorticoid insensitivity and physical inactivity may contribute to the development of this phenotype. Sutherland described clusters of obese versus non-obese asthmatic patients enrolled in clinical trials by the NHLBI Asthma Clinical Research Network. BMI was the most significant determinant of cluster membership (F = 57.1, p < 0.0001) followed by asthma symptoms (F = 44.8, p < 0.0001). Patients in the obese asthma clusters were classified as controlled (cluster 3) or uncontrolled (cluster 4). Disease onset in the uncontrolled obese asthmatics was significantly younger, 10.0 years compared to 16.1 years for the controlled obese asthmatics (p < 0.05). Uncontrolled obese asthmatics had persistently high symptom expression and persistently poor control. The uncontrolled obese asthmatics had the highest concentration of FeNO at 24.8 ppb and the greatest degree of airway hyperresponsiveness to methacholine among all the groups. Serum IgE and high sensitivity C-reactive protein (hsCRP) were elevated in obese asthmatics compared to non-obese asthmatics but did not differ significantly between obese asthma clusters. Obese individuals shared similar degrees of lung function impairment,
expression of adipokines, atopy and systemic inflammation (eg, hsCRP) compared to non-obese asthmatics. The patients in the uncontrolled asthma-obesity group had asthma of childhood onset, greater airway hyperresponsiveness to methacholine, greater eosinophilic airway inflammation, persistent symptoms and poor asthma control despite treatment with ICS. Glucocorticoid sensitivity was determined by expression of glucocorticoid receptor alpha (GCRα) and dexamethasone–induced expression of MAP kinase phosphatase-1 (MKP-1), an anti-inflammatory marker of glucocorticoid-induced activation. Obese asthmatics had a 25% lower expression of GCRα compared to non-obese asthmatics. Expression of GCRα in obese asthmatics was significantly and positively correlated with baseline log-transformed expression of MKP-1. A significant positive correlation between GCRα induction and dexamethasone induced MKP-1 expression was found in obese asthmatics. The insensitivity to glucocorticoids in obese asthmatics was directly associated with the degree of systemic inflammation, as indicated by an inverse association with hsCRP and GCRα. Increased production of obesity-related inflammatory cytokines may inhibit induction of MKP-1 by glucocorticoids. Enhanced glucocorticoid insensitivity was also demonstrated in patients with reduced serum 25(OH) vitamin D levels.

**Neutrophilic Obese-Asthma Phenotype**

Scott\cite{10,15} proposed a neutrophilic obese-asthma phenotype in a study demonstrating increased neutrophilic inflammation with distinct differences in males and females. A greater proportion of obese female asthmatics with late-onset asthma had neutrophilic asthma (airway neutrophils >61%) compared to nonobese asthmatic females (42.9% vs 16.2% p = 0.017). Levels of serum IL-6 were significantly higher in obese asthmatic females. When stratified by sex, a positive association between total plasma saturated fatty acids and sputum neutrophil percentages were found in asthmatic males (B-coefficient (95% CI) 0.108 (0.036–0.180); p = 0.004). Levels of monounsaturated fatty acids in males were associated with reduced neutrophilic inflammation. While obese and non-obese asthmatics had similar lung function, obese subjects were on a higher dose of ICS. Steroid resistance in obese patients may be related to neutrophilic inflammation. Obesity-induced increase in sputum neutrophils has been associated with increases in sputum IL-17. IL-17, which has been associated with poorer asthma control and lung function, may promote obesity–induced increase in sputum neutrophilia. Further studies are needed to better define this phenotype and establish its clinical characteristics.

**Pathophysiology**

While the different asthma phenotypes likely represent different endotypes, and certain pathophysiologic mechanisms may be more prominent in specific forms of obesity-related asthma, a high degree of overlap can be expected. The clinical presentation of obesity-associated asthma in a specific individual may have its underlying mechanisms based on a combination of mechanical, immunological, metabolic and microbiome processes. To better understand how obese asthmatics arrive at their clinical presentation, and ultimately what is the best approach to treatment, the underlying pathophysiologic mechanisms must be elucidated.

**Mechanical Effects**

In the late-onset non-atopic obese asthma phenotype, the pathophysiology seems to be mediated at least in part by mechanical changes; however, it may be possible that some of these changes are seen in early-onset obese asthmatics as well. In the obese state, the presence of excess fat both around the trunk and in the thoracic cavity can cause reduction in all lung volumes, but mostly in the functional residual capacity (FRC) and expiratory reserve volume (ERV). In fact, the reduction in FRC results in a decrease in ERV and flow.\cite{18} FEV1/FVC ratio is well preserved or increased in obesity, since both are affected to the same extent.\cite{19} As a result of these changes, obese patients are breathing at lower lung volumes, which in turn, leads to greater airway hyperresponsiveness and greater collapsibility of small airways.\cite{20} The heightened airway hyperresponsiveness is probably due to reduction in the tethering forces of the parenchyma on the attached airway, leading to airway narrowing and early closure of peripheral airways. This increases airway resistance, leads to limitations in expiratory flow when sitting, and even more so when supine.\cite{21} In fact, weight loss in late-onset non-atopic asthmatics improves airway hyperresponsiveness.\cite{22} Similarly, a small study demonstrated that bariatric surgery resulted in greater improvements in peripheral airway resistance, as captured by impulse oscillometry, but not by spirometry, in severely obese females.\cite{23} Furthermore, obesity is associated with greater airway compliance and increased airway wall...
thickness.\textsuperscript{24} Together, the change in airway mechanics leads to greater airway reactivity and air trapping with hyperinflation, and the mechanical changes may promote an inflammatory response in the airway as well.\textsuperscript{25} Alveolar ventilation can also be affected by obesity since airway closure prevents gas exchange, causing ventilation-perfusion mismatch.\textsuperscript{26} Distribution and degree of adiposity in the trunk, as opposed to other areas, may be a risk factor for why some obese individuals and not others develop late-onset non-atopic asthma with these mechanical changes.

**Inflammatory Changes**

For many phenotypes, asthma is an immunologically mediated disease. Furthermore, adipose tissue is an immunologically active organ, which contributes to the systemic inflammation of obesity. In addition to the adipocytes participating directly as secretors of immune mediators, up to 10% of non-adipose cells are lymphocytes, and even more can be macrophages.\textsuperscript{27} The combined immunologic effects of these two conditions contribute to the phenotypic manifestations in obese asthmatics.

**Effects on Th2 Disease**

Early-onset obese asthma is a Th2-high disease, with increased serum IgE levels, peripheral and tissue eosinophils, with associated increases in IL-4, IL-13 and IL-5. However, this pro-inflammatory Th2 state is mitigated by the immune suppression seen in obesity on several levels. CD4 function is decreased in obesity.\textsuperscript{28} There is Th1 skewing with the secretion of TNF-\(\alpha\), and Th2 functions are blunted in obesity.\textsuperscript{4} In obese individuals, Th1 and TH17 cells are increased relative to Th2 and regulatory T cells in adipose tissue.\textsuperscript{29} The downstream effects of this shift to Th1 in obesity are observed with respect to eosinophils. While submucosal airway eosinophils were increased in obese versus lean asthmatics, 30,\textsuperscript{31} sputum eosinophils are decreased in these patients.\textsuperscript{32,33} On the other hand, levels of IL-25, which is released by airway epithelial cells and activate innate lymphoid cells (ILC) to produce IL-13 and IL-5, are increased in obesity.\textsuperscript{34} Depending on the murine model of obesity and asthma, airway eosinophilia can be inhibited\textsuperscript{35} or promoted.\textsuperscript{36,37}

**Role of Adipokines**

The antagonistic adipokines, leptin and adiponectin, which are increased and decreased, respectively, in obesity, may also play a role in the pathophysiology of obesity-associated asthma. Leptin is associated with higher markers of atopy and airway hyperreactivity\textsuperscript{38} and increases proinflammatory cytokine TNF-\(\alpha\) and IL-6 expression from adipose tissue.\textsuperscript{39} Leptin is also associated with proliferation and survival of Th2 cells, ILC type 2 (ILC2) cells, as well as increased expression of type 2 cytokines, IL-4, IL-5 and IL-13.\textsuperscript{40} Leptin inhibits the activity and growth of regulatory T cells.\textsuperscript{41} In contrast, adiponectin, suppresses TNF-\(\alpha\) and IL-6,\textsuperscript{42} promotes expression of anti-inflammatory cytokines such as IL-10,\textsuperscript{43} and mitigates airway hyperreactivity and allergic airway inflammation.\textsuperscript{44} There are receptors for both leptin and adiponectin expressed on respiratory epithelial cells,\textsuperscript{22} therefore these adipokines likely have far-reaching effects in the lung.

**Role of Macrophages**

Adipose tissue macrophages play several roles in promoting the inflammatory state of obesity. As adipose tissue expands, adipocytes undergo hypoxia, resulting in necrosis that attracts pro-inflammatory macrophages. Along with the dramatic increase in the number of adipose tissue macrophages, a shift from M2 macrophages to M1 macrophages also occurs\textsuperscript{45} with resulting elaboration of the pro-inflammatory cytokines, TNF-\(\alpha\), IL-1\(\beta\) and IL-6.\textsuperscript{46,47} Together, the adipocytes and macrophages produce pro-inflammatory adipokines and other cytokines, creating the inflammatory state of obesity.\textsuperscript{22} This is reflected by increased C-reactive protein in obese asthmatic adults when compared to their normal weight counterparts.\textsuperscript{48,49} Macrophages also promote Th1 skewing of T cells,\textsuperscript{4} which mitigates any baseline Th2 inflammation.

Each of the cytokines perpetuated by adipose tissue macrophages can play a role in the pathophysiology of obesity-associated asthma. For example, in mice fed a high fat diet, IL-1\(\beta\) induces innate lymphoid cell type 3 (ILC3) in the lung to secrete IL-17A, which in turn, triggers airway inflammation and hyperresponsiveness. This pathway is dependent on NLRP3 (NLR family, pyrin domain containing 3) and IL-17A in mice. The elevated levels of ILC3 in the BAL of severe asthmatics suggest a similar pathway may be at play in humans.\textsuperscript{50} IL-17A is known to be a critical cytokine in non-atopic...
asthma. Serum IL-17A is elevated in obesity\textsuperscript{51} and sputum IL-17A is increased in obese versus lean asthmatics,\textsuperscript{34} suggesting that IL-17A may provide a link between obesity and asthma. Sputum neutrophils are elevated in obese asthmatic women,\textsuperscript{15,34,52} and an increase in sputum neutrophils is associated with elevated sputum IL-17, and with poor asthma control.\textsuperscript{53} Working in concert with IL-1β elaboration from adipose tissue, saturated fatty acids, cholesterol, cholesterol crystals and excess oxidative stress activate the NLRP-3 inflammasome, which acts on enzymes that activate IL-1β from its pro-form,\textsuperscript{54} which then promotes inflammation as above. NLRP3 is also critical in triggering inflammation related to diabetes associated with obesity.\textsuperscript{47}

IL-6 is a pro-inflammatory cytokine involved in the activation of neutrophils and their production of IL-17 in asthma.\textsuperscript{55} Adipose derived dendritic cells secrete IL-6, which then promotes Th17 differentiation\textsuperscript{56} and subsequent neutrophilic airway inflammation in asthma.\textsuperscript{57} Neutrophils are also the main source of IL-6 in the asthmatic airway.\textsuperscript{58} In a study involving two cohorts, non-severe and severe asthmatics, IL-6, which is a marker of obesity-related systemic inflammation and is elevated in metabolic syndrome, was associated with increasing BMI, hypertension, diabetes, severe asthma and poor asthma control as demonstrated by worse lung function and more exacerbations.\textsuperscript{59} In mice, IL-6 deficiency improves airway hyper-responsiveness and eosinophilic inflammation.\textsuperscript{60} Elevated IL-6 and signaling through the IL-6 trans signaling pathway characterizes a specific subset of asthmatics with frequent exacerbations, eosinophilia and submucosal macrophage and T cell infiltration.\textsuperscript{61}

TNF-α levels are elevated in patients with neutrophilic asthma\textsuperscript{62} and in patients with severe steroid-resistant asthma.\textsuperscript{63} TNF-α promotes broncho-constriction and airway hyperreactivity in murine models.\textsuperscript{64,65} Additionally, in an obese mouse model, TNF-α and macrophages were necessary for airway hyperreactivity.\textsuperscript{66} TNF signaling in ILC2s induces airway hyperreactivity in mice through the elaboration of multiple cytokines, IL-5, IL-6 and IL-13, among others.\textsuperscript{67} A small study suggested that elevated TNF-α levels could result in reduced surfactant A in obese asthmatics, which then impairs eosinophil resolution, resulting in an eosinophilic phenotype.\textsuperscript{68}

In addition to the heightened inflammation orchestrated by macrophages in adipose tissue, there is also macrophage dysfunction that may play a role in asthma. Efferocytosis, an anti-inflammatory process in which M2 macrophages remove apoptotic cells through phagocytosis, is blunted in obese asthmatics in a dose-dependent manner, and inversely associated with BMI and measures of oxidative stress. Conversely, efferocytosis is directly correlated with GR-α expression and MPK-1 induction by dexamethasone in peripheral blood mononuclear cells (PBMCs), markers of steroid responsiveness.\textsuperscript{49} Interestingly, efferocytosis is enhanced by glucocorticoids\textsuperscript{69} and leads to the production of anti-inflammatory mediators, such as IL-10, TGF-β and prostaglandin E2.\textsuperscript{70}

Innate lymphoid cells respond to intrinsic damage signals\textsuperscript{71} and also play a role in asthma pathogenesis. While ILC3s seem to perpetuate a non-atopic form of asthma, ILC2s produce IL5 and IL-13, which are critical in atopic asthma, and the levels of these cytokines are heightened in obese mice.\textsuperscript{72} The Th2 cytokines produced by ILC2 cells trigger M2 macrophages to produce IL-6, TGF-β and IL-10, which can have far reaching affects and contribute to the low-grade systemic inflammation of obesity.\textsuperscript{47}

The multitude of effects of obesity on systemic and airway inflammation, affecting both the Th1 and Th2 axes, create a complicated picture of how the immune system is involved in the pathophysiology of obesity-associated asthma.

**Role of Mitochondrial Dysfunction**

In addition to serving as the cell’s source of energy, mitochondria also sense dangers and signal threats. This results in release of reactive oxygen species and triggering the cellular danger response system. When this process occurs inappropriately, a proinflammatory cascade resulting in disease could occur. This oxidative stress reflects an imbalance between oxidative and nonoxidative processes.\textsuperscript{73}

Mitochondrial function is primarily determined by genetic and epigenetic factors, but other issues such as excess caloric and fat intake can modify function.\textsuperscript{74} The latter two can lead to oxidative stress which can cause cellular damage and insulin resistance.\textsuperscript{75} Mitochondrial dysfunction results in the increase in certain metabolites such as homocysteine and asymmetric dimethyl arginine (ADMA), which reduce arginine bioavailability, interferes with NO synthesis, and leads to oxonitrative stress in epithelial and vascular endothelial cells.\textsuperscript{76} This is the biochemical aberrancy seen with the metabolic syndrome.
Nitric oxide is a gaseous transmitter involved in smooth muscle relaxation, bronchodilation, mucociliary function, restoration of barrier dysfunction after wound repair, host defense and mitigation of airway inflammation, however excess levels are produced in atopic asthmatic airways due to effects of Th2 cytokines on inducible nitric oxide synthase.\textsuperscript{77} L-arginine is a substrate for NO synthase (NOS). Abnormalities in L-arginine, and therefore NO metabolism, can lead to NO uncoupling and oxidative stress (due to excess anion superoxide). NOS uncoupling is caused by deficiency of L-arginine, and results in preferential production of anion superoxide instead of NO. Arginase, an enzyme that metabolizes arginine, and results in arginine deficiency, is elevated in asthma and obesity.\textsuperscript{78} Asymmetric dimethyl arginine (ADMA), an inhibitor of NOS, is a product of regular protein degradation. ADMA can be further metabolized by dimethylarginine dimethylaminohydrolase (DDHA). As a result, low L-arginine and high ADMA, as reflected by the L-arginine/ADMA ratio in airway epithelial cells, can lead to reactive oxygen and nitrogen species, increasing the overall oxidative stress. The reduced ratio of L-arginine/ADMA reflects the elevated level of oxidative stress and reduced NO bioavailability in the airway that is promoted by both obesity and asthma and prevents normal bronchodilation of the airway.\textsuperscript{79}

Mitochondrial dysfunction has also been demonstrated in asthma\textsuperscript{80–82} and is associated with increased ADMA, which along with IL-4 in atopic asthma, induces oxonitrative stress and a cellular hypoxic response, and is associated with severe asthma in mice.\textsuperscript{83} ADMA and IL-4 together trigger further mitochondrial dysfunction.\textsuperscript{73} This sets up a vicious cycle where obesity and asthma can exacerbate each other.

The airways of obese asthmatics are NO deficient,\textsuperscript{78} reflecting loss of the physiologic function of NO. The mitochondria in airway epithelial cells of obese asthmatics undergo higher rates of respiration and produce more oxidants than those of their lean counterparts, but due to decreased nitric oxide bioavailability, nitric-oxide-dependent inhibition of mitochondrial respiration is prevented.\textsuperscript{84} The resulting production of reactive oxygen species can activate the inflammasome and cause mitochondrial dysfunction. In the airway, this results in higher levels of lipid peroxidases, such as 8-isoprostanes and 4-hydroxynonenal, which are elevated in asthma and obesity, and are associated with lower lung function and greater morbidity.\textsuperscript{85,86} Also, 13-S-hydroxyoctadecadienoic acid (13-S-HODE), a lipid metabolite derived from linoleic acid, drives severe asthma in an experimental model.\textsuperscript{87} The increase in oxidative stress, reflected by a reduced L-arginine/ADMA ratio is associated with reduced lung function and asthma QoL.\textsuperscript{88} The level of oxidative stress is associated with more severe asthma and is not mitigated by ICS. Levels of oxidative stress are associated with increased TGF-β1 expression, which in turn leads to airway remodeling that does not respond to ICS.\textsuperscript{89} Obese patients with severe late-onset asthma who had a lower L-arginine/ADMA ratio had more severe asthma symptoms, decreased exhaled nitric oxide and IgE levels.\textsuperscript{78,90} In addition, increased oxidative and nitrosative stress can result in post-translational modification and activation of histone deacetylase 2 (HDAC2) which is critical for the downstream effects of steroids in asthmatics, thus posing as the possible link between obese asthma and poor response to glucocorticoids.\textsuperscript{91,92} Promulgating the oxidative stress described above, there is also a decrease in the antioxidant defenses such as glutathione (major airway antioxidant) and superoxide dismutase. Overweight and obese children are more significantly affected by pollutants and irritants, especially nitrogen oxide, particulate matter\textsuperscript{93} and ozone,\textsuperscript{94} likely due to the dysfunctional pathways designed to manage oxidative stress.

**Microbiome, Diet and Nutrition**

**Microbiome**

The microbiome is the collective genome of the trillions of bacteria which live in the human intestinal tract. Early life establishment of the microbiome due to certain exposures such as early antibiotic use, Caesarean section, formula feeding and lack of exposure to animals, increase the risk of atopic asthma\textsuperscript{95} and obesity\textsuperscript{96} due to microbial dysbiosis. It is possible that the skewed microbiome leads to obesity, which in turn increases the risk of asthma through the mechanisms below.

The gut microbiome is less diverse in obese individuals compared to lean individuals.\textsuperscript{97} The more diverse the microbiome, the greater the mucosal immune defense.\textsuperscript{98} Obesity results in microbiome dysbiosis, reduced microbial diversity and an elevated ratio of *Firmicutes* to *Bacteroides*, which decreases with weight loss.\textsuperscript{99} The resulting decrease in mucosal immune defense, which is usually provided by a diverse microbiome, and the resultant increase in intestinal permeability may contribute to the increased level of serum LPS found in the plasma of obese individuals, the resulting
endotoxemia causing activation of nuclear factor kappa B (NF-κB) pathways, and increased expression of IL-6 and TNF-α. Treatment with antibiotics in mice mitigates the LPS endotoxemia and its associated inflammation, oxidative stress and body weight gain.

Some gut bacteria can convert polysaccharides into short chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which human intestinal enzymes cannot do. These SCFAs can be converted into ATP by the host. In mice, a high fiber/low fat diet increases the circulating levels of SCFA. SCFAs lead to enhanced hematopoiesis of dendritic cell (DC) precursors from bone marrow, but these DC have impaired ability to activate Th2 effector cells in the lung. With a high fiber diet, there was increased Bacteroides, leading to the increased synthesis of the short chain fatty acids, acetate, butyrate and propionate and reduced allergic inflammation in the lung. Propionate, in turn, is associated with reduced Th2 effector functions. Receptors for SCFAs can be found in non-gastrointestinal organs, suggesting that the effects of the microbiome can be as far-reaching as the lungs. SCFAs also lead to the increased development of anti-inflammatory colonic T cells.

In addition, SCFAs (propionate and butyrate) decrease LPS-induced NFκB activation and pro-inflammatory ROS and TNF-α production by neutrophils, likely by HDAC inhibition. In contrast, a low fiber/high fat diet induces dysbiosis, inhibits Treg function, and increases Th2 airway inflammation. In mice, a diet low in fiber was associated with increased airway eosinophils, Th2 cytokines, and IL-17A, and also promoted a gut microbiome with increased ratio of Firmicutes to Bacteroides. In contrast to SCFAs, levels of bile acids are increased in the setting of obesity-induced gut dysbiosis, and the levels of specific bile acids correlate with lung function decline.

The gut microbiome may affect obesity and asthma through mucosal communication between the intestinal and respiratory tracts when antigens are presented in the gut, and there are immunostimulatory or immunomodulatory effects in the lung. Composition of the gut microbiota may affect systemic levels of IL-17A, which are critical for neutrophilic recruitment. As noted above, Serum IL-17A is elevated in obesity and sputum IL-17A is increased in obese versus lean asthmatics, suggesting that IL-17A may provide a link between the microbiome, obesity and asthma.

The microbiome is not limited to the gut. The microbiome of the lung, mouth, nose and gut are different in asthmatics and obese individuals when compared to controls, but have similarities to each other, which demonstrates an additive effect in obese asthmatics, although the subjects in this study were mainly atopic. In severe asthmatics, the lung microbiome differs in obese and non-obese.

Diet and Nutrition

While the microbiome can clearly affect airway inflammation in obese asthmatics, components of the diet may provide a mechanism as well. Ingestion of a high fat meal acutely increases sputum neutrophilia, Toll like receptor 4 expression, and reduces bronchodilator response. A high fat diet is also associated with airway hyperresponsiveness in humans, although data are limited. A Western diet (high in palmitic acid) was associated with a greater inflammatory response than a Mediterranean diet (high oleic acid), as demonstrated with increased levels of TNF-α, IL-10, IL-18 and IL-1β. In animal models, a high fructose diet, even without obesity, is associated with elevated ADMA, reduced nitric oxide, and increased airway resistance. As discussed above, the abnormalities in NO metabolism are likely to play a role, through diet as well as obesity. Also, as noted above, in mice fed a high fat diet, airway hyperresponsiveness was associated with activity of ILC3, which produced IL-17A, as well as by IL-1β and NLRP3 inflammasome.

Fatty acids, which are elevated after a high fat meal, and in obese individuals, can activate TLR4, which then in turn, activates the NLRP3 inflammasome, which activates caspase-1 to cleave IL-1β making it functional. The relevance of this pathway is demonstrated by increased levels of IL-1β, TLR4 and NLRP3 in the lungs of obese asthmatics. In contrast, fruits and vegetables, which are high in antioxidants that can play a role in relieving the antioxidant stress of both asthma and obesity, have been demonstrated to improve asthma control.

Vitamin D deficiency is associated with excess weight as well as with asthma exacerbations, suggesting that it may play a role in the association between asthma and obesity. While many studies evaluating the role of vitamin D supplementation have not been performed, one short-term study did not show an improvement in control in asthmatics, but obese asthmatics were not specifically studied.
Comorbidities
Comorbidities such as metabolic syndrome, diabetes, hypertension, obstructive sleep apnea, depression and gastroesophageal reflux can not only lead to symptom misattribution, but also may play a role in exacerbating co-existent asthma in the obese.\textsuperscript{10} In post-menopausal women, the incidence of metabolic syndrome was similar among asthmatics and non-asthmatics, but the former had greater insulin resistance.\textsuperscript{121} Although the findings were not large in magnitude, patients with metabolic syndrome were found to have a greater degree of airway obstruction in several studies,\textsuperscript{122,123} and this was associated with their level of peripheral eosinophilia.\textsuperscript{122} In fact, patients with metabolic syndrome who underwent bariatric surgery did not have as much improvement in their asthma control as those who did not have metabolic syndrome, suggesting that the systemic inflammation due to underlying metabolic dysregulation, and not the excess weight, may be the culprit.\textsuperscript{124} High insulin levels, often associated with obesity, can trigger both centrally and peripherally mediated vagal-induced bronchoconstriction.\textsuperscript{125,126}

Genetics
Twin studies, family-based linkage studies and genome-wide association studies support the idea that obesity and asthma share a genetic basis.\textsuperscript{127–129} Furthermore, a common genomic inversion protects against both asthma and obesity.\textsuperscript{130}

Management
Inhaled Corticosteroids
The effectiveness of ICS has been well established in the management of asthma.\textsuperscript{131} The presence of obesity is also associated with a higher inflammatory state.\textsuperscript{115,132,133} When assessing pulmonary function, particularly FEV1, the treatment time from onset to peak FEV1 was longer in obese patients treated with ICS + LABA compared to patients with a normal BMI.\textsuperscript{134} A recent meta-analysis highlighted obese patients also had significantly lower FEV1 compared to normal BMI patients, and more likelihood to be on controller medications such as ICS, ICS + LABA, and oral corticosteroids.\textsuperscript{135} Studies have also noted a higher prevalence of higher ICS dose in obese patients compared to non-obese, reflective of asthma severity in this cohort.\textsuperscript{133,136–138} In addition, obesity not only was associated with a reduced response to ICS + LABA with regard to both FEV1 and FEV1/FVC ratio, but also was associated with a reduced response of ICS on FeNO.\textsuperscript{139}

When assessing asthma control, a similar relationship was described in a study that found asthma control days (ACD) also decreased significantly with increasing BMI in patients treated with beclomethasone.\textsuperscript{140} Obese patients also were less likely to achieve asthma control with ICS and ICS + LABA compared to non-obese patients and were 2.7 times less likely of achieving control compared to normal BMI patients.\textsuperscript{141} This further questions the effectiveness of ICS as a controller medication the higher the patient’s BMI.

The negative correlation between BMI and steroid effectiveness has been further studied in vitro, noting a blunted glucocorticoid induction of biomarker mitogen-activated protein kinase phosphatase-1 (MKP-1) in peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage (BAL) in obese asthmatics compared to non-obese patients.\textsuperscript{142} The reduction in (MKP-1) was also observed per unit increase in continuous BMI. In addition, baseline tumor necrosis factor (TNF)-\(\alpha\) expression was enhanced in both PBMCs and BAL in obese asthmatics, highlighting glucocorticoid insensitivity in this population.\textsuperscript{142}

Similar findings were described in another study specifically noting that IL-17 stimulation in obese adipose tissue leads to release of pro-inflammatory cytokines.\textsuperscript{143} In addition, glucocorticoid receptor GR-\(\alpha\)/GR-\(\beta\) ratio in adipose tissue responded differently to steroids in presence of IL-17A. It was further decreased in obese adipocytes whereas in lean adipocytes, IL-17A decreased GR-\(\alpha\)/GR-\(\beta\) ratio but not to the degree as in obese adipocytes, and did respond to steroids, thus leading to the conclusion that IL-17 can lead to steroid insensitivity via dysregulation of glucocorticoid receptors.\textsuperscript{143}

Obese patients not only have a higher inflammatory response compared to non-obese patients but are at risk for decreased forced vital capacity (FVC) and thus impairment in lung function secondary to a mechanical restrictive defect from distribution of body fat. In this scenario, ICS may not be as effective in obese patients who have decreased lung compliance secondary to body habitus.
Characterizing the inflammatory phenotype in obese patients can also be predictive of ICS response, where obese patients with eosinophilic inflammation are likelier to demonstrate effective response to ICS, whereas obese patients with neutrophilic inflammation and decreased FVC are unlikely and may worsen with increase in ICS.\textsuperscript{132,135} Similar association with ICS response and eosinophilic inflammation was also demonstrated in non-obese patients.\textsuperscript{144}

**Montelukast**

The role of leukotriene antagonists, particularly montelukast, in adult obese patients with asthma is limited. Obesity in general has been associated with an increased expression of 5-lipoxygenase pathway and also higher leukotriene production, which raised prospect of montelukast response in obese patients with asthma.\textsuperscript{145} In obese patients with an early onset atopic asthma, montelukast was an effective controller medication in improving asthma control test (ACT) score.\textsuperscript{146} Similarly, asthma control day (ACD) percentage also increased with increasing BMI in patients treated with montelukast.\textsuperscript{140} On the contrary, studies have noted ICS + LABA as well as ICS led to significantly higher forced expiratory volume in one second (FEV1), asthma symptom score, and less albuterol use, compared to montelukast alone, including when considering patient BMI.\textsuperscript{134,147}

**Biologics**

Since obesity-associated asthma includes at least two different phenotypes, the role of biologics may differ within the broad group of patients with the two conditions.

For patients with type 2 inflammation, a broad array of biologics has emerged over the past 20 years, particularly within the last 5 years. These include omalizumab, mepolizumab, reslizumab, dupilumab and benralizumab, in order of FDA approval for asthma. Omalizumab blocks type 2 inflammation through anti-IgE blockade. Mepolizumab and reslizumab block IL-5 directly, and benralizumab blocks the anti-IL-5 receptor, all leading to reduction of eosinophil counts. Dupilumab works uniquely by blocking both IL-4 and IL-13 through its antagonism of the IL4Rα. All of the aforementioned biologics block type 2 inflammation, and choice of the ideal agent depends on some key differentiating features such as perennial allergic sensitization, peripheral blood eosinophil count, FeNO, and comorbidities such as atopic dermatitis.

Given the heterogeneity of the mechanisms at play in the obesity-associated asthma phenotype, it is not surprising that biologics may not be equally effective in all patients with obesity. For those obese patients with neutrophilic asthma, or with alterations in the IL-17, IL-22 or IL-6 pathways the existing biologics are not applicable.\textsuperscript{6} Emerging biologics, such as the recently approved tezepelumab, which targets the upstream TSLP pathway, may have a role for obese asthmatics with non-type 2 inflammation. Tezepelumab improves the rate of exacerbations, irrespective of eosinophil count, which may suggest that it may be a promising tool in treatment of obese asthmatics with non-eosinophilic asthma.\textsuperscript{148} For those with type 2 inflammation, the biologics affecting the allergic pathways may be helpful, but not all biologics are equally effective.

As many of these biologics are relatively new, there are limited data on specific efficacy in obese patients, although there are some trends that have emerged over time. Biologics that require weight-based dosing, such as omalizumab and reslizumab, may have less benefit in obese asthmatics. In fact, a recent retrospective review of 340 patients with severe asthma on omalizumab, noted that obese patients, compared to those with normal weight, demonstrated worse outcomes. Specifically, obesity was significantly associated with a greater number of exacerbations, reduced ACT and worse asthma control as defined by the GINA guidelines, controlling for other confounders. Obese asthmatics on omalizumab were also less likely to have an improvement in FEV\textsubscript{1} after omalizumab compared to normal weight subjects.\textsuperscript{149} These findings are not surprising for a weight-based biologic; however, the lack of efficacy may extend beyond dosing issues. A major limitation of this study is the lack of data on possible neutrophilic airway disease in these subjects. Rather than a poor response to Xolair due to obesity, or due to inadequate dosing, it is possible that the subjects were not ideal candidates for Xolair, mechanistically.

In contrast, data for efficacy of dupilumab in obese asthmatics are more favorable. A post hoc analysis of the Phase 3 QUEST study of dupilumab demonstrated that in 1584 patients with elevated peripheral eosinophil counts and FeNO, there was a reduced annualized rate of asthma exacerbations, regardless of demographics. Demographics analyzed were gender, geographic region, age, and BMI. The greatest treatment effects were observed in those with higher blood eosinophil levels and FeNO.\textsuperscript{150}
Similarly, mepolizumab has favorable data for obese asthmatics. A 2021 post hoc meta-analysis of all of four phase IIb/III studies of mepolizumab, in which 32% of subjects reported obesity, there was a reduction in the rate of clinically significant exacerbations, health-related quality of life, and asthma control independent of comorbidities.151

Given the relatively recent use of biologics in the treatment of asthma, and the emerging understanding of obese asthma phenotypes, elucidation of the interaction between obesity and biologics is an important area for future research.

Microbiome and Metabolic Approaches
Addressing the microbiome and metabolic processes may be critical pathways to consider in the management and treatment of asthma associated with obesity. The microbiome comprises a great diversity of commensal bacteria species that colonize human body tissues and fluids, and dysbiosis is present in asthma and obesity. Aberrant metabolic processes are also present in the obese asthma phenotypes. Addressing the microbiome and metabolic dysfunction in a way that mitigates inflammation and obesity could help in the treatment of obese asthmatics.

Methods to ameliorate gut microbiome dysbiosis have been proposed in for obesity management and could have potential in the treatment of obese asthmatics. The use of probiotics is a common technique to modulate intestinal microbiota in the obese.96 Murine studies have shown probiotic use promotes weight loss115 and reduces inflammatory mediators152 which diminish obesity derived systemic inflammation. A high fiber diet, which increases SCFA concentrations, is another approach to alter the gut microbiota which could prove effective. A murine study showed high fiber diets correlated with reduced allergic airway responses, decreases in serum IgE and IL4 levels, and that this was mediated by SCFAs. In contrast, low fiber diets increased allergic airway disease.103 A recent NHANES survey demonstrated that a high fiber diet was associated with an increased odds of having asthma, supporting the role of the microbiome in human asthma.153

Several small human studies support the role of probiotics, which can alter the microbiome favorably, in asthmatic children. Use of probiotics improved lung function, rates of exacerbation and asthma control in children with asthma.154–156 However, studies in adults are lacking, and probiotics specifically in the obese-asthma phenotype has not been explored. The use of SCFA in the modulation of the unfavorable effects of obese-asthma dysbiosis is yet another potential avenue of investigation.

Bile acids, levels of which are also increased in obese asthmatics, and associated with poor lung function are another potential target. Murine studies with nitro-oleic acid (NO2-OA) demonstrate that treatment with this small molecule electrophile suppresses bile acid production, and is associated with improved lung function.107 A clinical trial investigating the use of NO2-OA in the treatment of obese asthmatics is underway.

The uncoupling of NO synthase mediated by asymmetric dimethyl arginine has been implicated in the deficiency of nitric oxide in obese asthmatics. The resulting oxidative stress is associated with poor asthma QoL and lung function.88 L-arginine is the substrate for NO synthase, and L-citrulline, a precursor of L-arginine, has been hypothesized as a potential treatment of obese asthmatics. In a small, proof-of-concept, open-label study, treatment with L-citrulline, improved asthma control and increased FeNO in obese asthmatics. Greater improvements in FEV1 were observed in patients with late-onset asthma.157 A larger, randomized clinical trial is necessary to confirm these findings. Other components of this pathway, such as arginase, which is upregulated in asthma, could be potential targets for treatment.

Weight Loss Approaches
Given the mechanical, inflammatory and metabolic consequences of obesity that play a role in modifying asthma, addressing obesity through weight loss, has the potential to be an effective approach. Obesity has numerous definitions, but the most prevalent definition is a body mass index (BMI) ≥30 kg/m². BMI classification further categorizes obesity into classes: Class I – 30.0 to 34.9 kg/m²; Class II – 35.0 to 39.9 kg/m²; Class III – ≥40 kg/m². A useful method of evaluating borderline obesity is by measuring abdominal obesity, which is defined as waist circumference ≥40 inches for males and ≥35 inches for females. As a result of the poor asthma control inherent to the obese asthmatic phenotype, exercise intolerance leads to a higher proportion of individuals who are inclined to sedentary lifestyles, and in turn insufficient physical activity tends to worsen obesity, and thus further exacerbating the negative effects. This, in turn, can be compounded by the recurrent or chronic use of systemic steroids, which can lead to further weight gain. Due to the
Numerous detrimental effects of comorbid asthma and obesity, weight loss is an attractive approach for optimizing asthma management in obese patients. Numerous studies have demonstrated significant improvements in both asthma symptomatic control and spirometric lung function with sufficient weight loss.\textsuperscript{5} Strategies for weight loss can be categorized into non-surgical and surgical weight loss approaches.

### Diet and Exercise Induced Weight Loss

Non-surgical weight loss, often referred to broadly as “lifestyle changes,” is frequently utilized as the initial approach for managing obesity. Lifestyle changes include numerous discrete weight loss interventions such as dieting, behavioral counseling and exercise regimens. A review of recent studies that focused on non-surgical weight loss in obese asthmatics revealed a wide range of weight loss strategies and program durations that were employed. Each specific weight loss intervention encompasses a variety of disparate methodologies; dieting can vary from strict calorie-restriction or meal replacement to more patient-centered approaches focusing on nutritional education. It has been hypothesized that simply transitioning from a typical western diet to a Mediterranean diet rich in anti-inflammatory nutrients could both be a viable method of diet while providing an additional benefit of reduced systemic inflammation.\textsuperscript{158}

A study of 22 massively obese asthmatics who were assigned to either a diet group or control group resulted in an approximately 15\% decrease in body weight on average over 3 months in the diet group. The diet group had significant improvements in asthma control, lung function and asthma quality of life compared to the control group.\textsuperscript{159} Özbey et al\textsuperscript{160} investigated a cohort of 55 obese adult asthmatics (median BMI 36.4) which were randomly assigned into a diet group or control group. The mean body weight in the diet group decreased significantly (−4.5 kg) and this correlated with significant improvements in asthma control, quality of life and pulmonary function in the diet group compared to the control group. Of note, patients with 5.0\% or greater weight loss had an even more pronounced improvement in FEV1 and FVC values, as well as ACT (Asthma Control Test) and AQLQ (Asthma Quality of Life Questionnaire) scores.\textsuperscript{160}

Studies have also indicated a combination of both diet and exercise shows a greater benefit, and so weight loss programs often utilize both approaches simultaneously. Freitas et al\textsuperscript{161} investigated a cohort of 55 grade II obese adults with asthma and found a significant difference between a weight loss program with both diet and exercise (consisting of aerobic and resistance muscle training) compared with a diet program with no exercise component. After 3 months, the diet and exercise group showed more significant clinical improvements as compared to the diet-only group, including: number of asthma symptom free days, lower prevalence of developing obstructive sleep apnea and less depressive symptoms.\textsuperscript{161}

### Surgical Weight Loss

In certain instances, more invasive surgical weight loss techniques may be the preferred option. Surgical weight loss procedures, also called bariatric surgery, are cited as the most effective intervention for producing sustained and significant weight loss. Bariatric surgeries include a variety of surgical techniques including Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch (BPD/DS), single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) and intragastric balloon. Differing from non-surgical weight loss techniques, bariatric procedures require candidates to meet strict prerequisite criteria. To qualify for bariatric surgery, patients must meet criteria defined as an adult with BMI ≥40 kg/m\textsuperscript{2} without comorbid illness or an adult with BMI 35.0 kg/m\textsuperscript{2} to 39.9 kg/m\textsuperscript{2} and at least one of the following: a serious comorbidity, impaired quality of life or disqualification from other surgeries due to obesity.\textsuperscript{162}

Studies on asthmatics after bariatric surgery have reported significant improvements in asthma control, airway reactivity, lung function and reduced asthma exacerbations.\textsuperscript{5} A meta-analysis of obese asthmatic adults that underwent bariatric surgery showed a significant increase in FEV1 and FVC after bariatric surgery.\textsuperscript{163} A recent retrospective review of 39 studies inclusive of 5185 patients compared non-surgical and surgical weight loss effects on asthma control. Overall, all methods of weight loss led to a reduction or cessation of asthma medication use, significant improvement in symptom scores, improvement in FEV1 and FVC; select studies showed a decrease in inflammatory mediators, improvement in airway hyperresponsiveness and decreased acute asthma-related health-care visits.\textsuperscript{164} However, the bariatric surgery cohort showed greater weight loss (22–36\%) compared with the non-surgical cohort (4.1–14.2\%), and
the bariatric surgery group also showed more consistent improvement with medication use, symptom scores, airway hyperresponsiveness, exacerbations and acute asthma-related health-care visits.\textsuperscript{164}

Available data indicate that all effective weight loss methods are likely to provide benefits in both objective and subjective metrics for obese asthmatic patients. However, weight loss of greater than 5% of total body weight is likely to produce a more significant improvement. Additionally, data suggest non-surgical approaches that combine diet and exercise offer a more significant clinical improvement than diet alone. Furthermore, surgical weight loss, although invasive and limited by compulsory selection criteria, may offer the greatest overall benefit for both overall weight loss potential and clinical asthma improvement. However, it should be noted that there are significant challenges to achieving effective and sustained weight loss. Less than 2% of eligible asthmatics undergo bariatric surgery,\textsuperscript{165} which suggests significant apprehension with elective invasive procedures. Non-surgical weight loss methods like low calorie diets can be difficult to maintain long term. Further investigations are needed to improve our understanding of the physiologic and pathologic effects of obesity on asthma, and to determine the most effective strategies for weight loss for individual patients.

**Conclusion**

With the rising rates of asthma and obesity in the United States, and the more severe phenotype of these patients, this population has the potential to pose a significant burden on the health-care system. Clarification of the different phenotypes and the underlying pathophysiologic mechanisms is critical for understanding the most effective approaches to treatment for this group of patients. The interplay of mechanical, inflammatory, microbiome and metabolic pathways creates a complicated picture of the obese asthma phenotypes. However, the pathways also provide potential targets for treatment. Although there are multiple categories of medication approved for the treatment of asthmatics, none of them is directed specifically towards obese asthmatics. While weight loss would be ideal in treating not only asthma among these patients, but also the multitude of other obesity-related comorbidities, future research is necessary to hone in on the pathophysiologic pathways contributing to the obese-asthma phenotypes, and the best approaches to treatment.

**Disclosure**

The authors report no conflicts of interest in this work.

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