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REVIEW

Gaps and Future Directions in Clinical Research on Obesity-Related Asthma

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ABSTRACT

Obesity is a major comorbidity for the development and worsening of asthma. It is associated with increased disease incidence, reduced response to inhaled and systemic steroids, increased asthma exacerbations, and poor disease control. Over the past two decades, we have learned that there are clinical asthma phenotypes associated with obesity, which have unique immune, inflammatory, and metabolic disease mechanisms. The objectives of this review are to provide a brief overview of the associations and gaps between these chronic inflammatory diseases and the role that traditional therapies have on treating patients with obesity-related asthma, and to describe new clinical research of therapeutic developments targeting mechanisms that are more specific to this patient population.

Keywords: Asthma; Obesity; Airway inflammation; Metabolic dysregulation

Key Summary Points

Obesity increases the risk of developing asthma and is associated with greater asthma morbidity and response to therapy.

There have been significant advancements in our understanding of how obesity impacts airway function and inflammation. Starting from initial epidemiological and clinical phenotyping studies, we have now moved into understanding that there are multiple metabolic and immune interaction pathways that culminate in greater disease severity.

This manuscript reviews several ongoing clinical trials specifically targeting mechanisms relevant to patients with obesity-related asthma, which involve mitochondrial—oxidative stress directed interventions, glucagon-like peptide-1 (GLP-1) agonists, nitrated fatty acids, and airway nitric oxide augmentation to name a few.

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INTRODUCTION

Obesity is a common condition experienced by many adults and its growing prevalence has often been referred to as a worldwide epidemic. Body mass index (BMI) is used to define someone as being *overweight* or *obese* with *overweight* being classified as someone with a BMI of 25 to $< 30\ kg/m^2$ and *obese* being classified as an individual with a BMI of $30.0\ kg/m^2$ or higher. Additionally, *severe obesity* is defined as an individual with a BMI of $40\ kg/m^2$ or higher. Prevalence of obesity in the United States has increased from 30.5% in 1999–2000 to 41.9% in 2020 [1]. Obesity is known to have profound effects on an individual's health and the role it plays in the pathogenesis and physiology of asthma has been brought into focus as the scope of the problem only continues to grow throughout the world. Prior studies have shown a dose-dependent relationship between obesity and asthma, with more obese patients having an increased risk of asthma incidence [2]. Because of this, obesity is recognized as a risk factor for the development of asthma and a significant phenotype comorbidity [3]. Obese patients who develop asthma later in life typically display lower levels of biomarkers related to T2-mediated inflammation [4]. Additionally, obese patients with asthma tend to have more severe disease and less efficacious response to conventional treatments in comparison to their lean counterparts [5]. The interplay between obesity and metabolism with asthma is a growing area of research, but there is still a significant amount of work to do in order to develop treatments that can benefit patients in this unique demographic. This review will provide a summary of obesity-related asthma, a review of the current and future directions of research in the field, and the potential impacts these discoveries may have for patients.

The aims of this review include:

- Provide an overview of the current impact of obesity and asthma on patients.
- Discuss current treatment modalities for obese patients with asthma.
- Review current and ongoing research, including ongoing clinical trials, for obese asthma.
- Examine the rationale behind current research strategies and discuss the impact these discoveries may have for patients.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DEFINITION AND IMPACT OF OBESITY-RELATED ASTHMA

Obesity-related asthma occurs when patients with a BMI $> 30\ kg/m^2$ have asthma. This cluster of patients is now recognized by the American Thoracic Society as a distinct phenotype due to the unique characteristics of the cohort [5]. Multiple prior studies have found that being overweight or obese increases the risk of an individual having asthma [2, 6] and a recent analysis of the International Severe Asthma Registry found that within a cohort of patients with severe asthma, 70.4% of patients were overweight or obese [7]. Patients with obesity-related asthma typically display a more severe disease process with less response to conventional asthma therapies in comparison to their lean counterparts. Prior studies have shown that patients with obesity-related asthma display more severe symptoms with increased medication use [8]. Additionally, patients with obesity-related asthma have also been found to have increased symptoms and decreased asthma-specific quality of life following hospital discharge despite control for other variables, including sex, age, race, smoking status, and socioeconomic status [9].

Patients with obesity-related asthma display a large amount of heterogeneity in expression of inflammatory and clinical biomarkers, which can make target identification for potential therapeutic interventions difficult. There is ongoing work looking at how metabolic derangements, cellular dysfunction, and alternate routes of inflammation relate to the pathogenesis of obesity-related asthma. These

topics will be discussed in detail later in this review.

CURRENT TREATMENTS AND MANAGEMENT STRATEGIES

Current management strategies for patients with obesity-related asthma rely heavily on maximal use of bronchodilators and inhaled corticosteroids despite less efficacy of these treatments for obese patients compared to their lean counterparts. Lifestyle modifications and biologic use are both being used more frequently in the treatment of this difficult to manage disease state, but targeted treatments for patients with obesity-related asthma are still lacking. Further research and development of disease-specific treatments are warranted to help patients improve asthma control and overall quality of life.

Conventional Therapies

Conventional asthma treatment plans involve short- and long-acting bronchodilators, leukotriene receptor antagonists, and inhaled corticosteroids. Presently, inhaled corticosteroids (ICS) have been the most studied conventional therapy for patients with asthma [10]. Unfortunately, patients with obesity-related asthma display reduced response to ICS therapy thought to be due to alternate pathways of inflammation at play in this disease process [11, 12]. Additionally, when compared to lean patients, obese patients are less likely to achieve good asthma control with the use of ICS in conjunction with long-acting beta agonists (LABA) [11]. There has been promise in the use of long-acting muscarinic agonist (LAMA) therapy for non-eosinophilic asthma, which is commonly observed among obese, late-onset asthmatics. A recent study looking at a post hoc analysis of data compiled from five phase III clinical trials of tiotropium found that it was effective as an add-on therapy in obese patients with moderate or severe asthma that were already on other asthma medications, including ICS and ICS-LABA [13–15]. Improvement in FEV1 was higher in patients on ICS monotherapy when tiotropium was added in comparison to patients on ICS-LABA at time of add-on therapy with tiotropium [13]. Due to this, it may be reasonable to add on LAMA therapy sooner in the typical treatment algorithm for patients with obesity-related asthma.

Insensitivity to Corticosteroids

Oral corticosteroids (OCS) are a mainstay of treatment in difficult-to-control asthma and asthma exacerbations. Unfortunately, patients with obesity-related asthma can display corticosteroid insensitivity. Prior studies looking at in vitro data have shown a reduced response to corticosteroids in obese patients with asthma [16]. This concept has been displayed in multiple studies where increasing BMI correlates with a reduced response to ICS therapy in patients with asthma [12, 17]. This may be attributed, in part, to the distinct inflammatory profile observed in obese patients with asthma; however, the exact cause has not been fully elucidated. Additionally, patients with obesity-related asthma have been shown to have a higher prevalence of alterations in corticosteroid pharmacokinetics, which can contribute to a reduced response to this class of medications [18]. The use of oral corticosteroids also carries risks, such as increased weight gain and metabolic derangements due to the side-effect profile of this class of medications, and may even adversely impair lung function in obese late-onset asthmatics with lower exhaled nitric oxide and T2 biomarkers [19]. Care should be taken to use systemic corticosteroids judiciously, as the weight gain associated with their use may exacerbate overall asthma control in this already challenging-to-manage population.

Use of Biologics

Newer biologic therapies have changed the landscape of asthma treatment for many patients with severe asthma. Unfortunately, the data on the use of biologic treatment in patients with obesity-related asthma are sparse. The majority of biologic therapies currently on the

market target mediators of T2 inflammation, including IL-4, IL-5, and their associated receptors. However, patients with obesity-related asthma often display low levels of the biomarkers associated with T2 asthma and instead have an inflammatory profile that has been classified as "T2-low" asthma with a less predominant eosinophilic phenotype [20].

There is ongoing work looking at the effectiveness of biologic therapies in this population. In one prospective study looking at obese patients with severe, persistent asthma, patients treated with omalizumab had an improvement in disease control and lung function along with reduced number of exacerbations and rescue medication use over a 12-month study period [21]. These data have been mixed though, with other investigations showing reducing efficacy of omalizumab in obese patients when compared to their lean counterparts [10, 22]. There are no randomized controlled trials looking at the effect of benralizumab in obese asthma, but a pooled post hoc analysis of two trials looking at the effect of benralizumab in severe asthma showed that patients with a BMI greater than 35 kg/m^2 were less likely to reduce exacerbation rates in comparison to patients with a BMI less than 35 kg/m^2 [23]. Tezepelumab is a new biologic that targets thymic stromal lymphopoietin (TSLP), a proinflammatory mediator high in the inflammatory cascade, with effect on T2- and non-T2-mediated inflammation. In a large, phase III, multicenter trial looking at the effect of tezepelumab on asthma control for individuals with severe, uncontrolled asthma, patients on tezepelumab had a reduction in exacerbation frequency in comparison to control subjects, regardless of peripheral eosinophil count [24]. While there are no large trials looking at the effect of tezepelumab in patients with obesity-related asthma, its use is promising for patients in this population due to its broad effects on T2 and non-T2 inflammation. Additional research is needed to better understand the effects of targeted biologic treatment on obese patients with severe, persistent asthma.

Lifestyle Interventions

While the detailed inflammatory mechanisms at play for obesity-related asthma have not been fully elucidated, the relationship between weight loss and improved asthma control is well established. Obese patients with asthma undergoing bariatric surgery were noted to have a significant reduction in BMI following surgical intervention with BMI of 51.4 ± 9.7 kg/m^2 dropping to 37.5 ± 7.8 kg/m^2 after 12 months [25]. These patients saw a statistically and clinically significant improvement in asthma control and quality-of-life scores and reported using less short-acting B-agonists at a 12-month follow-up visit [25]. Patients also displayed less response to methacholine following weight loss, relaying less airway smooth muscle hyperreactivity after BMI reduction [25]. This finding was replicated in a study looking at online weight loss interventions for obese patients with poorly controlled asthma. Patients participating in the weight loss program that were able to lose at least 5% of their initial weight displayed significant improvements in their asthma-related quality of life and reduced asthma symptoms [26]. Due to these positive findings, weight loss is often recommended for patients with obesity-related asthma as part of a multifaceted treatment strategy for this difficult to control disease process.

OVERVIEW OF CURRENT AND ONGOING RESEARCH—CLINICAL TRIALS/INTERVENTIONAL STUDIES

The ATS's first official workshop report on obesity and asthma was published more than a decade ago [5]. It outlined important questions remaining unanswered, including the understanding of the natural history of asthma in the obese through well-phenotyped longitudinal studies, investigating the role of comorbidities such as insulin resistance or metabolic syndrome, and determining the effects of obesity on innate and adaptive immunity. A second

ATS workshop on metabolic dysregulation in obesity provided additional key questions focusing on the role of mitochondrial dysfunction and how various metabolic influences on immune response in asthma phenotypes and endotypes contribute to the development of novel treatments for inflammatory lung diseases [27].

We have learned considerably since the publication of these documents and have answered several of the originally proposed questions related to obesity and asthma. For example, we now know that patients with obesity-related asthma experience more frequent exacerbations and show a reduced response to ICS compared to their lean counterparts. Additionally, obesity-related asthma contains a multitude of phenotypes, including obesity complicating any asthma phenotype or a predominantly female, late-onset, and low-T2 phenotype [19]. Insulin resistance and/or metabolic syndrome are metabolic dysregulations that can synergistically or independently worsen asthma morbidity [28, 29].

Mechanistically, obese subjects with asthma have abnormal airway mechanics and have been linked to increased T1 polarization, greater Th17 activation, and elevated IL-6 levels [30–33]. This, in turn, is associated with increased exacerbation risk. IL-1β and NLRP3 are upregulated in the airways of patients with obesity-related asthma and acutely increase after saturated fat ingestion [32]. In addition to innate and adaptive immune changes, there are important metabolic dysregulations in the airway epithelium of obese patients with asthma, including mitochondrial dysfunction and inducible nitric oxide synthase (NOS2) uncoupling, which lowers nitric oxide (NO) bioavailability while worsening airway oxidative stress [34].

Moving forward, clinical research studies on obesity-related asthma need to determine whether intervening on these specific mechanisms can improve clinical outcomes. This is a critical step in developing phenotype-driven treatments for this often difficult-to-treat patient population.

To illustrate how ongoing clinical studies are filling in knowledge gaps, we have compiled and summarized ongoing or recently completed studies in *clinicaltrials.gov* that have specific mechanistic-driven interventions to treat obese subjects with asthma. There are currently 45 registered clinical trials with specific interventions for this patient population. Of these, 56% are completed and 30% are recruiting or not yet recruiting. Studies range from behavioral and lifestyle modifications to weight loss surgical interventions, and drugs trials. For this paper, we focused on drug interventions that targeted different mechanisms underlying the obese asthma pathophysiology. For a current list of clinical trials evaluating interventions in patients with obesity and asthma, please see Table 1.

CURRENT AND FUTURE RESEARCH

Research looking at the unique pathways involved in the inflammation experienced by patients with obesity-related asthma is ongoing and covers a broad array of mechanisms due to the complex nature of the disease process. No targeted therapies currently exist for this population of patients, but therapeutic targets related to manipulation of metabolism and regulation of associated pathways have shown promise for future drug targets. Additional research is required to help identify possible therapeutics for patients in the future.

Mitochondrial Dysfunction and Related Therapies

The role of mitochondria and their function or dysfunction is a topic of interest in many disease states, and asthma is no exception. Mitochondria play an important role in cell structure and function and are vital in maintaining the balance between beneficial and harmful processes for the cell [35]. Prior investigation has shown altered mitochondrial structure and function can influence downstream disease processes in asthma [35, 36]. There is ongoing work looking at the basis for mitochondrial dysfunction in different cell types in the lung as well as investigation into whether mitochondrial dysfunction is a cause or consequence of

Table 1 Current clinical trials evaluating interventions in patients with concurrent asthma and obesity

Study name	NCT number	Intervention	Population	Outcome	Status
Effects of vitamin D supplementation in adolescents with asthma, obesity and vitamin D deficiency	NCT05431920	Dietary supplement: vitamin D# (25-hydroxy vitamin D)	Adolescents (12–17 years) with non-allergic asthma, obesity (BMI greater than percentile 95 for age and sex) and insufficiency/ deficiency of vitamin D (< 30 ng/ml)	Primary Evaluation of the effects of vitamin D supplementation daily during 3 months on asthma symptoms Secondary Evaluation of the effects of vitamin D supplementation daily during 3 months on the incidence of asthmatic crisis Other Evaluation of the effects of vitamin D supplementation daily during 3 months on lung function Evaluation of the effects of vitamin D supplementation daily during 3 months on IL-17A inflammatory biomarker	Recruiting
Vitamin D oral replacement in asthma	NCT03686150	Dietary supplement: vitamin D3 oral regimen	Children and adolescents (6–17 years) with physician-diagnosed asthma, BMI greater or equal to percentile 85 to age and sex, and serum levels of vitamin D 10 ng/ml less than 30 ng/ml at screening visit	Primary Evaluation of the best dosing of vitamin D supplementation based on PK analysis Evaluation of the optimal dosing of vitamin D supplementation based on the analysis of part 1 data and PK analysis Proportion of the participants in part 2 who achieve vitamin D levels equal or greater than 40 ng/ml	Completed

Table 1 continued

Study name	NCT number	Intervention	Population	Outcome	Status
Glucagon-like peptide-1 receptor agonist in the treatment of adult, obesity-related, symptomatic asthma (GATA-3)	NCT05254314	Drug: semaglutide pen injector 2.4 mg weekly Other: placebo	Adults (18 years and older) with obesity (BMI greater than 30 kg/m^2), history of physician-diagnosed, persistent (determined by the requirement of at least medium-dose inhaled corticosteroid or more) and symptomatic (ACQ 6 score equal or greater than 1.5 at enrollment time) asthma	Primary Efficacy of semaglutide on asthma control in individuals with symptoms, persistent asthma, and obesity; based on ACQ-7 score Impact of semaglutide on the serum levels of periostin in subjects with symptomatic, persistent asthma and obesity Secondary Impact on semaglutide on weight loss over time Efficacy of semaglutide once weekly on asthma control questionnaire-6 score in obese subjects with symptomatic and persistent asthma Elucidate the maximal dose of semaglutide tolerated by obese patients with persistent asthma Incidence of semaglutide treatment-related adverse effects in obese patients with asthma The changes in exhaled nitric oxide from baseline after 12 weeks of semaglutide treatment The changes in periostin serum levels from baseline after 12 weeks of semaglutide treatment	Not yet recruiting

Table 1 continued

Study name	NCT number	Intervention	Population	Outcome	Status
PrecISE (precision interventions for severe and/or exacerbation-prone asthma) network study	NCT04129931	Drug: MCT Drug: clazakizumab Drug: Broncho-Vaxom Drug: imatinib mesylate Drug: cavosonstat Other: placebo	Children and adults (12 years and older) with baseline poor or uncontrolled asthma and no change in asthma medications over the last 2 months and that currently use medium- or high-dose inhaled corticosteroids plus an additional asthma controller/biologic	Primary FEV1 percent predicted. Assessed prior to bronchodilator administration and measured at 16 weeks after the start of the treatment Asthma symptom control assessed via the ACQ-6 at 16 weeks after the start of the treatment CompEx events, which include exacerbations and deterioration events, assessed over 16 weeks after the start of the treatment Secondary FVC assessed prior to bronchodilator administration measured 16 weeks after the start of treatment FEV1 assessed after bronchodilator administration measured 16 weeks after the start of treatment Time to first exacerbation assessed over 16 weeks of treatment Symptom free days assessed over 16 weeks of treatment Asthma free days assessed over 16 weeks of treatment Healthcare utilization (i.e., asthma-specific emergency department visits, hospital admissions and ICU admissions)	Recruiting

Table 1 continued

Study name	NCT number	Intervention	Population	Outcome	Status
MitoQ for the Treatment of Metabolic Dysfunction in Asthma	NCT04026711	Drug: mitoquinol Drug: placebo oral tablet	Adults (18 years and older) with poorly controlled asthma and obesity defined as a BMI $\geq$ 30 kg/m^2	Primary Change in airway reactivity to methacholine through study completion and at 12 weeks Secondary Change in serum, sputum, and nasal lavage 8-isoprostanes through study completion and at 12 weeks Change in sputum cell counts through study completion and at 12 weeks Asthma symptom control assessment via the ACT through study completion and at 12 weeks Adherence to treatment measured by pill counts Marks AQLQ score through study completion and at 12 weeks ASUI results through study completion and at 12 weeks Lung function measured by FEV1 through study completion and at 12 weeks Lung function measured by FVC through study completion and at 12 weeks Change in lung impedance measured by forced oscillation through study completion and at 12 weeks Adverse effects assessed at each study visit through study completion and at 12 weeks	Recruiting

Table 1 continued

Study name	NCT number	Intervention	Population	Outcome	Status
Supplementing L-citrulline to overweight late asthma oNset phenotypes (SANDIA)	NCT03885245	Drug: L-citrulline Drug: matching placebo	Adults (18 to 65 years) with physician-diagnosed asthma with onset at 12 years or older with a BMI $\geq$ 30 kg/m^2	Primary Change in ACQ through study completion and up to 32 weeks to determine L-citrulline efficacy Change in ACT through study completion and up to 32 weeks to determine L-citrulline efficacy	Recruiting
Anti-inflammatory lipid mediators in asthma lipid anti-inflammatory mediators in asthma	NCT03762395	Drug: CXA-10 Drug: matching placebo	Adults (18 to 65 years) with a BMI $\geq$ 30 kg/m^2, with physician-diagnosed asthma and regular treatment with ICS, LABA and/or LAMA for at least 3 months	Primary Change in bronchial hyperresponsiveness assessed by methacholine challenge dose per spirometry through study completion and up to 18 weeks to determine CXA-10 efficacy Change in pre-bronchodilator FEV1 per spirometry to assess the efficacy of CXA-10	Active, not recruiting
Trial of roflumilast in asthma management (TRIM)	NCT03532490	Drug: roflumilast 500 mcg oral tablet Drug: placebo oral capsule	Adults (18 years old and older) with a BMI $\geq$ 30 kg/m^2 and a physician diagnosis of poorly controlled asthma	Primary Change in ACT after 24 weeks of treatment Secondary Changes in body weight during the duration of the study	Completed
Increased lung volume as controller therapy for asthma	NCT02953431	Device: CPAP	Adults (18–65 years) with a BMI $\geq$ 30 kg/m^2, physician-diagnosed asthma, serum levels of IgE $<$ 100 IU/ml, and a PC20 to methacholine $<$ 16 mg/ml	Primary Change in lung impedance in response to methacholine measured by forced oscillation Secondary Change in FEV1 and FVC during the duration of the study Change in asthma control in response to methacholine during the duration of the study	Recruiting

Table 1 continued

Study name	NCT number	Intervention	Population	Outcome	Status
Asthma L-citrulline pilot study	NCT02943161	Dietary supplement: L-citrulline	Adults (18–70 years) with a BMI $\geq$ 30 kg/m, physician-diagnosed asthma treated with controller medications for 4 weeks or longer, no smoking during the last year or a smoking history of $\leq$ 10 pack years and a V1 eNO $\leq$ 30 ppb	Primary Change in eNO levels before and after treatment with open label L-citrulline at 15 g/day after 2 weeks of treatment Secondary Change in plasma L-arginine/ADMA ratio before and after 2 weeks of treatment with L-citrulline at 15 g/day Other Change in ACQ scores after 2 weeks of treatment	Completed
PEEP as rescue therapy for asthmatics with elevated BMI	NCT02696980	Device: positive expiratory pressure	Adults (18 years and older) with a BMI $\geq$ 30 kg/m^2, an asthma diagnosis after 18 years of age, a PC20 to methacholine $<$ 16 mg/ml, and a serum level of IgE $<$ 100 IU/ml	Primary Change in respiratory impedance immediately before and after PEEP, patients will be expose to two levels of PEEP (PEEP 0 and PEEP 10) during and after methacholine, changes in respiratory impedance will be compared Secondary Change in respiratory symptoms immediately before and after PEEP, patients will be expose to two levels of PEEP (PEEP 0 and PEEP 10) during and after methacholine, changes in respiratory symptoms will be compared	Completed

Table 1 continued

Study name	NCT number	Intervention	Population	Outcome	Status
Antioxidant therapy in lean and obese asthmatics	NCT01317563	Dietary supplement: vitamins A, E, C, and selenium Dietary supplement: placebo	Patients (12–25 years) with physician-diagnosed persistent asthma on daily controller therapy, a FEV1 $\geq$ 60% predicted and lung responsiveness ($\geq$ 12% bronchodilator reversibility or PC20 MCT $\leq$ 16 mg/ml)	Primary Change in ACQ after 6 weeks of treatment Secondary Change in ASUI after 6 weeks of treatment Change in FEV1 after 6 weeks of treatment	Completed

BMI body mass index, *PK* pharmacokinetic, *ACQ* Asthma Control Questionnaire, *MCT* medium-chain triglycerides, *FEV1* forced expiratory volume in 1 s, *CompEx* composite exacerbation, *FVC* forced vital capacity, *ICU* intensive care unit, *ACT* asthma control test, *AQLQ* Asthma Quality of Life Questionnaire, *ASUI* Asthma Symptom Utility Index, *ICS* inhaled corticosteroids, *LABA* long-acting beta agonists, *LAMA* long-acting muscarinic antagonists, *PC20* provocative concentration resulting in 20% decrease in FEV1, *V1 eNO* visit 1 exhaled nitric oxide, *eNO* exhaled nitric oxide, *PEEP* positive end-expiratory pressure

lung disease. One aspect of mitochondrial function being studied is the distribution and movement of mitochondria in relation to other organelles and how this affects downstream signaling and inflammation. For example, the interactions between mitochondria and the endoplasmic reticulum or the sarcoplasmic reticulum can result in alterations of cytoplasmic and luminal calcium levels that can go on to affect protein regulation within the alveolar epithelium and airway smooth muscle [35, 37]. This has been shown to be altered in the presence of inflammatory cytokines with decreased mitochondrial movement when human airway smooth muscle cells are exposed to TNFα and altered calcium buffering in the presence of TNFα and IL-13 [37, 38]. These alterations in calcium buffering may play a role in the increased contractility and hyperresponsiveness seen within the airway smooth muscle of patients with asthma, but additional research is required to fully examine this pathway.

Another mechanism of mitochondrial dysfunction in asthma currently being investigated is the role of maintenance of appropriate metabolic processes and reactive oxygen species (ROS). The mitochondria are the site of the electron transport chain, which produces energy for the cell in the form of adenosine triphosphate (ATP) along with ROS that can go on to act as signalers that activate proinflammatory pathways [39]. Prior work by Winnica et al. has shown that isolated bronchial epithelial cells and platelets from obese patients with asthma show increased levels of glycolysis, basal and maximal respiration, and oxidative stress when compared to lean patients with asthma and health controls [40]. Additionally, cigarette smoke has been found to increase ROS generation within airway smooth muscle cells and airway epithelial cells exposed to ragweed pollen extract demonstrate increased production of ROS, particularly if pre-existing mitochondrial dysfunction is present at time of exposure [41, 42]. Prior work by Zifa et al. has identified mitochondrial polymorphisms present in patients with asthma in comparison to healthy controls, which may play a role in the interplay between environmental exposure and asthma development and/or severity [43].

Compared to lean patients with asthma, those that are obese have evidence for dysfunctional airway epithelial mitochondria, including greater rates of basal mitochondrial ROS production and increased glycolytic and respiratory rates [40]. These changes can profoundly impact cell homeostasis and activate downstream inflammatory pathways, contributing to airway inflammation and bronchial hyperreactivity. An ongoing pilot clinical trial (NCT04026711) is randomizing 40 obese adults with asthma to mitoquinone, a novel mitochondrial antioxidant (MitoQ), vs. placebo for 12 weeks, with the primary outcomes being methacholine responsiveness and asthma control. Secondary outcomes of this trial include exhaled 8-isoprostanes and lung function. Mitoquinone has been shown to reduce leptin-mediated mitochondrial ROS production as well as NLRP3 and caspase-1 expression in bronchial epithelial cells (BEAS 2B). This study will determine if, by reducing mitochondrial oxidative stress and downstream inflammation, MitoQ lessens obesity-mediated airway reactivity [44]. While the exact mechanisms of mitochondrial dysfunction are still being elucidated, it is clear that they play a role in the pathogenesis of obesity-related asthma. Additional research is required to better understand these pathways to help identify possible therapeutic targets.

Glycemic Management-Derived Therapies

Multiple prior studies have established the connection between metabolic syndrome and asthma and asthma symptoms [29, 45]. Poor glycemic control, having a diabetes diagnosis, and hyperinsulinemia have all been independently associated with increased asthma morbidity in association with obesity or independently from it. The use of metformin and glucagon-like peptide-1 receptor agonists have been linked to lower rates of asthma exacerbations [46, 47]. These studies suggest that diabetes treatments can have positive health effects in patients with asthma by improving glycemic control or through additional anti-inflammatory mechanisms. To this effect, the Glucagon-Like Peptide-1 Receptor Agonist in the Treatment of Adult, Obesity-Related, Symptomatic Asthma (GATA-3) study will randomize 100 adult subjects with poorly controlled obesity-related asthma to 2.4 mg of semaglutide weekly vs. placebo for 12 weeks. The primary outcome of the study will be asthma control and secondary outcomes will include exhaled nitric oxide, periostin, and adverse outcomes.

Endogenous Nitrated Fatty Acids—Signaling Electrophiles

Nitrated fatty acids are endogenous mediators that are formed through enzymatic and non-enzymatic processes. These compounds exert broad pleiotropic anti-inflammatory effects though key posttranslational modifications of Cys residues in proteins such as NfkB/p65, Keap1/Nrf2, PPARg and xanthine oxidase [48]. Conjugated linolenic acid, which shares some of the same pharmacological effects, reduced methacholine responsiveness in asthmatics without noticeable changes in airway inflammatory biomarkers [49]. A new study, Lipid Inflammatory Mediators in Asthma (LIMA), is randomizing patients with poorly controlled obesity-related asthma to CXA-10 (10-nitro-octadec-9-enoic acid) versus placebo, to determine the clinical efficacy of this compound in reducing methacholine responsiveness (primary outcome) and its impact on asthma control, lung function, and airway epithelial gene expression changes. The trial will also determine CXA-10's effect on bile salt metabolism (glycocholic acid and glycoursodeoxycholic acid) and gut dysbiosis and its relation to the study outcomes [50].

Increasing Nitric Oxide Airway Bioavailability

Obese patients with asthma have been found to have lower levels of fractional exhaled nitric oxide (FeNO) when compared to their lean counterparts [51]. Rather than reflecting less T2-mediated airway inflammation, less FeNO may be partly related to airway epithelial nitric oxide synthase (NOS2) uncoupling. When this occurs,

this enzyme preferentially produces anion superoxide instead of nitric oxide (NO), therefore contributing to airway oxidative stress, which is known to be greater in patients with obesity-related asthma [52]. Additional studies have shown that in non-obese patients with asthma, increased FeNO was associated with wheezing and atopy, while obese patients with asthma demonstrated lower levels of FeNO and were more likely to report wheezing [53]. These findings support the idea that obese patients with asthma represent a distinct phenotype of asthma, which has also been demonstrated from data in the Severe Asthma Research Program [4]. Ongoing investigation is being performed to determine how the inflammatory profile seen in obese patients with asthma can be modified to increase bioavailability of NO.

Nitric oxide synthase enzymes use oxygen and L-arginine to produce NO and L-citrulline, which can then go on to be recycled back into L-arginine [54]. The lower levels of FeNO observed in obese patients with asthma may be due in part to a metabolic imbalance with lower L-arginine levels and higher concentrations of asymmetric dimethyl arginine (ADMA), an endogenous NOS inhibitor, as these can cause NOS uncoupling with subsequent reactive oxygen species formation in lieu of NO synthesis [55]. L-Citrulline, a semi-essential amino acid, is converted into L-arginine in airway epithelial cells, recoupling NOS2 and preventing ADMA-mediated oxidative stress [34]. In a pilot proof-of-concept study of patients with poorly controlled obesity-related asthma, administration of 15 g of L-citrulline daily for 2 weeks increased airway NO bioavailability and the L-arginine/ADMA ratio while improving asthma control and increasing lung function [55]. To further determine the clinical efficacy of L-citrulline, the Supplementing L-citrulline to Overweight Late Asthma oNset Phenotypes, or SANDIA Trial, (NCT03885245), is a phase II randomized cross over study that will randomize patients with poorly controlled obesity-related asthma with normal baseline FeNO levels to either placebo or L-citrulline 15 g daily for 7 weeks. The primary outcome of the study is methacholine responsiveness; secondary outcomes include FeNO levels and lung function. Approximately half the participants will undergo bronchoscopy to evaluate L-citrulline's related changes in airway epithelial cell transcriptomics and to test whether L-citrulline increases nitrosoglutathione (GSNO), which is an endogenous bronchodilator [56].

Anti-IL6 Therapy

Obesity is well known to induce low-grade systemic inflammation that can affect multiple organs, including the lungs. Immune cells, including macrophages, are recruited to white abdominal adipose tissue (WAT). In obese WAT, there is an increase in M1-polarized macrophages, which produce inflammatory cytokines like TNF ∝ and IL-6 [57]. In individuals with asthma, having a larger visceral fat area has been associated with higher IL-6 and IL-8 levels in sputum [58]. Cross-sectional data from the Severe Asthma Research Program showed that patients with asthma that displayed higher levels of IL-6 had higher BMIs in comparison to patients with lower levels of IL-6 [30]. Moreover, obese subjects with high IL-6 levels were more likely to have lower FEV1 percent-predicted values and a history of more frequent asthma exacerbations [30]. A subsequent longitudinal study showed a linear association between plasma IL-6 levels with the predicted number of asthma exacerbations. In fact, for each pg/ml in baseline IL-6 levels, there was a corresponding 10% increase in the asthma exacerbation incidence risk ratio ($p = 0.008$) after adjusting for potential confounders [59]. Taken together, these data suggest that in patients with obesity-related asthma, IL-6 plays a potential causative role mediating greater asthma morbidity. To this effect, the NIH network Precision Interventions for Severe and/or Exacerbation-Prone Asthma (PRECISE Trial, NCT 04129931) is currently enrolling 600 patients with poorly controlled asthma to a 12.5 mg/4 weeks of clazakizumab for a total of 16 weeks. This is an adaptive phenotype-driven clinical trial simultaneously evaluating several novel interventions. The primary outcomes of the study are lung function (FEV1) and asthma control (ACQ-6) with secondary outcomes

including FEV1 PBD, FVC, healthcare utilization, and time to asthma exacerbation. While this study is not limited to patients with obesity-related asthma, the analysis will evaluate the efficacy of clazakizumab in this subgroup of patients.

Positive Airway Pressure for Patients with Late Onset Obesity-Related Asthma

Lung function in late-onset, non-allergic, obesity-related asthma is characterized by an increased tendency for distal airway closure and air trapping secondary to abnormally collapsible airways [60]. Positive end expiratory pressure has been shown to mitigate the onset of airway narrowing brought on by methacholine challenge and airway closure once it is established [61]. To test the efficacy of positive end expiratory pressure in non-allergic obesity-related asthma, a pilot study of 20 patients with obesity-related asthma is recruiting participants that will be randomized to continuous positive airway pressure (CPAP) (10 cmH_2O) versus sham. The duration of CPAP will be determined in the dose titration phase. The effect on response to inhaled methacholine, lung function, and asthma control will be determined in patients with asthma and a BMI $\geq$ 30 kg/m^2 and in healthy controls without asthma. The primary outcome of the study will be the change in impedance of lung in response to methacholine measured by forced oscillation, and the secondary outcomes will be the changes in spirometry and asthma control (NCT 02953431).

CONCLUSIONS

Patients with obesity-related asthma represent a multitude of disease phenotypes that do not typically respond to Th-2 focused treatments for asthma. The complicated interplay between metabolism, inflammation, and environmental influences result in a variety of novel pathophysiologic mechanisms that represent potential drug targets for future therapeutics. Ongoing research is promising, but additional investigation is required in order to provide patients with this difficult disease improved symptomology and overall improved quality of life.

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Disclosures. Andi Hudler, Isaias Raymundo Ramirez Diaz, and Sunita Sharma have nothing to disclose. Fernando Holguin is an adjudication committee member at INSMED.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Not applicable.

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