Obesity and asthma

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Obesity has been well recognized as an important comorbidity in patients with asthma, representing a unique phenotype and endotype. This association indicates a close relationship between metabolic and inflammatory dysregulation. However, the detailed organ-organ, cellular, and molecular interactions are not completely resolved. Because of that, the relationship between obesity and asthma remains unclear. In this article, clinical and epidemiological studies, as well as data from experimental animal work, are being summarized to provide a *state of the art* update on this important topic. Much more work is needed, particularly mechanistic, to fully understand the interaction between obesity and asthma and to develop novel preventive and therapeutic strategies. (J Allergy Clin Immunol 2020;146:685-93.)

Key words: *Asthma, obesity, metabolism*

Abbreviations used
AHR: Airway hyperresponsiveness
BMI: Body mass index
FCR: Functional residual capacity
FVC: Forced vital capacity
HDM: House dust mite
HFD: High-fat diet
NLRP3: NACHT, LRR and PYD domains-containing protein 3
NO: Nitric oxide
OVA: Ovalbumin
SNP: Single-nucleotide polymorphism

The comorbidity of obesity in certain patients with asthma has recently been identified as a unique asthma endotype and phenotype. Obesity is the result of complex metabolic dysregulation, based on an imbalance of calorie uptake and use, including both sugar and lipid metabolism. Furthermore, obese patients show a certain type of subclinical chronic inflammation, which can be detected to some degree in the blood. Clinical and experimental data indicate that this type of inflammation may contribute to airway inflammation, decreased lung function, and asthma exacerbation. However, the organ-organ interaction between the adipose tissue, the lung, and other organs, as well as the contribution of the innate and adaptive immune cells and the molecular nature of this complex metabolic-inflammatory network, needs to be understood in much more detail. Over the last few years, clinical, epidemiological, and experimental studies have provided a more detailed insight into this complex interrelationship. This article summarizes recent observations.

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OBESITY AND ASTHMA—CLINICAL AND EPIDEMIOLOGICAL EVIDENCE

Obesity and asthma: Adults

Data noted in the literature regarding obesity and asthma are inconsistent. It is generally accepted that obesity is a risk factor for adult asthma. Ten years ago a workshop report of the American Thoracic Society officially documented obesity as a risk factor for asthma in all demographic groups.[1] Asthma in the obese may represent a unique phenotype of asthma, with a more severe disease outcome that does not respond as well to conventional therapy. Factors that could contribute to the pathogenesis of asthma in the obese include both mechanical factors and altered inflammation and immune responses related to the obese state.[1] A meta-analysis of prospective epidemiologic studies has quantified the relationship between categories of body mass index (BMI) and incidence of asthma in adults and has concluded that the more overweight the individual is, the greater is the likelihood of them developing or having asthma.[2] A separate "asthma-obesity" respiratory metabolic phenotype was also confirmed in a clinical study involving obese asthmatic, lean asthmatic, and obese nonasthmatic subjects. It has been shown that obese asthmatic patients are characterized by a respiratory metabolic fingerprint fully different from that of patients independently affected by asthma or obesity.[3] A cluster analysis of the phenotype of asthma and obesity in a cohort of 250 clinical trial participants confirmed the heterogeneity in expression of clinical and inflammatory biomarkers of asthma in obese individuals.[4] In a large population-based study in Norway involving more than 23,000 adults, an association of metabolic syndrome and asthma incidence in adults was detected; moreover, this association was observed for both men and woman with or without allergic rhinitis, and allergy status.[5] The strongest association with asthma incidence was found for waist

circumference and high glucose levels, but little evidence was found for other biomarkers such as elevated triglycerides, reduced high-density lipoprotein cholesterol, or hypertension.

A longitudinal American cohort study with more than 4000 participants with 25 years of follow-up data found that BMI was a stronger predictor of asthma incidence in women (not men) than metabolic syndrome. Other obesity-associated factors such as biomechanical, inflammatory, and metabolic abnormalities that are not part of the metabolic syndrome (according to the National Cholesterol Education Program Adult Treatment Panel-III definition, metabolic syndrome is present if 3 or more of the following 5 criteria are met: waist circumference >40 inches [men] or >35 inches [women], blood pressure >130/85 mm Hg, fasting triglyceride level >150 mg/dL, fasting high-density lipoprotein cholesterol level <40 mg/dL [men] or <50 mg/dL [women], and fasting blood sugar >100 mg/dL) can explain the association of high BMI with asthma.[6]

Obesity in adults measured by BMI, waist circumference, or waist-to-height ratio was positively associated with current asthma. Again, the relationship between obesity and current asthma was stronger with increasing insulin resistance only, and not with other components of the metabolic syndrome (hypertriglyceridemia, hypertension, hyperglycemia, and systemic inflammation). None of these components by themselves were effect modifiers of the obesity-asthma association.[7]

In contrast, a recent retrospective Spanish study including 809 hospitalized patients found no significant relationship between overweight or obese patients and hospital readmissions due to asthma exacerbation. These data indicate that obesity does not seem to be a determining factor in the risk of asthma exacerbations. These conflicting data indicate the complex relationship between metabolic dysregulation, airway inflammation, and asthma exacerbation.[8]

Obesity and asthma: Sex, ethnic, genetic factors

Initially, data indicated a role of female sex as a confounding risk factor in obesity and asthma, but a systematic review did not support this.[2] Both asthma and obesity are multifactorial diseases with hereditary predisposition; therefore, some studies have attempted to establish potential genetic or ethnic features of asthma-obesity comorbidity. No ethnic differences in asthma-obesity association have been reported to date, but candidate gene studies have detected a few genes associated with asthma and BMI, such as protein kinase C alpha, leptin, beta-3 adrenergic receptor, and DENN domain containing 1B,[9-12] although the main single-nucleotide polymorphism (SNP) did not replicate in the independent cohorts.[12] A gene-by-environment analysis found 7 SNPs in asthma-associated locus 17q21, which were associated with BMI only among subjects with asthma in 2 independent cohorts.[13] Mendelian randomization studies constructed a weighted allele score using SNPs known to be associated with BMI and demonstrated that the score of BMI-associated SNPs was strongly associated with asthma both in adults[14] and in school-age children.[15]

Obesity and asthma: Children, adolescents

As opposed to sex, age demonstrates differences in asthma-obesity association. Although a US study confirmed the association between the metabolic syndrome, obesity, and decreased parameters of lung function in adolescents,[16] a Brazilian study indicated that severe asthma in adolescents was also significantly associated with some components of metabolic syndrome, including insulin resistance, but independent of BMI.[17] Perhaps this is due to the definition of obesity according to BMI, but recent studies suggest that BMI z scores may be unreliable, particularly among children and adolescents with severe obesity.[18]

Moreover, unlike adults, in pediatric studies another interesting reason—consequences trend—in asthma-obesity association was determined. A US pediatric study confirmed the impact of asthma history and asthma medication use on the obesity incidence in childhood. Children with a diagnosis of adolescence asthma had a highly increased risk of developing obesity during childhood and adolescence compared with children without asthma.[19] Thus, there is no clear-cut obesity-asthma relationship in the group of children and adolescents.

Obesity and asthma: Maternal obesity

Interestingly, maternal obesity during pregnancy can influence the incidence of asthma in children. A meta-analysis of 24 clinical observation studies reported that children whose mothers were obese during pregnancy were at a higher risk of asthma occurrence. The inclusion criteria for maternal obesity were both high BMI before or at the beginning of pregnancy and high gestational weight gain. Most studies reviewed high BMI before or at the beginning of pregnancy as well as combined with high gestational weight gain. Three studies observed high gestational weight gain only. Because this analysis included only a few studies with an underweight population, the study may have been underpowered.[20]

Hence, much becomes known about asthma in obese adults, but there are still many unresolved issues and blank spots on the map, especially with asthma-obesity association in children and adolescents, such as reliable biomarkers in both children and adolescence, characteristic of different endotypes of asthma in obese individuals, both adults and children, the role of the microbiome, the possibility of anti-inflammatory treatment, and many others. Obviously, further research is needed to clarify the points.

EXPERIMENTAL MODELS

The development of allergic and other noncommunicable systemic diseases is a multifactorial process in which, besides genetic predisposition, the environment (allergen exposure, nutrients) and immunologic mechanisms play a decisive role. In particular, the highly complex interactions of different cell types of the immune system and tissues cannot be imitated *in vitro*. Therefore, mouse models offer the opportunity to study the complex interactions between the fatty tissue and the inflammatory processes in the lung. For investigation of the underlying mechanisms of obesity and asthma, several murine models have already been established and are commonly used for basic research. To induce overweight and fat accumulation in mice, a high-fat diet (HFD) with 40%kcal up to 60%kcal is used most frequently over a period of several weeks. As readouts of successful obesity-like changes in the weight measurements of mice increase, body composition and glucose/insulin levels in the blood can be used.[21] Experimental asthma with an allergic airway inflammation can be induced by either ovalbumin (OVA) or house dust mite (HDM) extract; however, the application protocols differ. With OVA an intraperitoneal sensitization and a

subsequent intranasal challenge is applied, to induce airway hyperresponsiveness (AHR) and a T_H2/eosinophilic response.[22] On the contrary, the application of different HDM methods leads to 3 different phenotypes of allergic airway inflammation —eosinophilic, mixed, and neutrophilic asthma.[23] Besides selecting a suitable asthma model, choosing the right mouse strain for working in the field of immunologic diseases is crucial. As an example, C57BL/6 mice exhibit a T_H1 response, in contrast to BALB/c mice, which are T_H2 prone.[24] Jovicic et al[25] investigated the different immunoinflammatory outcomes in response to HFD feeding of BALB/c and C57BL/6 mice, resulting in differences in T-cell populations and dendritic cells. In addition, the C57BL/6 mice exhibited a significantly higher weight gain after several weeks of HFD compared with the HFD-fed BALB/c mice.[25]

Eosinophils seem to be differentially affected by HFD depending on the induced asthma model. We have previously shown that obesity induced by an HFD lowered the threshold of allergen sensitization in AKR mice. AKR mice are known to be prone to obesity and AHR phenotype. The lowered allergen-sensitization threshold is associated by increased proinflammatory macrophages ($CD11b^+$/$CD11c^+$), increased serum IL-6 levels, and airway eosinophilia correlated positively with body weight.[26] Calixto et al[27] reported with an HFD-OVA model reduced levels of eosinophils in bronchoalveolar lavage and increased levels of inflammatory cytokines IL-5, TNF-α, and IL-10 compared with lean mice. The results by Everaere et al[28] suggest in turn increased eosinophil bronchoalveolar lavage level in HFD mice sensitized and challenged with HDM. Next to eosinophils, increased AHR is associated with the negative effects of obesity on asthma. CD38 is known to contribute to AHR by mediating an upregulation of TNF-α in alpha smooth muscle cells.[29] Increased expression of CD38 in the lungs of HFD-OVA mice indicate that CD38 plays a role in AHR of obese mice.[30] After knocking out the adaptive immunity in HFD-fed recombination activating gene $1^{-/-}$ mice, AHR was nevertheless measurable, suggesting its dependency on the innate immunity.[31] Furthermore, NACHT, LRR and PYD domains-containing protein 3 (NLRP3) and IL-17 are important mediators for the development of AHR in obese mice, because obese *Nlrp3*$^{-/-}$ or *Il17*$^{-/-}$ mice did not develop AHR.[31] The NLRP3 inflammasome being relevant in the correlation of obesity and asthma is also seen in a significant increase in NLRP3 mRNA expression in the lungs of HFD-OVA mice.[32] In the recombination activating gene $1^{-/-}$ and leptin-deficient *ob/ob* mice with diet-induced obesity, an increase in pulmonary IL-17^+ type 3 innate lymphoid cell was present.[31] The exacerbation of asthma by not only type 3 innate lymphoid cells but also type 2 innate lymphoid cells was demonstrated in obese HDM mice, indicating the involvement of innate lymphoid cells.[28]

Increased production of mucins is a pathophysiological characteristic of asthma. Hao et al[33] showed in an HFD-OVA model that the obese OVA-treated mice had an increased mucin production of mucin 5AC and Munc18b compared with the lean OVA-treated mice, implying the negative effects of an HFD on the mucus hypersecretion. It has further been observed that vitamin D might be important in the interaction of vitamins with the proinflammatory outcomes of obesity and asthma. The vitamin D level in the groups of mice subjected to OVA and HFD were lowered compared with the level in lean OVA mice.[32]

Childhood obesity is known to be a risk factor for asthma.[34] On investigating this risk factor in a mouse model, it was found that an early postnatal overweight induced by maternal HFD during lactation leads to early-onset obesity. This is further accompanied by adipocytokine and insulin signaling in the lung by enhancing cytokines such as IL-6, IL-13, IL-17A, and TNF-α, resulting in an increased airway hyperreactivity in the adult mouse.[35]

In obesity, several adipokines, mediators produced by adipocytes, play a crucial role in the exacerbations of diseases related to obesity. The adipokine leptin, a hormone regulating the appetite, is upregulated in obese individuals. It has been shown that the increased levels of leptin in obese mice lead to an exacerbation of allergic asthma and increased AHR.[36,37] More recent studies investigated the pathways of leptin and its impact on the immune system. Leptin exacerbates the allergic response by targeting the pathways of mammalian target of rapamycin complex 1, mitogen-activated protein kinase, and STAT3 in T_H2 cells.[38] The subsequently enhanced production of T_H2 cytokines takes place by leptin inducing X-box binding protein 1, a protein affecting the cytokine secretion of T and B cells.[36] In contrast to leptin, adiponectin is an anti-inflammatory adipokine, which is reduced in obesity.[39] A former study showed the attenuating effects of adiponectin in an allergic airway inflammation of OVA-treated mice.[40] Recently, in an OVA/HFD mouse model I found that the protecting effects of adiponectin are partially regulated through the adenosine monophosphate–activated protein kinase pathways, which are important for the regulation of cellular metabolism.[41] Adipokines seem to have an important impact not only on the metabolism but also on the immune system, thereby being relevant mediators in the obesity-associated asthma.

The obese-asthma phenotype is in most cases resistant to corticosteroids, due to its nonallergic mechanisms. HFD/HDM mice treated with the corticosteroid dexamethasone did not show lowered AHR compared with the nontreated mice. However, the dexamethasone treatment influenced the nitric oxide (NO) metabolism by reducing the inducible nitric oxide synthase expression in the lung, suggesting that the NO metabolism is involved in the obese-asthma-phenotype.[42] However, some studies about effective treatment of the obese asthmatic disease in mice have been published. As an example, celastrol, a natural bioactive compound, has an anti-inflammatory effect and is further able to reduce AHR in allergic asthma.[43] Zeng et al[44] demonstrated celastrol to have further positive effects in asthmatic mice, including a decrease in T_H17 mRNA expression in the lung and attenuating AHR in celastrol-treated HFD-OVA mice. The Notch signaling pathway is known to be on the one hand important in the allergic airway inflammation, but on the other hand Notch signaling is also able to regulate metabolism.[45,46] Therefore, the y-secretase inhibitors, which are blocking the Notch signaling pathways, might be an effective treatment, leading to a decrease in the T_H17 response and alleviated AHR in y-secretase inhibitor–treated HFD/OVA mice.[47] Moreover, weight loss or bariatric surgery can lead to improvements in disease control.[48] To analyze the underlying mechanism, a mouse experiment was conducted, comparing the effects of dietary weight loss and bariatric surgery. Both interventions reduced the AHR compared with the continuous obese mice. In a model of HDM airway inflammation and dietary weight loss, positive effects of the weight loss on the airway inflammation were seen in the reduction of AHR.[48] Kim et al[49] also demonstrated a reduced AHR in HFD/OVA mice after weight loss. They further suggest TNF-α to be an important mediator linking asthma and obesity, because TNF-α increased in HFD/OVA mice

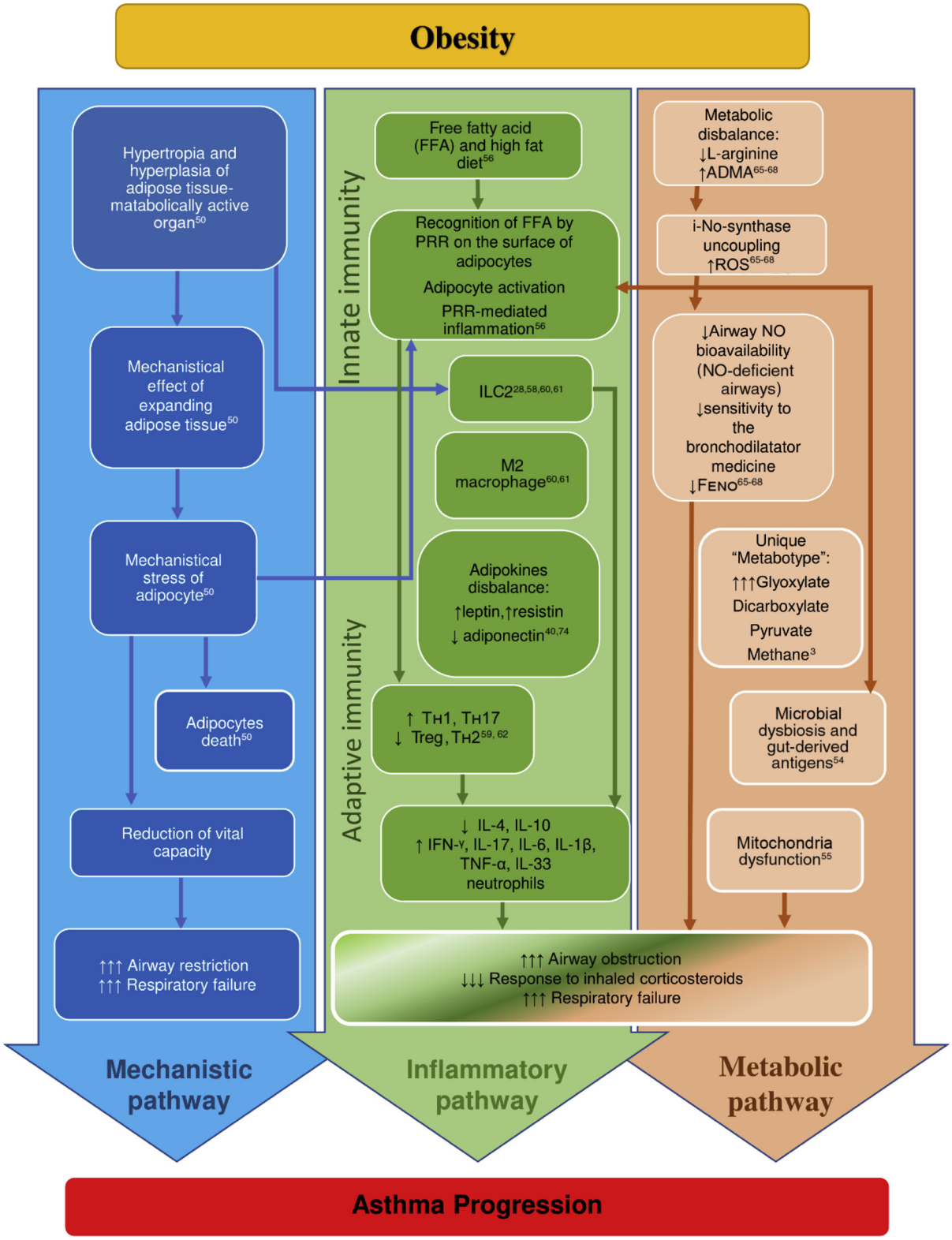

FIG 1. Bidirectional regulation between metabolic and inflammatory pathways promotes progression from obesity to asthma severity. Schematic overview input of the 3 pathways (inflammatory, metabolic, and mechanistic) to asthma progression in obese patients. Immunometabolic (inflammatory and metabolic) pathways impact lung dysfunction by increased airway obstruction (promotion of the airway obstruction or/and reducing the response to inhaled corticosteroids), whereas the mechanistic pathway alters lung function by increased airway restriction way. Both effects (obstruction and restriction) lead to respiratory failure and asthma progression in obese patients.[3,28,40,50,54-56,58-62,65-68,74] *ADMA*, asymmetric dimethyl arginine; *FENO*, fractional exhaled nitric oxide; *ILC2*, type 2 innate lymphoid cell; *PRR*, pattern recognition receptor; *ROS*, reactive oxygen species; *Treg*, regulatory T.
■ ■ ■-defined components of the pathway
→ → →-proposed links between the components

TABLE I. Top 5 key points about asthma-obesity comorbidity

Top 5 key points
● Obesity is a risk factor for asthma in adults.
● Significant weight loss can improve asthma control.
● Maternal obesity is a risk factor of asthma incidence in offspring.
● Obesity-associated asthma is a heterogeneous pathology, not only classical phenotype in women with late-onset, weight-loss response, and corticosteroid resistance.
● Decreased bioavailability of NO in the airway of obese individuals may result in enhanced airway obstruction.

TABLE II. Top 5 open questions in the field of asthma-obesity association

Open questions
● Is the asthma and obesity syndrome the umbrella of different endotypes?
● What are reliable biomarkers in both children and adolescence?
● What is the cause-effect relationship between asthma and obesity in children and adolescence?
● Which component of the metabolic syndrome is the most important risk factor for asthma?
● What is the contribution of the gut or lung microbiome to obesity and airway disease?
● What are the mediators in the organ-organ interaction (adipose tissue and the lung)?
● What anti-inflammatory treatment targeting adipose tissue–related inflammation provide additional benefit to bronchial asthma?

but decreased in the lungs after weight loss. The crucial role of TNF-α is further supported by the fact that blocking TNF-α leads to improvements in AHR in an obese-asthma model.[49] Mouse models provide a great possibility to study basic mechanisms and possible treatments in the correlation of obesity and asthma, but certainly the evidence for translation needs to be confirmed in human cohorts.

MECHANISTIC STUDIES (HUMAN AND MOUSE)

Detailed metabolic assessment: Immune-metabolic interventions

Association of asthma and obesity has been demonstrated in numerous epidemiological studies; however, the exact underlying mechanisms and detailed pathogenic link for this association are not well understood. A large number of factors are postulated including inflammation and immunometabolic dysregulation,[50-54] microbial dysbiosis,[55] mitochondrial dysfunction,[56] free fatty acid receptors,[57] glucagon-like peptide pathway,[58] and innate lymphoid cells (Fig 1).[28]

It has been shown that obese asthmatic patients are characterized by a respiratory metabolic fingerprint fully different from that of patients independently affected by asthma or obesity. A unique "asthma-obesity" respiratory metabolic phenotype was defined by nuclear magnetic resonance–based metabolomic, characterized by high levels of metabolites such as glyoxylate and dicarboxylate, pyruvate, and methane, and named as "metabotype."[3]

Adipose tissue is a metabolically active organ critically involved in the regulation of systemic energy balance and metabolic homeostasis and in the case of hypertrophy and hyperplasia of adipose tissue is followed by change in cytokine secretion, oxygen depletion, necrosis, increased recruitment of immune cells, and dysregulated fat metabolism, leading to further inflammation. The precise triggers of obesity-associated inflammation are poorly understood. Several potential mechanisms have been suggested, including intestinal antigens (increased circulation of gut-derived antigens, such as LPS) and various dietary components (eg, free fatty acids), which can initiate inflammation via pattern recognition receptors on adipocytes, as well as mechanical stress, adipocyte death, and hypoxia associated with the interactions between expanding adipocytes and extracellular matrix can trigger inflammation.[51]

Lymphocytes account for up to 10% of nonadipocyte cells in human adipose tissue and include T cells, B cells, natural killer cells, natural killer T cells, and type 2 innate lymphoid cells.[59] Although most research on obesity, inflammation, and comorbidities has been focused on the role of innate immunity, particularly on pattern recognition receptor–mediated inflammation, recent studies point to an important role for the adaptive immune system.[60] T_H2 cells control several aspects of adipose tissue integrity and metabolism. IL-33 produced by epithelial cells serves as an important regulator of T_H2 cells. IL-33 induces innate lymphoid cells to secrete IL-5 and IL-13, which activate eosinophils, which in turn secrete IL-4, which promotes M2 macrophage polarization and induces the differentiation of beige adipocytes.[61,62] Anti–IL-33 biologics may play a special role in this population. In contrast to lean individuals, the immune cells in the adipose tissue of obese individuals operate in a proinflammatory T_H1 state in which cytokines, such as TNF-α, secreted from adipocytes and immune cells, contribute to preserve tissue integrity while adapting to the metabolic needs associated with overnutrition. In addition, obesity is associated with an increase in the portion of T_H1 and T_H17 cells relative to the portion of T_H2 cells and regulatory T cells.[60] Decreased numbers of regulatory T cells in adipose tissue, observed during obesity, are also believed to contribute to the development of inflammation and insulin resistance.[63]

A positive association between asthma and obesity with eosinophilic or noneosinophilic inflammation in overweight patients was determined in a Macedonian pediatric study. Although the lung function parameters did not differ between asthmatic children with and without obesity and obese children without asthma, the parameters of systemic inflammation (C-reactive protein, fibrinogen) were higher in obese patients without

asthma only, whereas asthmatic children both overweight and not overweight had identical profiles of eosinophils and IgE; thus, no direct influence of atopy in the association between asthma and obesity was verified.[64]

The airways of obese asthmatic subjects have been shown to be NO deficient. This could contribute to airway dysfunction and reduced response to inhaled corticosteroids.[65,66] According to data from numerous studies, this could be explained by metabolic imbalance, which is characterized by lower L-arginine levels and higher concentrations of asymmetric dimethyl arginine, which could induce airway epithelial inducible NO synthase uncoupling, promoting reactive oxygen species formation and causing oxidative stress. This in turn reduces airway NO bioavailability and the airway's ability to bronchodilate normally.[66-69] Airway concentrations of asymmetric dimethyl arginine are greater in asthmatic adults and children when compared with controls, and L-arginine levels are lower in otherwise healthy obese and overweight subjects.[70-72] Obese patients with late-onset asthma in the Severe Asthma Research Program who had decreased L-arginine to asymmetric dimethyl arginine ratios were noted to have increased respiratory symptoms, reduced lung function, lower IgE levels, and reduced fractional exhaled nitric oxide.[65] In a clinical study, it has been shown that in obese asthmatic subjects with low or normal fractional exhaled nitric oxide levels, daily L-citrulline (a byproduct of the enzymatic production of nitric oxide from the amino acid arginine, catalyzed by nitric oxide synthase) added to maintenance asthma controller therapy restored NO airway bioavailability, improved lung function and asthma control, and determined that late versus early-onset male or female asthma phenotypes have a differential response to L-citrulline supplementation.[73]

Immunologic and microbiome alterations in obese asthmatic, nonobese asthmatic, and obese nonasthmatic subjects and their healthy counterparts were investigated in a US clinical study involving 200 subjects. Obesity was associated with elevated proinflammatory signatures, which were enhanced in the presence of asthma. Changes in immunologic processes and microbiota composition are accentuated in obese patients with asthma due to the additive effects of both disease states.[74]

Adipose tissue strongly contributes to the establishment of an inflammatory state being an important source of adipokines. Among adipokines, adiponectin is an important component of organ cross-talk with adipose tissue exerting protective effects on various pathophysiological processes.[75] Adiponectin levels decrease with obesity, unlike other adipokines, which increase, including leptin, resistin, and TNF-α. Protective effects of adiponectin were demonstrated against airway inflammation and oxidative stress in a murine model of obesity-related asthma.[41]

The correlations between obesity, adipose tissue inflammation, and asthma make inflammatory signaling pathways a potential target for the treatment or the prevention of these pathologies. However, a better understanding of the molecular mechanisms underlying obesity-asthma association is required to develop effective therapeutic or prophylactic strategies.

Mechanical effect of obesity on pulmonary function

Although the physiology of obesity and its effects on lung function have been the subject of intense investigation over the last 50 years, the recent observation of the association between asthma and obesity has raised new questions about the mechanical effects of obesity on the lungs, and the mechanisms that drive breathlessness in the obese and are still not well understood.[76,77]

It is well accepted that mass load of adipose tissue around the rib cage, abdomen, and in the visceral cavity changes the balance of inflationary/deflationary pressure on the lung and leads to the reduction of functional residual capacity (FRC).[78-80] Abdominal mass reduces the downward movement of the diaphragm and limits the room for lung expansion on inflation, but the effect of obesity on total lung capacity and residual volume is modest even in severe obesity.[81-83] Therefore, reduction in FRC leads to a decrease in the expiratory reserve volume.[82] Indeed, the expiratory flow decreases in obese individuals,[84,85] but this occurs in proportion to the lung volume[86]; therefore, decrease in expiratory flow in an obese individual is unlikely to indicate bronchial obstruction, unless the flow measurements have been normalized for the reduction in vital capacity.[76,77] The spirometric variables FEV_1 andforced vital capacity (FVC) tend to decrease with increasing BMI, but are usually still within the normal range in obese adults.[86-89] In obese children, spirometric data and mechanical effect of adipose tissue on the pulmonary function are different from those in adults and results remain controversial.[90,91] A Chinese study demonstrated that overweight and obesity are high risks for children's respiratory symptoms and diseases, but pulmonary function was not adversely affected by obesity in schoolchildren.[91] At the same time, the Childhood Asthma Management Program study showed that an increase of 5 units in BMI was associated with a decrease of more than 1% in FEV_1/FVC.[92]

The FEV_1/FVC ratio is also usually well preserved or increased in obesity and also in morbid obesity.[84-88,93] This finding indicates that both FEV_1 and FVC are affected to the same extent and the major effect of obesity is on lung volumes, with no direct effect on airway obstruction.[76] It is known that mechanical properties of the airways, such as resistance and reactance, are highly dependent on lung volume and are, therefore, affected by any reduction in FRC.[76,77] Obesity does not influence airway reactivity in patients with asthma, and it is associated with more symptoms only in those with less severe disease.[94] When BMI is used as a criterion of obesity, it does not take into account any differences in fat distribution, but abdominal and thoracic fat are more likely associated with reductions in lung volumes because of the direct effect on the diaphragm movement and the mechanical effect on the lungs rather than lower body fat.[76,93] Bariatric surgery also improves asthma in subjects with morbid obesity.[95] The reduction in lung volume induced by the obese state is likely a major contributor to the decreased airway dysfunction in the obese, but whether tissue mechanics are also affected is not clear.[77] The apparent reduction in airway caliber in the obese is attributable to the reduction in lung volume rather than to airway obstruction.[76] Nevertheless, the mechanical effect of obesity on the respiratory system contributes to airway dysfunction and could worsen asthma.

Weight loss, diet interventions, exercise, and asthma control

Weight loss in obese adults with asthma can improve asthma control, lung function, and quality of life,[96-101] but data regarding the level of weight loss and detailed changes in lung function and airway inflammation are heterogeneous. An Australian

randomized controlled trial assessed whether weight loss can be achieved in obese asthmatic children using dietary intervention, and whether changes in asthma outcomes occur after diet-induced weight loss. Indeed, dietary intervention can induce weight loss in obese asthmatic children, with subsequent significant improvements in lung function, clinical outcomes, and asthma control, but systemic and airway inflammation in sputum and exhaled airway did not change after weight loss.[96]

Another Australian study investigated the effect of weight loss achieved not only by dietary intervention but also by exercise and combined dietary restriction and exercise on airway inflammation and clinical outcomes in overweight and obese adults with asthma. In obese adult asthmatic subjects, 5% to 10% weight loss resulted in clinical improvement of asthma control and quality of life. Diet and combined interventions caused a more pronounced decrease in body weight and, therefore, better asthma control. In contrast to children, adults also showed changes in systemic and airway inflammation: reduced neutrophilic airway inflammation in women was associated with gynoid (fat around the hips, thighs, and breast) adipose tissue reduction, whereas in men a reduction in dietary saturated fat was detected. The exercise intervention resulted in a significant reduction in sputum eosinophils.[97] Adding exercise to a short-term weight-loss program helped to achieve greater weight loss, and this was also accompanied by improvements in lung function, anti-inflammatory biomarkers, and vitamin D levels, as well as reductions in airway and systemic inflammation.[101] Studies on the effects of weight loss in patients with severe asthma are unique. Results of a Latin-American open, prospective, randomized study involving 30 patients with severe uncontrolled asthma and obesity showed that the weight-loss program consisted of low caloric intake and weight-loss medicine intake (sibutramine or orlistat) and was associated with significant improvements in asthma control. However, this improvement was not accompanied by changes in markers of airway inflammation or bronchial reactivity, but by an increase in FVC. These results suggest that weight loss in an obese patient with severe asthma improves asthma control by mechanisms not related to airway inflammation.[98] An American clinical trial involving 330 moderately and severely obese adults with uncontrolled asthma showed that marked weight loss of 10% or greater (which was achieved by calorie reductions and physical activity) was required to produce clinically meaningful improvement in asthma. The effects of smaller weight changes (<10%) were not associated with significant benefits for asthma control or other clinical asthma outcomes in the current population.[99]

Thus, further research is needed to establish causality and possible common pathophysiological mechanisms, as well as the consequent clinical and therapeutic implications, between these 2 conditions.

IS ASTHMA A RISK FACTOR FOR OBESITY?

Several studies have shown the correlation between childhood obesity and the resulting increased risk for developing asthma.[102] So far little is known about the reversed order of asthmatic children having a higher risk for obesity incidence. A longitudinal study in the United States of early-life history of asthma demonstrated a higher risk of becoming obese in later childhood and adolescence.[19] A European study demonstrated that not only asthma but also childhood wheezing and allergic rhinitis may lead to an increased risk of developing obesity later in childhood.[103] Furthermore, asthmatic children tend to be less physically active compared with healthy children.[104] Interestingly, the use of rescue medication may reduce the risk of developing obesity later in adulthood; however, this effect is independent of physical activity, and it is speculated that there is a direct effect of the β-agonists on the adipocytes.[19] Further investigations are needed to fully understand the underlying mechanisms behind both entities.

CONCLUSIONS

Recent clinical, epidemiological, and experimental data strengthen the cause-effect relationship between obesity and asthma. Obesity is the result of metabolic dysregulation on the level of sugar and lipid metabolites. The adipose tissue is functionally highly active, which is reflected by the presence of local and systemic subclinical inflammation. This inflammatory response seems to contribute to airway inflammation, lung function, and asthma exacerbation. However, many open questions remain, which need attention through concerted research actions (Tables I and II). It is the hope that a better understanding of the interaction between metabolic and inflammatory dysregulation will lead to novel approaches to combat this important endotype of patients with asthma.

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What do we know?

- **Obesity is an important comorbidity in a subset of patients with asthma**
- **Low-grade systemic inflammation of obesity contributes to airway inflammation and asthma exacerbation**
- **Highly heterogeneous pathogenesis of the obesity-associated asthma**
- **Significant weight loss can improve asthma control**

What is still unknown?

- **Organ-organ interactions between adipose tissue and the lung**
- **Reliable biomarkers for new tailored therapeutic approaches**
- **Quality and different endotypes of asthma and obesity comorbidity**
- **Cause-effect relationship between asthma and obesity in children and adolescence**

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