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Pediatric obesity and severe asthma: Targeting pathways driving inflammation

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ABSTRACT

Asthma affects more than 300 million people of all ages worldwide, including about 10–15% of school-aged children, and its prevalence is increasing. Severe asthma (SA) is a particular and rare phenotype requiring treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic glucocorticoid courses to achieve symptom control or remaining "uncontrolled" despite this therapy. In SA, other diagnoses have been excluded, and potential exacerbating factors have been addressed. Notably, obese asthmatics are at higher risk of developing SA. Obesity is both a major risk factor and a disease modifier of asthma in children and adults: two main "obese asthma" phenotypes have been described in childhood with high or low levels of Type 2 inflammation biomarkers, respectively, the former characterized by early onset and eosinophilic inflammation and the latter by neutrophilic inflammation and late-onset. Nevertheless, the interplay between obesity and asthma is far more complex and includes obese tissue-driven inflammatory pathways, mechanical factors, comorbidities, and poor response to corticosteroids. This review outlines the most recent findings on SA in obese children, particularly focusing on inflammatory pathways, which are becoming of pivotal importance in order to identify selective targets for specific treatments, such as biological agents.

1. Introduction

Asthma is a global health problem affecting more than 300 million people of all ages and ethnic groups worldwide [1] and approximately 9% of children in the US and 15% of school-aged children in Europe [2,3]. Asthma prevalence has significantly increased in recent years [4,5] and factors such as dietary habits, exposure to environmental tobacco smoke, and pollution are likely to be involved in this changing epidemiology [6]. Severe asthma (SA) has been recently attracting interest. In this particular phenotype of asthma, other diagnoses have been excluded and potential exacerbating factors have been addressed. The definition requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic glucocorticoid courses needed to achieve symptom control, or that asthma remains "uncontrolled" despite this therapy [7,8]. Obesity is both a major risk factor and a disease modifier of asthma in children and adults. While obesity is defined according to a body mass index (BMI) threshold, recent studies suggest that BMI z-scores may be unreliable, particularly in children and adolescents with severe obesity [9,10]. Worldwide, the prevalence of being overweight or obese between 1980 and 2013 has increased by 47.1% for children [11] mostly due to dietary habits, increased sedentary habits activities, and reduced time spent on physical activities. According to data from the CDC, in the US, 17% of children are obese, while 15% are overweight [12]. Similar data are available for almost all

Abbreviations: AHR, Airway Hyperresponsiveness; AT, Adipose Tissue; BAL, BronchoAlveolar Lavage; BMI, Body Mass Index; FEV_1, Forced Expiratory Volume in 1 s; FVC, Forced Vital Capacity; $FEF_{25-75\%}$, Forced Expiratory Flow at 25–75% of FVC; ICS, Inhaled CorticoSteroids; IgE, Immunoglobulin E; ILC, Innate Lymphoid Cells; IL, Interleukin; LABA, Long-Acting Beta 2 Agonists; SA, Severe Asthma; TSLP, Thymic stromal lymphopoietin.

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high-income countries worldwide. Several longitudinal epidemiological studies show that obesity often precedes incident asthma. Camargo et al. found an odds ratio of 2.6 of developing late-onset asthma with a BMI greater than 30 kg/m^2 [13]. A meta-analysis of prospective studies showed a dose-response relationship between obesity and asthma, with an odds ratio of incident asthma 1.9 in the obese group [14]. Nevertheless, the interaction between asthma and obesity begins as early as the fetal period: maternal obesity and weight gain during pregnancy have been independently associated with approximately 15–30% increased risk of asthma in the offspring [15,16]. Interestingly, asthma may lead to obesity too: in a recent study, asthmatic children showed an increased risk of becoming obese during a 10-year follow-up period [17]. However it is also important to note that asthma diagnosis in children is often wrong [18,19]; breathlessness on exercise, both in lean and obese children, is more often due to deconditioning rather than exercise induced bronchoconstriction or laryngeal dysfunction [20]. Hence when assessing manuscripts associating asthma and obesity, it is essential to critically assess how carefully the diagnosis of asthma has been made. However, there is increasing evidence supporting the definition of an "obese asthma" phenotype [21,22]. Of note, two main sub-phenotypes of obese asthma have been proposed according to age by Holguin et al. [23]. The first refers to early onset asthma (under 12 years of age), with obesity worsening pre-existing asthma, with more severe airway obstruction, lower quality of life, increased bronchial hyperresponsiveness, and greater use of health care resources compared with early non-obese asthma. These children are usually atopic with high IgE levels and have positive skin prick test (high Type 2 inflammation biomarkers – *T2-high*), with predominant eosinophilic inflammation with no gender difference [24,25]. The second phenotype refers to late-onset, often severe, asthma, developing in obese non-allergic children > 12 years of age or adults (often females, thought to be due to direct effects of estrogens and progesterone and higher fat percentage and subcutaneous deposition than boys), usually being more symptomatic but showing a predominant neutrophilic/paucygranulocitic inflammation (*T2-low*) and with a very poor response to ICS and long-acting beta 2 agonists (LABA) [26,27]. However, this classification may be oversimplified as different endotypes may underlie a single phenotype. Thus, the pathogenetic mechanisms need to be better defined. Mechanistically, obesity-associated asthma can be driven by non-T2 pathways, such as the nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, interleukin (IL)− 1β, or type 3 innate lymphoid cells (ILC3) [28]. Furthermore, it remains poorly understood which clinical outcomes of asthma are specifically affected by obesity; and the effects of obesity may be different across age groups. Elderly patients are susceptible to adverse health outcomes of asthma and treatments, and sarcopenia interacts with obesity and might worsen clinical outcomes [29]. As a whole, obese children generally show an increased asthma severity [30–32], with worse symptom control and quality of life [33,34]. Notably, both asthma and obesity are recognized as having hereditary components, but a genetic link between the two conditions has not been described. One study showed that *CHI3L1* gene expression could be induced by a high-fat diet and thereby contribute both to obesity and to asthma development [35]. Notably, Wang et al. found seven SNPs in 17q21 (a locus strongly associated with early onset asthma) associated with increased BMI only among subjects with asthma [36].

This review outlines the most recent findings on SA in obese children, focusing on inflammatory pathways characterizing asthma, SA and the obese-asthma phenotype, some of which may represent targets for specific treatment such as monoclonal agents. The knowledge gaps and future research directions are also addressed.

2. Inflammatory endotypes in asthma

2.1. Type 2 inflammation and related biomarkers

Asthma is a complex multifactorial disease; it is a description, not a diagnosis, and there are many different "asthmas" [37]. Some but not all are characterized by chronic inflammation of the airways. Evidence shows that genetic predisposition, environmental factors, and uncontrolled inflammatory processes can contribute to the development of epithelial barrier dysfunction both in the skin and the bronchial mucosa, a condition increasing the risk of allergic sensitization. On the bronchial mucosal surface, allergens, as well as respiratory viruses, affect the epithelial barrier's permeability, creating a vicious circle between inflammation and barrier damage [38,39]. Recent studies have tried to elucidate the inflammatory patterns (*endotypes*) underlying different phenotypes of asthma [40]. The evidence so far suggests that asthma can be grouped into two main endotypes, T2-high and T2-low, with T2-high being the most common, especially in childhood. T2-high typically occurs in allergic patients with an early onset of the disease: in these patients, the immune response involves Th2 cells, type 2 innate lymphoid cells (ILC2), immunoglobulin E (IgE)-producing B cells, natural killer T (NK-T) cells, mast cells, basophils, eosinophils and relates cytokines [41,42]. In T2-high asthma, non-allergic alarmins, such as Interleukin (IL)− 25, IL-33, and thymic stromal lymphopoietin (TSLP) are released mainly by airway epithelial cells when damaged by exposure to pollutants, environmental tobacco smoke, viruses or colonizing bacteria [43–45]. Such cytokines activate ILC2, which releases Th2 cytokines, such as IL-5, IL-13, and IL-4 [46,47] (Fig. 1). Among them, IL-4 polarizes Th2 cell differentiation and switches B-lymphocyte immunoglobulin synthesis to IgE production and expression of VCAM-1 in endothelial cells, that mediates eosinophil, basophil, and T cell-specific recruitment. IL-5 is the major cytokine involved in eosinophil production and survival, while IL-13 is a survival factor for basophils and eosinophils and is involved in mucus gland hyperplasia and remodeling [48–50].

2.2. T2-low inflammation and related biomarkers

T2-low asthma has been described more frequently in adults than in children and comprises neutrophilic and paucigranulocytic asthma [51]. The specificity of neutrophilic inflammation is complicated by the many confounding factors that can contribute to sputum neutrophilia, including the use of ICS, air pollution, respiratory infections, sensitization to aspergillus, gastroesophageal diseases, and environmental tobacco smoke exposure. In one study, sputum total neutrophil count was associated with lower pre- and post-bronchodilator FEV_1, suggesting that neutrophilic airway inflammation may have a role in persistent airflow limitation in asthma [52]. Analysis of patients included in the Severe Asthma Research Program (SARP) study identified two subgroups with moderate-to-severe asthma and frequent healthcare use despite treatment with high doses of inhaled or oral corticosteroids; one of these subgroups also showed reduced lung function [53,54]. The majority (>83%) of those with reduced lung function had sputum neutrophilia alone or in combination with sputum eosinophilia. Further, it has been observed that the early-onset/severe-lung function cluster had the best response to fluticasone/salmeterol, while the early-onset/comorbidity cluster, including children with obesity, had a poor clinical response to these controller treatments [55]. The combination of neutrophilia and eosinophilia in sputum appears to identify a more severe phenotype [27]. In contrast, in a cohort of children with SA and multiple atopic sensitizations, a subgroup of patients showed neutrophils within the epithelium [56]: these patients had better symptom control and better lung function, different to what has been observed in adults. In neutrophilic asthma, inflammation is characterized by the production of cytokines, such as IL-17, IL-21, and IL-22 by Th1 and Th17 cells [57]. It should also be noted that IL-6, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage

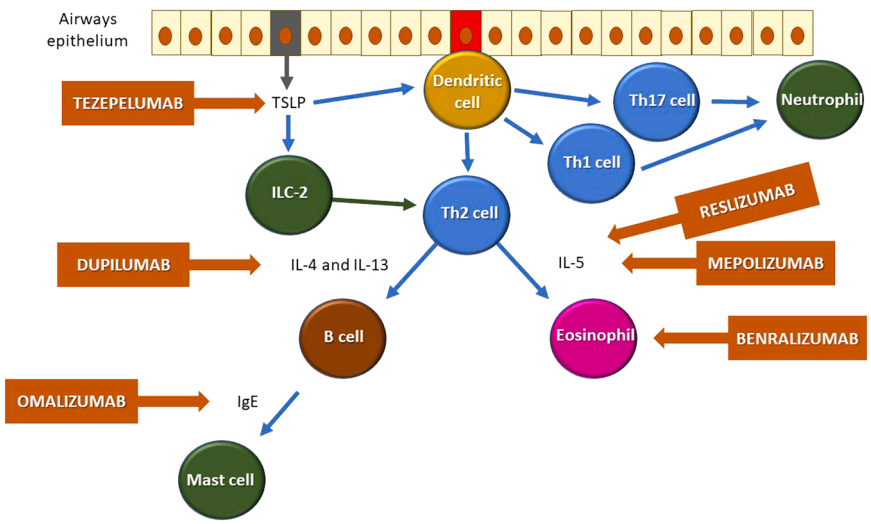

Fig. 1. Targets for currently available biologics in severe asthma treatment. The figure shows the main pathways underlying bronchial mucosa inflammation in asthma and the six currently available biological agents with their specific targets.

colony-stimulating factor (GM-CSF), IL-8, CXCL1, CXCL5, and CXCL8, produced by airway epithelial cells, have a role in the activation of the neutrophils [58,59], and increased levels of IL-6 have been found in asthmatic patients, especially in SA in adults [60], but not in children [61]. Also ILC3 (involved in IL-17 secretion) and pro-inflammatory macrophages have key roles in neutrophilic asthma [62] while both serum IL-17 and IL-17 + T cells have been associated with asthma severity in children [63]. Another important mechanism in the development of neutrophilic asthma is inflammasome activation, following microbial exposure: the NLRP3 inflammasome, an intracellular multiprotein complex, induce the autoactivation of pro-inflammatory caspase-1, and the consequent production of the mature form of pro-IL-1β and pro-IL-18. This process induces Th17 cell-dependent inflammation [64]. In fact, patients with neutrophilic airway inflammation show high levels of IL-1β and caspase-1 in the sputum [65]. Moreover, it has been shown that NLRP3 inflammasome activation in alveolar epithelial cells promotes myofibroblast differentiation of lung-resident mesenchymal stem cells, potentially playing a role in airway remodelling [66,67]. Lastly, it has been shown that human tumor necrosis factor-like weak inducer of apoptosis (TWEAK), a cell surface-associated type II transmembrane cytokine expressed in several inflammatory cell types, such as monocytes and lymphocytes, may stimulate bronchial epithelial cells to produce pro-inflammatory IL-8: indeed, TWEAK sputum levels were increased in children with non-eosinophilic asthma characterized by greater asthma severity and poorer control of symptoms in a recent study by Kim et al. [68].

3. The "obese-asthma" phenotype in childhood: cross-talking of inflammatory processes

3.1. Adipose tissue-driven inflammation

With the excess adipose tissue (AT), hypoxic death of some adipocytes promotes the proliferation of M1 macrophages, which are known to favor a pro-inflammatory activity and induce insulin resistance. The number of macrophages in the adipose tissue of humans is usually low (4%) but can reach up to 12% in obesity [69]. Conversely, Treg cells, which are antagonists to M1, are abundant in lean adipose tissue; the imbalance between Treg and M1 macrophages contributes to obesity-related inflammation [70]. Moreover, several studies have demonstrated that chronic inflammatory conditions, such as obesity, are characterized by a rise in circulating Th17 lymphocytes, which secrete IL-17, which in turn stimulates, through GCS-F and IL-8 production, neutrophil recruitment to the sites of inflammation. Th17 also induces the release of pro-inflammatory cytokines, such as IL-6 [71], which has a role in the polarization of T cells into Th17 cells [72] and may reduce adiponectin secretion, further contributing to the inflammation process [73]. In fact, adiponectin has anti-inflammatory properties [74]: it has been shown that adiponectin suppresses macrophage differentiation into M1 [75,76], activates anti-inflammatory IL-10, and reduces pro-inflammatory cytokines (IFN-γ, IL-6, TNF-α) [77]. Interestingly, adiponectin has also been recognized as a pro-inflammatory actor in some autoimmune diseases: this may be due to the presence of different adiponectin isoforms with different effects on inflammation [78]. As a whole, obesity is characterized by reduced circulating serum levels of adiponectin and increased levels of IL-6 and TNF-α, similarly to what happens in type 2 diabetes, metabolic syndrome, or cardiovascular disease inflammation [79]. Adipocytes also produce leptin, an adipokine whose long isoform has anorexigenic effects and can be found in the hypothalamic centers, showing food intake regulation properties [80,81]. Obesity is characterized by increased leptin levels due to over-expression in AT [82,83], but also by resistance to its anorectic actions. Moreover, it should be noted that leptin induces secretion of pro-inflammatory mediators in obese patients, such as IL-6, TNF-α, and IFN-γ [84,85], and also promotes the activity of pro-inflammatory Th17 cells [86]. Unsurprisingly, higher leptin levels in obese adolescents correlate inversely with FEV_1, FVC, and FEV_1/FVC, and both leptin and adiponectin levels correlate with abnormal exercise-induced bronchoconstriction in children with asthma [87]. Resistin is another adipokine involved in the inflammatory process through the expression of IL-6 and TNF-α, as well as in the differentiation of macrophages into pro-inflammatory M1 [88]. In obese AT, NLRP3 inflammasome is also activated due to exposure to saturated fatty acids, such as palmitate and stearate, and oxidative stress [89]. This complex drives inflammation to many organs through the activation of M1-type macrophages [90].

3.2. The complex inflammatory interplay between asthma and obesity

The interplay between asthma and obesity is complex and has not yet been completely elucidated. A growing amount of evidence shows that obesity is associated with low-grade systemic inflammation, the so-called "meta-inflammation" [91], which may interact with asthma inflammation, regardless its endotype or severity, both in terms of promoting or worsening the disease [92]. When considering the interplay between asthma and obesity at a molecular level, interestingly, the four cytokines with a prominent pro-inflammatory role in T2-high

asthma (IL-4, IL-5, IL-13, and IL-33) contribute to maintaining the lean state. Moreover, IL-4 and IL-13 induce the expression of two anti-inflammatory cytokines (TGF-β and IL-10) by M2 macrophages [93] and reduced IL-33 levels represent a risk factor for metabolic syndrome [94] and are associated with increased body mass index [95]. In studies evaluating the endotype in obese adult asthmatics, a neutrophil dominant inflammatory pattern was found in the airway lumen and was associated with higher levels of IL-17A [96,97]. Notably, in the lungs of obese mice, which typically exhibit airway hyperresponsiveness (AHR) with the exception of IL-17A deficient animals, increased IL-17A was found in association with AHR and neutrophilic inflammation [28]. The obesity-related asthma phenotype is also associated with the presence of increased interleukin levels, such as TNF-α, which increase in parallel with BMI in subjects with asthma [23,98] (Table 1). Data are contradictory about the role of IL-6 in obesity and asthma. Some studies showed increased serum IL-6 levels significantly associated with BMI percentile in children and adults [99], but not with asthma severity [61]. Innate immune responses involving both Th17 pathways and macrophage activation by ILCs could also have a role in both obesity and asthma: Zheng et al. reported increased sputum neutrophils in "non-atopic obese asthmatics" but found higher sputum macrophage counts in those with "atopy-obesity overlap" [100]. These results confirm the findings in obese mice: a significant elevation of inflammatory cytokines, such as IFN-γ, IL-4, IL-17A, TNF-α, IL-1β, and IL-6, was found after 48 h of ovalbumin sensitization. Furthermore, bronchoalveolar lavage (BAL) analysis in obese mice showed a greater influx of macrophages and lower eosinophil numbers [101]. A recent meta-analysis found that low concentration of serum adiponectin is associated with higher asthma incidence while higher leptin levels were associated with asthma both in adults and children [102]. Several studies have reported a role for leptin in promoting airway inflammation in asthma, since leptin may alter airway epithelium, stimulating the upregulation of ICAM-1 and increasing the secretion of different cytokines, including IL-6, CCL11, G-CSF and vascular endothelial growth factor (VEGF). Leptin-deficient mice showed reduced lymphocyte and eosinophil numbers in BAL, demonstrating that leptin plays an essential role in inducing allergic airway inflammation [103]. In addition, an in vitro study showed that exogenous leptin exposure promotes the expression of IL-4, IL-5, and IL-13 in Th2 cells [104], and Sideleva et al. found that increased leptin levels are associated with AHR [105]. Other studies showed that leptin treatment augmented allergen-induced AHR but did not affect eosinophil influx or Th2 cytokine expression, suggesting that leptin is also capable of augmenting AHR through a mechanism independent of Th2 inflammation [106]. A few cross-sectional studies have reported positive associations of serum leptin levels with asthma severity, asthma control, lung function, and asthma severity in children and in adults [107,108]. One study found an association between serum leptin levels and asthma control assessed by the Asthma Control Questionnaire (ACQ) [109]. Another recent longitudinal study applied a causal approach to mediation analysis showing that leptin partly (> 60%) mediated the association between high body adiposity and persistent asthma over time [110]. Taken together, these results support that leptin may be a mediator that contributes to explaining the association between obesity and both asthma persistence and control. Regarding other cytokines and mediators underlying obesity and asthma, cysteinyl leukotrienes, a group of inflammatory lipid mediators, have also been found to be elevated in obese asthmatic children [111] and may be considered a trigger for airway remodeling, by altering the phenotype of small-airway epithelial cells in vitro [112]. Leukotriene D4 (LTD4) treatment increases the expression of inflammatory cytokines [IL-1α, IL-1β, IL-6, epidermal growth factor (EGF), TNF-α, GM-CSF, eotaxin] in small-airway epithelial cells (SAECs) in a time- and dose-dependent manner and induces NLRP3 inflammasome activation, which activity is involved in both obesity and asthma. Increased sputum concentrations of IL-1β and increased NLRP3 and TLR4 expression in sputum cells have been reported in obese as compared with non-obese asthmatic patients [113,114]. Furthermore, LTD4 treatment increases goblet cell hyperplasia, with structural alterations in SAECs, such as the loss of cilia and excessive accumulation of mucin. Airway smooth muscle cells show hypertrophy, hyperplasia, and lead to increased thickness of the airway in asthma even early in the disease progression [115]. Airway smooth muscle cells can also have a pro-inflammatory role [116,117], while obesity – by modulating the mechanism of cell contraction in airway smooth muscle cells – is a risk factor for increased AHR in asthmatic individuals [118]. Moreover, obesity-related complications, such as hyperglycemia and hyperinsulinemia, as well as exposure to increased levels of free fatty acids, may contribute to AHR and remodeling via epithelial damage and airway smooth muscle proliferation [119–122]. Insulin resistance has been found to negatively affect asthma control independent of body weight, promoting AHR [123–127]. Notably, metabolic syndrome is characterized by mitochondrial dysfunction, which is also present in airway epithelial cells in asthma [128] and beneficial effects of mitochondrial-targeted antioxidants have been observed in metabolic syndrome and asthma [129–132]. Finally, upregulation of small GTPases in Th-cells has been described in children with non-allergic obese asthma phenotype [133]. These novel biological mechanisms, if confirmed in future studies, may offer more therapeutic targets in pediatric obese asthma.

Table 1
Main factors involved in the interplay between Asthma and Obesity.

Environmental factors	*Diet*
	Vitamin D levels
	Pollutants, including tobacco smoke exposure
Genetic Factors	*Nucleotide polymorphisms (SNPs) in 17q21*
	CHI3L1 gene expression (induced by hyperlipidic diet)
	Other genes involved in asthma or obesity pathogenesis
	Epigenetic modifications
Lung Growth	*Dysanapsis*
	Mechanical factors influencing respiratory physiology
Inflammatory cytokines	*IFN-γ*
	IL-17A
	TNF-α
	IL-1β
	IL-6
	Cysteinyl Leukotrienes
Adipokines	*Adiponectin*
	Leptin
	Resistin

3.3. Lung function, symptoms, and poor response to ICS in obese asthmatics

Many studies have shown that obese adults have worse control of asthma, with more emergency room evaluations and hospital admissions, lower lung function and quality of life, and greater use of systemic corticosteroid courses than normal-weight adults. Studies on children are less numerous but similarly show worse asthma symptoms and control [34], increased risk of exacerbations [30,134] and hospitalization, reduced response to corticosteroids [135–137], and lower quality of life [138] than normal-weighted peers. Interestingly, some recent studies suggest that obesity may not represent a factor increasing at least the risk of severe exacerbations [139,140].

When considering lung function, obese patients may show restrictive or obstructive patterns at spirometry. Recent studies have deepened our understanding of the effect of obesity on lung function, showing that, while in adult asthmatics, the main detrimental effect of obesity seems to be related to mechanical factors, with restrictive pattern spirometry (small reduction of both FEV_1 and FVC and normal or mildy increased FEV_1/FVC ratio as well as reduced total lung capacity and residual volume when considering static lung volumes) [141–143], in children with obesity, an obstructive pattern is usually observed, with slightly higher levels of FEV_1 and FVC and lower FEV_1/FVC ratio due to a disproportionate increase in FVC compared to FEV_1, when compared

with normal-weight peers [144–147]. Forno et al. confirmed such data, regardless of asthma status, in a recent metanalysis, including both adults and children from 62 studies, also showing a significant decrease in $FEF_{25–75\%}$ among overweight and obese children, further confirming the reduction in peripheral airway caliber [148]. In previous studies, Forno et al. reported that obstructive patterns in obese children might be caused by dysanapsis [149], a term coined by Green et al. to describe a disproportionate growth between lung parenchyma volume relative to airway caliber, leading to increased FEV_1 and FVC, with more marked effect on FVC [150], and later defined by the European Respiratory Society as an airflow obstruction with a reduction of FEV_1/FVC associated to normal FEV_1 levels [151].

Further studies demonstrated that both asthma and obesity are independently associated with dysanaptic growth of airways but with stronger effects from overweight [152,153]. Data from the ISAAC study confirmed a linear decline in FEV_1/FVC with increasing BMI, but no association was found with bronchial hyperreactivity, skin prick test, or total IgE [154]. In other words, available evidence suggests that obesity influences lung growth determining incongruences between the growth of the parenchyma and reduced growth in diameter of the airway, which seems to play an important role in airflow reduction in obese children. Mechanisms underlying dysanapsis in the overweight have not been well elucidated, but some authors have suggested that adipokines could regulate the growth and development of the lugs and airways [155,156].

Unsurprisingly, both dysanapsis and suffering from current asthma have been found to be significantly related to the visceral fat index independently of the total fat mass [157]. The degree of airway obstruction caused by dysanapsis has clinical consequences: available evidence shows that there is poorer control of symptoms in asthmatic patients with obesity-related dysanapsis, with more emergency department evaluations, hospitalizations, severe exacerbations, systemic corticosteroid courses, and increased use of medications and rescue medications [149].

However, typical adult mechanical factors may also influence lung function in the pediatric age, since a more restrictive “adult” ventilatory pattern usually appears in adolescence, when thoracic and abdominal fat deposition reduces diaphragm excursion and tidal volume breaths [158,159], which cause alveolar hypoventilation and reduction of lung volumes, with increased airways resistance, ventilation inhomogeneity, reduced compliance of the respiratory system with a reduction in Functional Residual Capacity (FRC) and increased respiratory rate and work of breathing favoring AHR [160–163]. Moreover, obese subjects may suffer from atelectasis of peripheral lung regions, hypoxia-induced pulmonary vasoconstriction and increased pulmonary pressures, interstitial oedema, and pulmonary hypertension [164]. This itself might cause or worsen symptoms such as breathlessness and wheezing. The multiple effects of obesity on respiratory function and physiology may interfere with the delivery of inhaled medications to the small airways and contribute to the resistance to ICS often observed in obese patients with asthma [165,166]. Regarding corticosteroid response, Sutherland et al. reported that obese asthmatics show a reduced ability of dexamethasone to induce MKP-1 (a glucocorticoid responsive gene) in peripheral blood mononuclear cells and in bronchoalveolar lavage cells, causing resistance to corticosteroids [167]. Moreover, genetic polymorphisms could reduce the efficacy of ICS in obese asthmatics by conferring higher resistance, lower receptor binding, and/or lower retention of medication in the lung. However, it should be noted that poor response to ICS may be attributed to the underlying pattern of inflammation, especially when it is characterized by predominant neutrophilic / paucigranulocitic inflammation [168]. Obese asthmatics are more symptomatic but less inflammatory, compared with non-obese patients [26]. This raises a question about obesity-related mechanisms underlying the symptomatology. Cough is one of the key symptoms of asthma and was significantly associated with poor asthma control or disease severity [169–172]. Chronic cough is associated with obesity and gastroesophageal reflux disesases (GERD) [173]. Given the similarity in the demographic features (middle-aged female predominance) of patients with chronic cough and those with obesity-associated asthma [26,174], it is tempting to speculate that cough is one of major symptoms affecting clinical outcomes in obese patients with SA. However, cough has not been properly measured in most clinical trials of SA. Further studies are warranted to investigate obesity-related symptoms and underlying mechanisms affecting clinical outcomes in patients with SA. Interestingly, Orries et al. reported that poor adherence to ICS may be a characteristic of the pediatric obese asthma phenotype [175]. In this study, they analyzed data from 566 asthmatic children aged 4–13 years, who used ICS as maintenance therapy, showing that excess weight was associated with a trend towards increased odds of parent-reported nonadherent behavior and objectively measured general nonadherence, but only in moderate-to-severe asthma, and nonadherent behavior seemed to be mostly intentional. However, it is possible that poor adherence relates to the fact that ICS treatment is not working, either because the diagnosis is wrong, or because the inflammatory phenotype is non-eosinophilic (above). Lastly, obese children are also at higher risk for developing obstructive sleep apnea syndrome (OSAS, which should be as a pro-inflammatory condition per se), obesity hypoventilation syndrome, GERD (although the relevance in asthma is questionable) [176], dysfunctional breathing, and a sedentary lifestyle, with consequent deconditioning that could all contribute to worsening respiratory symptoms [177].

4. Pharmacological treatment of severe asthma in childhood: the role of monoclonal antibodies in targeting inflammatory pathways and potential application in the obese phenotype

4.1. Cellular and molecular pathophysiology of SA in childhood

About 5% of all asthmatic children aged > 6 years show poor control of the disease, with frequent exacerbations and/or persistent airflow obstruction despite maximal prescribed therapy. Such patients have been defined as having “problematic severe asthma”, including both those affected by “difficult-to-treat asthma”, with modifiable underlying factors (poor adherence, poor control of comorbidities, environmental or social factors), and those affected by “severe, therapy-resistant asthma” (SA) who have persistent symptoms despite optimization of the basics of asthma management [178,179].

SA is defined by the ERS/ATS guidelines as asthma requiring treatment with high dose ICS plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy [7,8]. SA affects about 0.23–0.5% of children and adolescents [180]. SA is a complex and heterogeneous disease for which clinical classification does not predict response to treatment and to novel therapies, such as monoclonal agents in particular. So, in the last 10 years, research has been focused on identifying SA endotypes (cellular and molecular mechanisms) and related biomarkers in order to tailor the treatment to each patient [181].

T2-high triggered by airborne allergens is the most common SA endotype in childhood, with blood eosinophilia, eosinophilic inflammation driven by IgE and cytokines, such as IL-4, IL-5, IL-13 [182,183]. In allergic asthma, inhaled aeroallergens are captured by conventional dendritic cells, processed and exposed to T cell receptors of naïve CD4 + T lymphocyte, which are induced to polarize towards Th2 pattern, in a specific cytokine milieu [184]. In non-allergic eosinophilic asthma, ILC2 are the main drivers of inflammation and are activated by alarmins (TSLP, IL-25, and IL-33), which are secreted by epithelial cells after being triggered by infections, irritants, and epithelial damage. This cascade leads to eosinophils recruiting [185].

The T2-low asthma endotype is usually more common in adolescents and adults and is characterized by neutrophilia: here, inflammation is driven by Th1 and Th17 (IL-8, IL-17, and IL-22), which are activated after interacting with environmental factors, including infections and pollutants, through toll-like receptors (TLRs) and pattern recognition

receptors (PRRs). Three main inflammatory patterns have been described in T2-low asthma on the basis of the prevalence of immune cells found in the airways: neutrophilic, mixed, and pauci-granulocytic [186].

In childhood, SA is almost exclusively associated with persistent eosinophilic airway inflammation and T2-high endotype. Notably, there is some evidence of persisting airway eosinophilia even without increased levels of Th2 cytokines in BAL fluid (Il-5, IL-4, and IL-13). Thus, some authors have suggested that in pediatric SA, innate mediators such as IL-33 may have a more important role than Th2 cytokines [187,188]. However, such lack of increased levels of Th2 cytokines could be related to the steroid sensitiveness of Th2 cytokines themselves in treated patients more than actually reduced levels in untreated disease (which for obvious ethical reasons cannot be determined). Regarding T2-low asthma in pediatric SA, such an endotype seems uncommon in school-age asthma and more common in preschoolers, but findings from BAL fluid analysis have demonstrated neutrophilia with a mixed pattern of type 2, type 1, and Th17 inflammation, which may actually represent concomitant bacterial infection or suppression of type 2 inflammation by corticosteroids [189]. Moreover, ILC2 are more numerous in the airways of children with SA and show higher activation by IL-33 [179,190,191].

4.2. Overview of currently available biologicals

In 2003, the marketing of the monoclonal agent omalizumab gave start to the era of personalized treatment in asthma [192]. In September 2022, six monoclonals are available on the market, five of which have been authorized under 18 years of age, with differences by country (Table 2). Such treatments, targeting a single molecule, receptor, or antibody, have selected activity when compared to corticosteroids, limiting side effects and showing efficacy in terms of improved control of asthma, both in children and adults [193]. Considering that monoclonals interfere with selected components of the inflammatory cascade, patients should be carefully evaluated in order to select the most appropriate drug on the basis of their endotype (Fig. 1). However, there is an ongoing debate about which biomarkers should be used and related cut-offs [194,195].

Omalizumab is a humanized monoclonal IgG1 antibody directed against IgE: this molecule is capable of neutralizing the circulating IgE, thus preventing their binding with high-affinity receptors on immune cells and related activation of allergic inflammation, as well as reducing the expression of the high-affinity receptor of IgE (FcR) on the surface of mast cells, basophils, eosinophils, and neutrophils, thereby inhibiting their release of inflammatory mediators [196]. Omalizumab is indicated in patients with severe allergic asthma older than 6 years of age, but in some countries, in those older than 12 the presence of $FEV_1 < 80\%$ may be required. Omalizumab is administered subcutaneously every 2 or 4 weeks, and the dosage depends on the patient's weight and the total IgE level (patients should have IgE values between 30 and 1500 IU/mL and be allergic to at least one perennial allergen). The efficacy and safety of omalizumab have been demonstrated in several randomized controlled trials and "real-life" studies, showing mainly local reactions in the injection site (redness, pain and itch) and headache [197]. Omalizumab

Table 2
Currently available monoclonal agents for the treatment of severe asthma (with different authorization by country).

Biological agent	Mechanism of action	Patients	Indication	Dosage	Biomarkers predicting response	Most common side effects
Omalizumab (Xolair®)	Anti – IgE (binds circulating IgE)	≥ 6 years	Severe allergic asthma with sensitization to at least one perennial aeroallergens (+ FEV1 <80% in patients ≥ 12 years) and IgE 30–1500 IU/mL	• SC injection every 2–4 weeks (75–600 mg depending on weight and IgE levels)	• IgE levels • Blood eosinophils ≥ 260 cells/uL • FeNO ≥ 19,5	Reaction at the site of injection, arthralgia, fatigue, headache, abdominal pain, dizziness.
Mepolizumab (Nucala®)	Anti - IL-5 (binds circulating IL-5)	≥ 6 years	Severe eosinophilic asthma	• 100 mg SC every 4 weeks in patients ≥ 12 years (> 40 Kg) • 40 mg SC every 4 weeks in patients 6–11 years (< 40 Kg)	• Blood eosinophils ≥ 300 cells/uL • Blood eosinophils ≥ 150 cells/uL in patients with well characterized eosinophilic asthma or requiring regular OCS	Reaction at the site of injection, infections, back pain, headache, eczema, abdominal pain, nasal obstruction
Reslizumab (Cinqaero®)	Anti – IL-5 (binds circulating IL-5)	≥ 18 years	Severe eosinophilic asthma	• Intravenous infusion every 4 weeks, 3 mg/Kg	• Blood eosinophils ≥ 400 /uL	Reaction at the site of injection, increase of CPK, myalgia
Benralizumab (Fasenra®)	Anti - IL-5 (binds to receptor)	≥ 12 years (USA) ≥ 18 years (UE)	Severe eosinophilic asthma	• 30 mg SC, first 3 doses 4 weekly, then every 8 weeks	• Blood eosinophils ≥ 300 /uL	Reaction at the site of injection, nasopharyngitis, headache
Dupilumab (Dupixent®)	Anti - IL-4/13 (binds to receptor)	≥ 6 years	Severe asthma with type2 inflammation (peripheral eosinophilia and/or, high values of FeNO)	• Patients taking OCS or with severe AD or CRSwNP: first dose 600 mg SC, then 300 mg every 2 weeks. • Other cases: first SC dose 400 mg, than 200 mg every 2 weeks. • In children 6–11 years: 15–30 Kg: 100 mg every 2 weeks (or 300 mg every 4 weeks); 30–60 Kg: 200 mg every 2 weeks (or 300 mg every 4 weeks); ≥ 60 Kg: 200 mg every 2 weeks.	• Blood eosinophil ≥ 150/ uL • FeNO ≥ 25 ppb	Reaction at the site of injection, conjunctivitis, eye pruritus, bleparitis, oral herpes, transient increase in eosinophils
Tezepelumab (Tezspire®)	Anti – TLSP (binds circulating TLSP)	≥ 12 years	Severe asthma, regardless of endotype	• 210 mg SC every 4 weeks	• Blood eosinophils ≥ 150/uL • FeNO ≥ 25	Reaction at the site of injection, pharyngitis, arthralgia, back pain.

has proven effective in reducing the number of asthma exacerbations, hospitalizations, as well as viral-induced exacerbations through enhancement of the antiviral response mediated by IFNα [193,198,199]. However, it is still unclear how long the treatment should be continued in each patient nor what happens after its suspension in childhood. Real-world studies on this subjects are becoming available, showing the long-term effectiveness and safety of omalizumab after 24 months from its suspension [200]. Omalizumab is particularly effective in patients with comorbidities, such as atopic dermatitis, food allergy, and polysensitization, and eosinophil count ≥ 300 cells/μL and high levels of IgE and FeNO [201]. With regard to long-term safety, analysis of clinical studies published in the last 10 years has not shown an increased incidence of neoplasia in subjects treated with omalizumab [202]. The ongoing PARK (Preventing Asthma in High Risk Kids) study is evaluating omalizumab efficacy and safety in children aged 2–3 years at high risk of asthma development [203].

Mepolizumab is a murine humanized immunoglobulin IgG1 monoclonal antibody directed against circulating IL-5, which is pivotal for the differentiation and recruitment of eosinophils. As a consequence, mepolizumab acts by inhibiting the activation of eosinophils [204]. Mepolizumab is approved for the treatment of patients older than 6 years of age with SA characterized by frequent exacerbations and eosinophilic inflammation with eosinophil count ≥ 150 cells/μL. Mepolizumab is administered subcutaneously every 4 weeks at a dose of 100 mg for adults and children > 12 years of age (or >40 Kg) and 40 mg for children > 6 years (or < 40 Kg). Efficacy and safety have been evaluated in subjects older than 12 years in the DREAM and MENSA study, while the SIRIUS study included patients older than 16 years, showing a reduction in the number of asthma exacerbations and in the administration of oral corticosteroids, and consequent improvement of quality of life [205–207]. The more recently published results from the MUPPITS-2 study, including subjects aged 6–17 years living in disadvantaged urban communities (predominantly Black and Hispanic children) showed that adjunctive therapy with mepolizumab reduced asthma exacerbations, but did not affect other asthma outcomes [208]. Regarding side effects, in the COSMEX study, adults with SA underwent treatment with mepolizumab for 172 weeks showing mainly local reactions at the injection site, back pain, asthenia, and respiratory infections. Similarly to omalizumab, there is no clear indication of the optimal duration of the treatment [209]. The few studies have been conducted or including children aged 6–11 years, confirming mepolizumab's efficacy and safety both in the short and long term [208,210,211].

Reslizumab is an IgG4 kappa monoclonal antibody capable of binding circulating IL-5, which is approved for use in SA with eosinophilic inflammation in adults and is administered intravenously at a dosage of 3 mg/kg every 4 weeks [212]. Reslizumab showed significant improvement in lung function, exacerbations, asthma symptoms, and asthma-related QoL in the phase III BREATH clinical program, including four placebo-controlled efficacy and safety studies in patients with SA aged ≥ 12 years, with better response in those with eosinophils > 400/μL [213,214]. Nevertheless, this drug is currently not licensed in subjects under the age of 18 years.

Benralizumab is a monoclonal antibody of murine origin that binds to both the subunit of the IL-5 receptor and the FcγRIIIa receptor expressed on natural killer cells, inducing rapid and marked depletion of eosinophils via apoptosis. Benralizumab is administered subcutaneously at a dosage of 30 mg every 4 weeks for the first three doses, then every 8 weeks [215], and is approved for the use in SA with eosinophilic inflammation in patients > 12 years in the USA (while it currently cannot be prescribed in those younger than 18 years in Europe). Its efficacy in terms of decrease in the annual asthma exacerbation rate and improvement in FEV_1 as well as in asthma symptoms has been reported in the CALIMA and SIROCCO studies, including patients aged 12–75 years, with better response in those with eosinophils > 300/μL [216,217]. It should be noted that Benralizumab significantly and rapidly reduce eosinophil levels as demonstrated also in the sputum, and some Auhtors suggest that this effect could favour or worsen respiratory infections [218].

Dupilumab is a fully human IgG4 monoclonal antibody directed against the alpha subunit of the IL-4 receptor, capable of blocking both IL-4 and mediated signal transduction from IL-13. Two types of IL-4 receptors have been described: type 1 is expressed in blood cells, while type 2 is expressed in the airways and skin. In the latter, the alfa subunit is coupled to the low-affinity receptor for IL-13, forming a heterodimer capable of binding both IL-4 and 13. When IL-4 or IL-13 bind to their receptors, a cascade is activated involving the production of specific transcription and translation factors determining the activation of Th2 responses [219]. Dupilumab was firstly approved for subcutaneous administration in patients more than 12 years old with moderate-to-severe asthma and eosinophilia (≥ 300 cells/μL) at a dosage of 400 mg followed by a dosage of 200 mg every 2 weeks or 600 mg followed by a dosage of 300 mg every weeks (Table 2).

Two large RCTs evaluated the efficacy and safety of dupilumab: The QUEST study enrolled more than 1500 patients aged > 12 years with moderate-severe asthma despite daily ICS therapy, showing a significant reduction in the number of exacerbations, with better response in patients with eosinophils ≥ 300 cell/μL and FeN0 > 25 ppb [220]. The VENTURE study evaluated the efficacy of dupilumab in severe steroid-dependent asthma independently of the value of eosinophils in the peripheral blood, showing that dupilumab reduced the number of exacerbations and the use of oral steroids as well as determined an improvement in FEV_1 values [221]. The recently concluded VOYAGE study confirmed the efficacy and safety of dupilumab in patients between 6 and 12 years with type 2 asthma phenotype (eosinophils ≥ 150/μL) [222]. Dupilumab is generally well tolerated, and among the most common side effects are reactions at the injection site (edema, pain, itching), conjunctivitis, blepharitis, ocular itching, and oral herpes.

Tezepelumab is a fully human anti-TSLP monoclonal IgG2 antibody, recently approved for add-on maintenance therapy of SA without phenotype or biomarker limitations in patients aged > 12 years. TSLP is produced mainly by lung epithelial cells activated in response to environmental triggers such as viruses, bacteria, fungi, allergens, irritants or physical injury [223]. Tezepelumab binds to TSLP, preventing its interaction with its receptor complex, predominantly on dendritic cells, and inhibiting the consequent activation of a signaling network including JAK1/2-STAT3/5 system, phosphoinositide 3 kinase (PI3K), mitogen-activated protein kinases (MAPK) and nuclear factor-KB (NF-kB). Such pathways induce Th cell polarization towards the Th2 immunophenotype, but also favor the polarization towards Th17, so that it could represent an option in T2 low asthma [224]. Moreover, TSLP activates ILC2 [225]. The efficacy and safety of Tezepelumab were evaluated in several RCTs, such as the NAVIGATOR and PATHWAY studies, showing a reduction in annualized rate of asthma exacerbations and increased pre-bronchodilator FEV_1, independently of baseline blood eosinophil counts and reduces the levels of FeNO, blood eosinophils and serum IgE [226,227]. The most commonly reported side effects are sore throat, arthralgia, and back pain.

4.3. The present and future of monoclonal antibodies in obese asthmatics

A patient-tailored nutritional approach, together with weight loss strategies, is needed in order to improve disease control in obese asthmatics. As expected, a systematic review by Juel et al. showed that weight loss was associated with a 48–100% reduction in asthma symptoms and medication use, with increased asthma control [228]. Some studies on children found similar benefits in terms of improvements in asthma-related quality of life and asthma control [229–231]. In these patients inhaled treatment and inhalation technique should be optimized and periodically reviewed, while adherence should be warranted. However, since obese and overweight asthmatics usually show a poor

corticosteroid response and higher airway hyperreactivity with a persistent obstructive pattern at spirometry, these patients are likely to require different approaches besides daily ICS-only therapy. Adjusting medical treatment is of great importance, including the introduction of add-on therapies such as LABA, but the response to treatment should be carefully monitored. In SA, biologics could represent a useful strategy, but most of them target Type 2 mediated inflammatory pathways, so they could be less effective in those patients who show persistent T2-low inflammation, with elevated levels of interleukins such as IFN-γ and IL-6 [232]. The recent marketing of Tezepelumab could represent a new option in obese asthmatics, considering its effects on the first steps of the bronchial inflammation cascade. Nevertheless, several specific inhibitors of non-T2 immune responses have been evaluated or are currently under investigation for asthma treatment. Anti-TNF agents have been tried but with severe side-effects, including secondary infections leading to reduced interest in further research [233]. Some studies evaluated IL-33 and IL-25, two alarmins which together with TSLP induce ILC2 activation and Th2 cell polarization [234], as potential targets for asthma therapy. Itepekimab, a human monoclonal antibody against IL-33 administered subcutaneously to patients with moderate-to-severe asthma at the dosage of 300 mg every 2 weeks, recently showed efficacy in improving asthma control, quality of life and lung function in patients with moderate-to-severe asthma [235]. Regarding the IL-23/IL-17 pathogenic axis, Risankizumab, an anti-IL-23 monoclonal antibody, was found not effective in reducing sputum neutrophil count and the rate of asthma exacerbations [236]. Brodalumab, a fully human monoclonal antibody targeting the IL-17 receptor, improved asthma symptoms and lung function only in a subset of patients with marked bronchodilator reversibility [237]. Several other molecules interfering with various upstream targets of T2 inflammation, as well as with some downstream kinases (such as those involved in the JAK pathways), are being developed, but none of these therapies is currently being investigated in childhood [238]. Some trials are ongoing on phosphodiesterase (PDE)3 inhibitors (acting as bronchodilators) and PDE4 inhibitors (having anti-inflammatory effects) [239] as add-on therapies in uncontrolled asthma. Moreover, some mitogen-activated protein kinases (MAPK) inhibitors have been shown to restore corticosteroid sensitivity in peripheral blood mononuclear cells from patients with severe asthma [240]. Moreover, as obese inflammation may be related to neutrophilic inflammation and Th17 activation [241] other medications may be useful. Regarding children who are both obese and allergic, it has been hypothesized that mast cells may be involved in the pathogenesis; thus, mast cell stabilizers may have the potential as an additional therapy for this phenotype [242]. Further studies on specific treatments for different asthma pheno/endotypes will contribute to identifying and improving strategies for increasingly personalized asthma management. Lastly, considering the role of IL-6 in contributing to the obese-asthma phenotype, specific monoclonals could represent another option for obese asthmatics. Tocilizumab, a humanized anti-IL-6 receptor antibody, has been used for more than 10 years in the treatment of rheumatoid arthritis and other rheumatological conditions, and has been widely used during the COVID-19 pandemic in order to reduce the onset and progression of the cytokines storm. Nevertheless, there are only some case reports available in the literature on its potential role in treating SA [243].

5. Conclusions

The link and interplay between asthma and obesity are complex and not completely elucidated, especially in children (Table 3). Considering the many factors that affect (in multiple ways) responses to inhaled treatments and, therefore, involved in SA pathogenesis in these patients, international guidelines should include specific strategies to manage asthma in obese patients, especially in children and adolescents. In the near future, research should attempt to identify specific biologic agents directed toward T2-low phenotypes cytokines.

Table 3
Unmet needs / knowledge gaps in the obese-asthma pheno/endotype.

- Exploring knowledge gaps in the inflammatory pathways of the link between obesity and asthma and identify new molecular targets and biomarkers, especially in children
- Understanding how gut microbes may induce inflammation and metabolic disease
- Identifying the role of metabolites associated with certain foods or diets to assess disease risk
- Evaluating obesity-related asthma symptomatology, mechanisms, and the impact of specific symptoms on clinical outcomes
- Investigating the role of genetic variants and how prenatal or early-life environments might influence the epigenome; potential role of epigenetic alterations as biomarkers
- Evaluating the role of dietary supplementation as a treatment strategy in childhood

CRediT authorship contribution statement

MDC, MG and ED conceptualized the study, drafted the initial manuscript, reviewed the literature and critically revised the final manuscript. AK, WJS, AB, DP contributed to the review of the literature and data collection. They also actively participated in manuscript drafting, critically reviewing it. All authors read and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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