REVIEW PAPER

JMS Journal of Medical Science

Mechanisms behind corticosteroid resistance in obesity-induced airway inflammation – a review

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doi: https://doi.org/10.20883/medical.e1034

Keywords: obesity related asthma, corticosteroid resistance, NLRP3 inflammasome, glucocorticoid receptor, bariatric surgery, GLP-1 analogs

Received 2024-04-30
Accepted 2024-09-26
Published 2024-09-30

How to Cite: Włodarczyk P, Sułkowska A, Matshaba VI, Czerwiński F, Piotrowski I. Mechanisms behind corticosteroid resistance in obesity-induced airway inflammation – a review. Journal of Medical Science. 2024 September;93(3);e1034. doi:10.20883/medical.e1034

ABSTRACT

Obese non-eosinophilic asthma is defined as more severe asthma with severe symptoms, moderate airway hyperresponsiveness, elevated blood neutrophils, elevated biomarkers of non-type-2 inflammation, and low responsiveness to inhaled corticosteroids. Increased BMI is associated with a faster decline of FEV1 and FVC in adult asthmatics. The increased leptin concentration is connected with asthma by its ability to induce airway remodelling. Obesity-associated airway hyperresponsiveness is possibly mediated by NLRP3 inflammasome, IL-1β, and ILC3 cells. Increased sputum expression of NLRP3 and IL-1β is linked with increased neutrophil numbers, airflow obstruction, and worse asthma control. Accumulation of proinflammatory cytokines like IL-17, IL-1β, TNF-α, and reactive oxygen and nitrogen species contributes to corticosteroid resistance in obese asthmatics. The processes on the cellular level leading to steroid hyporesponsiveness include a reduced level of glucocorticoid receptor (GR) isoform – GR-α, the dysregulation of the isoforms concentration GR-α/GR-β, increased phosphorylation at Ser 226, and decreased expression of histone deacetylase 2. The best way to improve sensitivity to corticosteroids in this patient group is weight loss. Bariatric surgery is the most effective solution. However, patients may find it beneficial to implement lifestyle changes or to use GLP-1 analogues. Identifying underlying mechanisms of resistance to corticosteroids in obese asthmatics will allow for more effective asthma treatment in the future and could lead to long-term reduction of treatment costs.

Introduction

Asthma is described by The Global Initiative for Asthma (GINA) as a heterogeneous disease characterised by chronic airway inflammation and a history of intense, varying over time symptoms such as wheezing, coughing, tightness in the chest, and shortness of breath with expiratory

airflow limitation [1]. Severe asthma refers to individuals who cannot achieve good control despite high doses of optimal medication. The European Respiratory Society, as well as the American Thoracic Society Task Force, have revised the definition of severe asthma to include asthma that requires step 4–5 asthma treatment protocol according to GINA (high-dose inhaled corticosteroids (ICs) and LABA or leukotriene modifier), or systemic corticosteroids for over 50% of the previous year to prevent it from being uncontrolled or remained uncontrolled despite this therapy [2]. In severe asthma, a higher body mass index (BMI) is an aggravating factor in disease control, and obese patients often require higher doses of ICS [2]. BMI correlates with the risk of new asthma onset in men and women [3]. According to the British Thoracic Society Difficult Asthma Registry, 48% of adult severe asthmatics are obese compared to a 25% prevalence of obesity in the general British adult population [4]. This may result from the obesogenic effects of systemic corticosteroids used in this population [3]. Obese adults are at higher risk of asthma exacerbations and mechanical ventilation than lean adults [3]. Cluster analysis applied on a large cohort defined cluster "obese non-eosinophilic asthma" as late-onset, of predominantly female sex, high symptoms, low atopy, low sputum eosinophils, moderate airway hyperresponsiveness, reversibility of obstruction, and low responsiveness to inhaled corticosteroids [5]. A chronic low-grade systemic inflammatory state is characteristic of obesity, and the levels of C-reactive protein (CRP) and IL-6 are elevated in obese asthmatics, which corresponds with neutrophilic airway inflammation [6]. This observation aligns with the fact that obese asthmatics have reduced responses to conventional asthma treatment. A study on adult-onset obese asthma patients revealed that severe obesity, elevated blood neutrophils, and elevated biomarkers typical for T2-low inflammation are associated with more severe asthma [7]. T2-low airway inflammation is characterised by airway remodelling and poor anti-inflammatory response. Its immunopathogenesis involves intrinsic neutrophil abnormalities, inflammasome pathway activation, and IL-17 pathway activation [2]. Obesity significantly affects asthma patients' corticosteroid resistance, with its plasma concentration after oral administration negatively correlated with BMI and prednisone clearance being positively correlated with BMI [8]. Therefore, to control their asthma symptoms, obese asthmatics are prescribed higher doses of corticosteroids, which leads to iatrogenic side effects and increased healthcare costs. The relation between asthma and obesity underlines the importance of understanding the mechanisms behind corticosteroid resistance in obese asthmatics. It may allow us to find a more effective treatment and improve asthma control.

Decreased pulmonary function

Monitoring pulmonary function, especially forced expiratory volume in 1 second (FEV1), is crucial for asthma control since it reflects airway obstruction, the essence of asthma pathophysiology [9]. Decreased FEV1 is a significant sign of severe asthma and has been correlated with increased BMI. Another parameter that obesity affects is forced vital capacity (FVC), which may result from the accumulation of adipose tissue, limiting the mobility of the thorax and diaphragm. A 2022 meta-analysis found that BMI was inversely related to pulmonary function parameters FEV1 and FVC. Additionally, increased BMI was associated with a faster decline of FEV1 and FVC in adult asthmatics with a BMI greater than 25 kg/m2 [10,11]. However, this obesity-associated phenomenon was not observed in patients without asthma [11]. Reduced FEV1 in obese asthmatics could result from airway synapsis, a physiological imbalance between the calibre of the airways, and the expansion of lung parenchyma [12]. Increased BMI was associated with dysanapsis in children with and without asthma. Additionally, dysanapsis in obese asthmatics is related to severe exacerbations and higher systemic steroid use [12]. The processes behind decreased pulmonary function in obese asthmatics remain unclear, necessitating further investigation beyond the direct physical impact of obesity [9].

Obesity and asthma: adipokine influence on the course of the disease

Obesity alters the inflammatory system regulation, which tends to cause an imbalance between

the pro-inflammatory and anti-inflammatory markers. Accumulation of excessive fat in obese patients results in excess macronutrients in the adipose tissues. Obesity promotes the release of proinflammatory mediators like leptin, resistin [13], Tumor necrosis factor α (TNF-α), IL-6 [14] and interleukin 1 (IL-1) family (including IL-1β [15] and IL-18 [16]) [17,18]. It is suggested that the imbalance between the pro-inflammatory and anti-inflammatory cascade in obese individuals increases the risk of asthma and its severity [19]. Behind the development of obesity lies an increased triglyceride supply, leading to hyperplasia and hypertrophy of the adipose tissue [20]. Hypertrophied adipocytes secrete proinflammatory mediators affecting macrophage activity, further releasing pro-inflammatory cytokines. In addition, the adipocyte experiences hypoxia and accumulation of cytotoxic molecules mediating cellular stress and exacerbating the local inflammatory response [21,22,23]. Obese patients have higher levels of leptin, associated with airway hyperactivity, and an increase in the expression of other pro-inflammatory markers such as TNF-α and IL-6 [24,25,26]. A 2023 study by Wanatabe et al. showed that the building up leptin-producing monocytes might be involved in asthma pathogenesis [27]. A Zhigang Tian study showed that leptin modulates the immune system functions, including activation, differentiation, stimulation of proliferation, and activation of immune cells such as macrophages and natural killer cells [28]. Based on a review article by Matarese et al., leptin polarises helper T cell cytokine production towards a proinflammatory phenotype (Th1 cells producing Interferon-gamma, IL-2) while inhibiting the production of anti-inflammatory cytokines (Th2 cells producing IL-4) which as a result induces inflammatory response and activation of monocytes, CD4+, and CD8+ T cells [29]. Previous studies in overweight patients demonstrated that single nucleotide polymorphisms (SNPs) of leptin (LEP) and adiponectin (ADIPOQ) gene sequences are modified, potentially losing their shielding effect against atopy and asthma instigation. Obesity-induced LEP and ADIPOQ gene modifications are associated with a higher risk of the development of obese asthma phenotype [30]. Leptin plays a significant role in respiratory and lung function, and the expression of leptin receptors in bronchial epithelial cells and lung fibroblasts relates to airway remodelling in asthma [31]. Leptin-induced bronchial remodelling is characterised by goblet cell metaplasia, smooth muscle hypertrophy, increased angiogenesis and airway epithelial cell hypersecretion [32]. Additionally, obesity promotes low levels of anti-inflammatory adipokines, such as adiponectin, which acts as a leptin antagonist. Adiponectin has down-regulating effects on the inflammatory system as it counteracts leptin's effects by inhibiting eosinophil recruitment, further promoting inflammatory response in obese patients [33].

NLRP3 inflammasome–IL-1β–ILC3 axis

Kim et al. proposed that obesity-associated asthma and airway hyperresponsiveness may be caused by inflammation mediated by components of the innate immune response – NLRP3 inflammasome, IL-1β, and ILC3 cells, which are activated in the lungs during nutritional excess [34]. Pattern recognition receptors (PRRs) expressed by macrophages, monocytes, dendric cells, neutrophils, and epithelial cells play a crucial role in activating this innate immune response. PRRs include the membrane-bound Toll-like receptors (TLRs) and cytosolic PRRs like Nod-like receptors (NLRs). PRRs can induce an innate immune response by activating inflammasomes – intracellular oligomeric complexes present predominantly in immune and epithelial cells [35]. The NLRP3 inflammasome constitutes pro-caspase-1, an apoptosis-associated speck-like protein containing CARD (ASC) adaptor protein and nucleotide oligomerisation domain-like receptor protein 3 (NLRP3). Two separate processes are needed for the activation and assembly of NLRP3 inflammasome. First, pathogen-associated molecular patterns (PAMPs) are identified by PRRs, such as Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4). Activation of assembled inflammasome requires a second signal, provided by danger-associated molecular patterns (DAMPs) like extracellular ATP, potassium efflux, and monosodium urate crystals. The NLRP3 inflammasome activation promotes the autocatalysis of pro-caspase and the activation of caspase 1, which converts pro-IL-1β and pro-IL-18 into active forms [36,35,37,38]. Simpson

et al. discovered that the sputum macrophages of neutrophilic asthmatics exhibit higher expression of TLR2, TLR4, NLRP3, caspase-1, and IL-1β [31]. Higher sputum expression of NLRP3 and IL-1β was associated with increased sputum neutrophil numbers, airflow obstruction, and worse asthma control in asthmatics treated with ICs [40]. The high intake of saturated fatty acids (SFAs) is an independent risk factor for asthma development, and high plasma levels of SFAs after a high-fat meal are associated with higher sputum neutrophil percentages. SFAs bind to PRRs, mainly TLR4, triggering proinflammatory processes like the assembly of the NLRP3 inflammasome, activation of caspase-1, and IL-1β release [41]. Epithelial barrier function may be affected by IL-1β, and mucin expression may be elevated by IL-1β and IL-17a stimulation, indicating a possible connection between enhanced inflammasome expression and impaired barrier function [42]. Neutrophil-predominant asthma may be driven by IL-17 produced by TH17 lymphoid cells, which may also be involved in corticosteroid resistance [44]. IL-1β could be essential for regulating IL-17 lung production – blocking the IL-1 signalling by IL-1R antagonist – anakinra led to abolishing the IL-17 pathway [34]. Group 3 Innate lymphoid cells (ILC3s) can mimic the function of Th17 cells, and it was suggested that the production of IL-17 by ILC3s might be a significant contributor to airway neutrophilic inflammation [34]. Unfortunately, a phase II study using a human anti-IL-17 receptor monoclonal antibody (brodulimab) in subjects with moderate and severe asthma did not show a therapeutic effect [44]. In obese mice, the obesity-induced airway inflammation and airway hyperresponsiveness are driven by IL-1β and mediated by an expanded population of pulmonary IL-17+ ILC3 cells. ILC3s produce neutrophil chemoattractants like TNF-α, Granulocyte-mac-

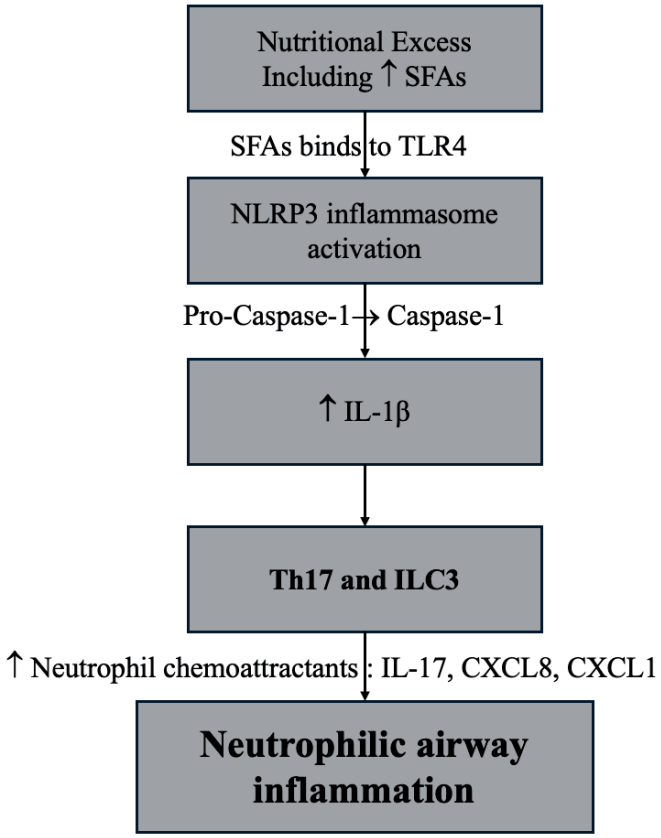

Figure 1. Processes leading to airway inflammation in obese asthmatics. SFAs- saturated fatty acids; TLR4- toll-like receptor 4; NLRP3 – nucleotide oligomerization domain-like receptor protein 3; Th17 – Th17 lymphoid cells; ILC3 – innate lymphoid cells 3; SFAs bind to pattern receptors like TLR4, triggering the assembly and activation of the NLRP3 inflammasome. This promotes the activation of caspase-1 and the release of IL-1β by M1 lung macrophages. IL-1β stimulates Th17 lymphocytes and ILC3 to produce neutrophil chemoattractants like CXCL1, CXCL8, and IL-17, which leads to airway neutrophilic inflammation.

rophage colony-stimulating factor (GM-CSF), chemokine (C-X-C motif) ligand 8 (CXCL8, also known as interleukine-8), and chemokine (C-X-C motif) ligand 1(CXCL1) after IL-1β stimulation [45]. Dexamethasone did not affect the expression of CXCL8 and CXCL1 in ILC3s after IL-1β stimulation, indicating that the IL-1β-ILC3-CXCL8/CXCL1 axis may be associated with corticosteroid resistance and neutrophilic inflammation which are the characteristics of adult-onset obese asthmatics [41]. In a mouse model of severe asthma, a highly specific NLRP3 inhibitor called MCC950 decreased the production of IL-1β and the release of Th2 cytokines and chemokines, preventing airway hyperresponsiveness and decreasing asthma inflammation [46]. The results of another study showed that MCC950 can successfully lower NLRP3 inflammasome-mediated IL-1β release from peripheral blood mononuclear cells (PBMCs) from asthma patients as well as healthy subjects, and the most significant effects occurred in PBMCs from severe asthmatics [47]. This study demonstrated the therapeutic potential for NLRP3 inflammasome inhibition in clinical settings and may represent a new management approach in severe, T2-low asthma. The impact of nutritional excess in obese asthmatics on innate immune response is illustrated in **Figure 1**.

Alterations of glucocorticoid receptor function in obesity-related asthma leading to corticosteroid resistance

Khali et al. describe two types of corticosteroid resistance among asthmatics. Type 1 – cytokine-induced is associated with increased production of certain cytokines and chronic corticosteroid exposure, and Type 2 – primary cortisol resistance is connected with mutations in the glucocorticoid receptor (GR) gene [37]. Glucocorticoid action in cells is mediated by a specific receptor protein, the glucocorticoid receptor (GR). It is expressed in almost all human tissues and organs [48,49]. Alternative splicing of pre-mRNA generates two isoforms of the human glucocorticoid receptor- GR-α and GR-β. GR-α (active isoform of GR) mediates glucocorticoid action, and GR-β (innate isoform of GR) acts as its dominant inhibitor and is unable to bind steroids [48,49]. A body of literature has shown that one of the main causes of steroid resistance in severe asthma is the defect in GR-α and dysregulation of the GR-α/GR-β ratio [41,48,49]. According to some studies, IL-17 cytokines are up-regulating GR-β and down-regulating GR-α [50,51]. Zijlstra et al. showed that reduced glucocorticoid sensitivity positively correlates with neutrophilic airway inflammation [49]. Th17 lymphocytes play a major role in the induction of neutrophilic airway inflammation. Recently, scientists have indicated that Th-17 cytokines such as IL-17A and IL-17F can be an important response mediator to glucocorticoid treatment [50,51]. In respiratory epithelial cells, IL-17A and IL-17F induced the expression of GRβ, which mitigated GRα's anti-inflammatory effect and increased corticosteroid resistance [52]. High levels of IL-17 cytokines have been reported in chronic inflammatory disorders such as obesity. It may lead to steroid resistance in obese individuals with asthma [49–51,53]. A study by Kim et al. revealed that increased NLRP3 inflammasome/IL1-β activation significantly contributed to corticosteroid resistance [34]. This effect may be explained by the fact that IL-1β modulates the TH17 cell differentiation and IL-17 production, and asthmatics resistant to corticosteroids showed increased Th17 cell counts and levels of IL-17A [54]. GRs recruit histone deacetylase 2 (HDAC2) to mediate their anti-inflammatory activity as a key transcriptional co-repressor [55,56]. Studies have shown that the expression of HDAC2 is reduced in severe asthma [57]. The reduced expression of HDAC2 is an effect of increased oxidative and nitrative stress, which leads to the nitration of HDAC2 and its degradation, ubiquitination, and inactivation [48,58]. Obesity-related metabolic dysfunction causes increased oxidant production by activated airway epithelial cells from oxidative and nitrosative bursts [59]. Uncoupling of the NOS (nitric oxide synthase) is a potential mechanism behind increased oxidant production in airway epithelial cells [60]. Arginase is an enzyme that metabolises the L-arginine (substrate for NOS) to L-ornithine and urea [61]. Asthmatics present with increased arginase expression, leading to reduced L-arginine availability for NOS [61]. This, in turn, can lead to an increased level of endogenous NOS inhibitor – asymmetric dimethylarginine, causing enhanced production of reactive nitrogen and

oxygen species in airway epithelial cells. All those changes can result in the inactivation of HDAC2 and reduced response to corticosteroids [62]. Furthermore, the glucocorticoid action may be alternated by the phosphorylation status of GR [48]. Phosphorylation at Ser211 enhances GR activity, and phosphorylation at Ser226 has an inhibitory effect [48,49]. Other studies have suggested that an imbalance between the phosphorylation of Ser211 and Ser226 of GR, which is regulated by MKP (Mitogen-Activated Protein Kinase Phosphatases), may contribute significantly to steroid resistance in obese asthmatics [49]. MKP is an anti-inflammatory marker of glucocorticoid-induced activation. Obese asthmatics with poor response to steroids have significantly reduced MKP expression. Induction of MKP by glucocorticoids may be inhibited by increased release of pro-inflammatory cytokines associated with obesity. MKP is a phosphatase that inactivates p38 MAPK (p38 mitogen-activated protein kinase) via dephosphorylation [25,49,63]. Increased level of p38 MAPK was observed in peripheral blood mononuclear cells and bronchoalveolar lavage in obese asthmatics. It leads to the phosphorylation of GR at Ser226, which inhibits transcriptional activity, promotes nuclear export, and has an inhibitory effect on GR function [41]. Additionally, mediated by NLRP3 inflammasome release of IL-1β could induce Ser226 phosphorylation, which may increase steroid hyporesponsiveness neutrophilic asthma [40,41]. Described mechanisms behind corticosteroid resistance in obese asthmatics are illustrated in **Figure 2**. Lea et al. highlighted that inhibitors of p38 MAPK can help restore corticosteroid sensitivity in peripheral blood mononuclear cells of patients with severe asthma [55]. Clinical trials showed the beneficial effects of using p38 MAPK inhibitors in chronic obstructive pulmonary diseases, with the levels of inflammatory biomarkers significantly reduced in two clinical trials [65,66]. TNF-α secreted by macrophages increases the sputum neutrophilia and induces airway hyperresponsiveness. A study by Jiang et al. showed that TNF-α significantly increased TNF-α and IL-6 mRNA expression and decreased mRNA and protein levels of GRα via NF-κB and p38 MAPK signalling pathways in nasal epithelial

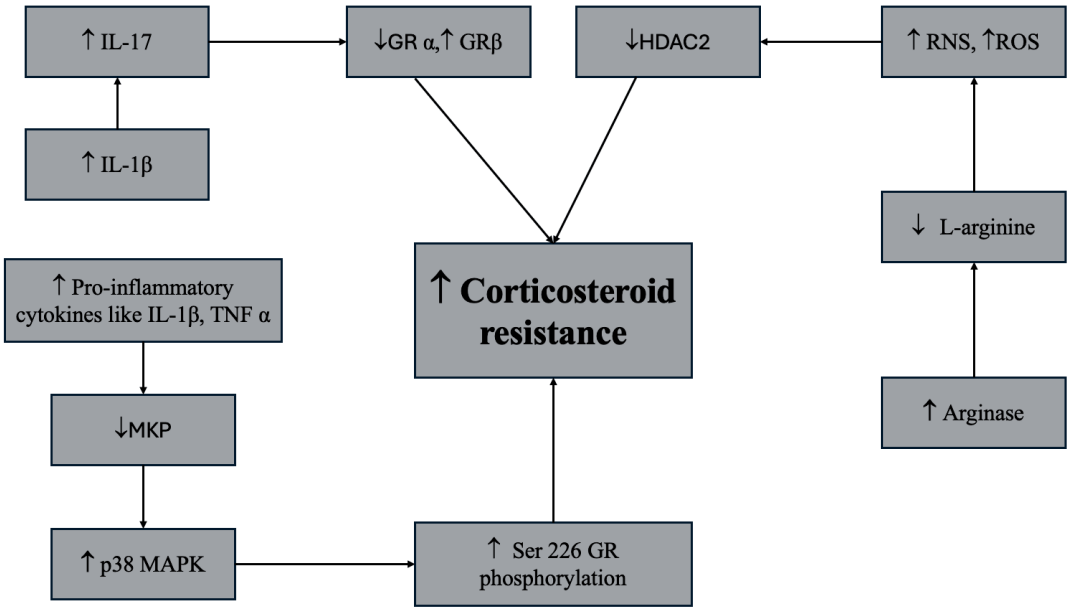

Figure 2. Mechanisms behind corticosteroid resistance in obese asthmatics. GR-glucocorticoid receptor; GR-α – α isoform of glucocorticoid receptor, GR-β – β isoform of glucocorticoid receptor and down-regulating GR-α; HDAC2-Histone deacetylase 2; RNS – reactive nitrogen species; ROS- reactive oxygen species; TNF-α-Tumor necrosis factor α MKP Mitogen-Activated Protein Kinase Phosphatases; p38 MAPK – p38 mitogen-activated protein kinase. IL-1β stimulates Th17 lymphoid cells to increase the release of IL-17. IL-17 cytokines down-regulate active GR-α and upregulate innate GR-β isoform; Higher expression of arginase leads to lower levels of L-arginine – substrate for nitric oxide synthase. Those changes lead to increased production of RNS and ROS. Increased oxidative stress results in lower expression of HDAC2 and reduced GR-mediated anti-inflammatory activity; Reduced expression of MKP results from the accumulation of pro-inflammatory cytokines like TNF-α and IL-1β. The result of lower expression of MKP is an increased level of p38 MAPK, which leads to the GR phosphorylation at Ser226- which has an inhibitory effect on GR.

cells of patients with chronic rhinosinusitis, leading to reduced corticosteroid response [67]. The use of golimumab (another anti-TNF-α drug) in severe asthma was terminated after the phase 2 study due to the increased risk of severe infections [68]. Holgate et al. failed to demonstrate the clinical efficacy of etanercept in patients with severe asthma. However, no unexpected safety findings were observed [69]. Future research must evaluate the long-term benefit profile of anti-TNF-α medication in severe neutrophilic asthma.

Bariatric surgery as a way to lose weight and increase asthma control

Post-bariatric surgery patients have a more significant weight loss (22–36%) compared to patients who received non-surgical treatment (4.1–14.2% weight loss) [70]. Post-bariatric surgery weight loss improves airway responsiveness, asthma control, lung function, and the quality of life of obese asthmatics, reducing exacerbations and hospitalisations [18,71,72]. Guerron et al. showed that as early as 30 days post-bariatric surgery, the number of prescribed asthma medications was 27% lower than the pre-operation. The reduction was progressive over time, and asthma medication use was lower by 48% two years after surgery than the pre-operative average. There was no significant difference in the reduction of asthma medication use depending on the type of surgery (Sleeve gastrectomy, Adjustable gastric band, Duodenal switch, Roux-en-Y gastric bypass), and all bariatric procedures showed a similar pattern [71]. The concentration of pro-inflammatory markers TNF-α, leptin, IL-6, IL-8, and IFN-gamma has decreased with weight loss in obese asthmatic patients after bariatric surgery [18,73]. The underlying mechanisms for these improvements must be elucidated. Womble et al. suggested that vertical sleeve gastrectomy in mice would improve glucose tolerance, airway inflammation, resistance, and fibrosis induced by obesity and chronic allergen challenge [74]. Research has also shown that bariatric surgery can influence the gut microbiome [75], which has been studied for its role in obesity-induced conditions like asthma. Obesity increases proinflammatory molecules in the blood and alters the gut microbiome, with a decreased abundance of *Akkermansia muciniphila* directly associated with asthma severity [76]. By raising the gastrointestinal pH, bariatric surgery induces a substantial shift in the gut microbiome, with increased *Akkermansia muciniphila* abundance at three months and sustained through 12 months [9,75]. The positive effect of bariatric surgery on lung function in the obese population has also been reported. Nguyen et al. study found that obese patients after laparoscopic gastric surgery experienced an improvement of 12% in FEV1, 9% in FVC, 15% in peak expiratory flow (PEF), and 30% in forced expiratory volume at 25–75% of FVC after 12 months. The improvement occurred as early as three months post-intervention. The fraction of patients with an abnormal FEV1/FVC ratio (defined as less than 0.8) declined from 9.6% before surgery to 1.9% after surgery [77]. Due to the invasive character of bariatric surgery, the number of obese asthmatics with severe symptoms who can be operated on is limited.

Additionally, severe asthma increases the operational risk. Lifestyle changes, including diet and exercise interventions, are not as effective as bariatric surgery but might help more patients lose weight and positively impact asthma course [78]. A randomised study showed that even 5% weight loss is associated with improved asthma control and significant increases in FEV1 and FVC [78]. Scott et al. showed an association between gynoid fat reduction and neutrophilic inflammation in women. In contrast, in men, there is a correlation between reduced saturated fat consumption and absolute counts of sputum neutrophils [79]. Asthmatics in the diet group who improved asthma symptoms had significantly lower consumption of calories, carbohydrates, total fats, saturated fats, and polyunsaturated fatty acids (PUFA) [78]. Saturated fats and PUFA consumption lead to inflammatory responses [78]. Mediterranean Diet rich in antioxidants and cis-monounsaturated fatty acids was associated with reduced asthma symptoms in children and lung function improvement [80]. Increased physical activity augments weight loss, improves lung function, and has anti-inflammatory effects. Aerobic training reduces the fractional exhaled nitric oxide (FeNO) and serum levels of proinflammatory mediators like IL-4, IL-6, TNF-α, CCL2, and leptin and increases the levels of anti-inflammatory

cytokines like IL-10 and adiponectin [81]. Physical activity and caloric restriction improve the level of 25(OH)D by reducing visceral fat tissue and increasing the availability of fat-soluble vitamin D. Reduced serum levels of vitamin D are associated with worse asthma control and exacerbation [82].

GLP-1 analogues

Insulin resistance (IR) associated with obesity is an independent risk factor for adult asthma development. Studies have shown that IR in patients with asthma is related to decreased lung function and lower response to treatment with corticosteroids and β2-adrenergic agonists [83]. A group of medications widely used in type 2 diabetes known as glucagon-like peptide 1 (GLP-1) receptor agonists may also improve asthma control in obese asthmatics. They enhance glucose tolerance and are linked with weight reduction, downregulation of inflammatory response, and reduced cardiovascular risk in obese patients [84,85]. GLP-1 receptor agonists work similarly to the hormone GLP-1, which is primarily secreted by intestinal enteroendocrine L-cells in response to food intake. In patients with diabetes, GLP-1 receptor agonists increase insulin secretion and suppress glucagon release [85]. The potential mechanisms behind weight loss caused by GLP-1 analogues are appetite suppression, lowered food intake, slowdown of gastric emptying, and prolonged satiety [84]. The average weight loss varies depending on dosage, administration route, and drug type. For instance, studies on two agonists showed that the mean weight loss with liraglutide (administered daily, subcutaneously) was 4.8–7.2 kg [85], and with semaglutide (administered once a week, subcutaneously) was 10–15 kg [86]. Research performed on obese asthmatic murine model reported increased levels of GLP-1 receptors in lung epithelial cells, and administrations of GLP-1 receptor agonists reduced levels of neutrophils and, thereby, airway inflammation in those mice [87]. Foer et al. reported that patients with asthma and type 2 diabetes who received GLP-1 receptor agonists had fewer asthma exacerbations than patients treated with other medications [88]. Although the current results are promising, to obtain more convincing evidence, randomised, placebo-controlled trials addressing both obesity and asthma are required to evaluate the effectiveness of using GLP-1 receptor agonists in obese asthmatics.

The beneficial effect of azithromycin on severe asthma course

Studies have shown that low-dose azithromycin can effectively treat severe asthma [89,90]. Macrolide antibiotics have two essential properties: anti-bacterial and anti-inflammatory [90]. Gibson et al. conducted a study for over 48 weeks on 420 adult patients with severe asthma who were administered 500 mg of azithromycin two times a week. The number of exacerbations significantly decreased, and quality of life improved in the azithromycin-treated group compared to patients who were administered placebo [90]. Those effects were observed in both non-eosinophilic and eosinophilic types of asthma. Thomas et al. evaluated the long-term impact of azithromycin on asthma remission in patients with persistent, uncontrolled asthma. After 12 months in the azithromycin arm, the proportion of patients that achieved remission was significantly higher compared to the placebo arm (50.6% vs 38.9%; $p = 0.032$) [91]. Currently, an ongoing study will evaluate the effect of azithromycin on asthma exacerbations in obesity-induced asthma [92].

Further studies are needed to find out how azithromycin reduces the number of asthma exacerbations. Possible mechanisms include pulmonary bacterial clearance and stimulating both IL-6 and IL-17 pathways. In conclusion, azithromycin may be a practical addition to asthma treatment in patients who are most vulnerable to exacerbations and who cannot control asthma symptoms with appropriate inhaled therapy [90,93].

Conclusions

Obese asthmatics tend to present with more severe asthma, experience more exacerbations, and require higher doses of ICs or even need to use systemic steroids to achieve satisfactory asthma control. It may lead to iatrogenic side effects and higher medical costs, which underlines the importance of understanding the mech-

anisms behind steroid resistance in obese asthmatics. Unfortunately, most of the research is still theoretical, and further exploration is required to understand the mechanisms behind corticosteroid insensitivity in this patient group. Identifying underlying resistance mechanisms to corticosteroids in obese asthmatics will allow for more effective asthma treatment in the future and could lead to long-term reduction of treatment costs. Some promising therapies may improve disease control in obese asthmatics, including blocking IL-1β signalling, using anti-TNF-α-medications, or using anti-IL-17a antibodies; however, future research needs to evaluate the long-term benefit profile of anti-TNF-α medication in severe neutrophilic asthma. Currently, research suggests that the best way to improve asthma control and reduce the demand for the use of ICs in obese asthmatics is weight loss. Currently, bariatric surgery is the most effective solution. However, patients may find it beneficial to implement lifestyle changes or use GLP-1 analogues.

Methodology – Search strategy

Papers published between 2005 and 2023 were identified by PubMed literature searches using the terms: "obese asthma"; "NLRP3 inflammasome", "IL-1β"; "IL-17", "ILC3", "corticosteroid resistance"; "steroid-resistant asthma"; "glucocorticoid receptor ";" Histone deacetylase 2"; 'Mitogen-Activated Protein Kinase Phosphatases'; "bariatric surgery"; "GLP-1 analogues"; Additional publications were selected through the internet from the references of those papers. Only articles in English were considered.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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