Asthma Exacerbations and Glucagon-Like Peptide-1 Receptor Agonists: a Review of the Current Evidence

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ABSTRACT

Asthma is a chronic inflammatory disease involving multiple mediators and cytokines. While our current treatments have shown significant therapeutic benefits, there still appear to be some patients who, despite aggressive therapy, good adherence, and inhaler technique, continue to have exacerbations. Exacerbations lead to loss of lung function, exposure to systemic corticosteroids, effects on quality of life, and even mortality. There is a large number of glucagon-like peptide-1 (GLP-1) receptors in the lung even compared with other organs, and studies have shown evidence of reduced exacerbations in asthmatics treated with GLP-1 receptor agonists (GLP-1 RA). While weight loss may affect lung mechanics, evidence of inflammatory changes has been revealed that could explain this relationship. This article will review the data behind these conjectures and outline potential clinical utility and the need for future studies to truly understand the role of GLP-1 receptors in the lung.

PLAIN LANGUAGE SUMMARY

Obesity is a common issue and a comorbidity that negatively impacts asthma outcomes. Weight loss can improve asthma outcomes, and evidence shows that a particular type of therapy currently indicated for diabetes that assists in weight loss and targets receptors that are abundant in the lungs will outperform other therapies. GLP-1-receptor agonists may particularly help overweight patients who have asthma to control the disease as best as possible and prevent exacerbations.

Video Abstract

Keywords: Asthma; Obesity; Phenotype; Weight loss; Inflammation
Key Summary Points

- Obese patients with asthma are at high risk of therapy resistance and exacerbations.
- Obese patients with asthma with or without metabolic syndrome/diabetes may well have different phenotypes of asthma.
- Current therapy options are insufficient for this phenotype.
- GLP-1 signaling with significant receptors found in the lungs is an exciting novel target for treatment of chronic airway inflammation in asthma.
- GLP-1 RAs may improve asthma control and decrease exacerbations with mechanisms including weight loss/mechanical changes as well as anti-inflammatory effect.

DIGITAL FEATURES

This article is published with digital features, including a video abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.21346428.

INTRODUCTION

Asthma is a common illness; estimates are that it affects 4% of the global population [1], with rates continuing to increase every year. Asthma control continues to be globally elusive, and exacerbations continue to plague our patients. Current pharmacologic therapy includes inhaled corticosteroids (ICS)/formoterol as required (PRN) or regular low dose ICS stepping up to combination inhaled steroids and long acting beta agonists (ICS/LABA) with additional therapies including leukotriene receptor antagonists (LTRA) or long acting anti-muscarinic agents (LAMA) to biologics, all on top of reliever therapies which can be a beta agonist or an ICS/Formoterol combination. In 1999, the European Respiratory Society (ERS) [2] defined therapy-resistant asthma as persistent asthma symptoms or evidence of obstruction despite 6 months of appropriate guideline-based asthma management. Subsequently, the ERS and American Thoracic Society [3] defined severe asthma as asthma requiring high-dose inhaled corticosteroids (ICSs) plus a second controller medication. Persistent and severe asthma has a prevalence of 5–10% among patients with asthma, with these patients using a disproportionally large amount of all asthma resources [4]. The knowledge regarding the pathophysiological mechanisms of asthma and different phenotypes of asthma has led to multiple and increasing therapeutic options. Biologic drugs for severe asthma, especially those with the high-T2 phenotype (type 2 inflammation describes an inflammatory pathway involving a subpopulation of CD4^+ T cells known as Th2 cells that secrete IL-4, IL-5, and IL-13) of disease, have completely revolutionized our treatment, allowing the opportunities precision medicine approach [5]. Despite the availability of different treatments that have been proven to be effective in most patients when used properly and regularly, we still do not have overall satisfactory asthma control [6] and continue to have significant levels of asthma exacerbation [7] and healthcare costs [8]. There is a group of patients with low-T2 airway disease that presents a particular challenge, with outcomes even with current biologics in this group being inferior to those who have high-T2 disease [9]. Current options for low-T2 disease include macrolides and bronchial thermoplasty, and further options would be welcomed [10]. Asthma and the comorbidity of obesity with and without concomitant diabetes is a particular subgroup of patients [11]. Both T2 and non-T2 inflammation can be found in obese patients with asthma. These obese patients show an association with a non-eosinophilic phenotype that is characterized by late-onset asthma in middle-aged females with high expression of...
symptoms [12] and who may have some resistance to current therapeutics, including steroid resistance [13], tend to have poorer asthma control and higher risk of exacerbation [14].

As such, new treatment options are required, and current data that will be reviewed make the glucagon like peptide-1 receptor antagonist (GLP-1 RA) class a potential novel asthma therapy. We will review the relationships between asthma and diabetes, obesity, and weight loss, followed by a description of the GLP-1 RAs and the data on this class in asthma outcomes. At the end of the article, we have provided a case report from the first author’s practice to put a clinical context to the data presented.

Asthma and Diabetes Mellitus

Both asthma and type 2 diabetes (T2D) are common conditions around the world, affecting hundreds of millions of people [15, 16], with obesity levels also increasing worldwide in similar if not higher numbers, especially in developing countries as they adopt a more western lifestyle [17]. Inflammation seems to play a central role in all these conditions, but the exact mechanisms are still not fully understood. T2D is a multifactorial disease characterized by a decrease in insulin sensitivity and by a defect in insulin secretion and chronic inflammation [18].

Asthma is associated with respiratory comorbidities such as obstructive sleep apnea syndrome [19] as well as systemic diseases such as obesity [20], diabetes mellitus [21], and metabolic syndrome [22]. The association can be explained by many potential factors, including low-grade systemic inflammation [23], genetic pleiotropy [24], oxidative stress [25], and use of corticosteroids [26, 27]. There may be a synergistic effect of the interaction of this asthma phenotype of asthma and obesity on the increase in circulating levels of inflammatory cytokines as well as the mechanically led lung function changes. Asthma has been associated with an increased risk of T2D in women, regardless of body mass index (BMI), indicating that chronic inflammation is likely a contributory factor [28]. T2D and asthma may share common pathophysiology with respect to chronic inflammation [29]. For example, it has been postulated that the altered gut flora results in insulin resistance, which is a hallmark of T2D, via numerous pathways including lipopolysaccharides (LPS). LPS is thought to result in low-grade inflammation, which is also implicated in the airway inflammation in patients with asthma as discussed below.

Decreased lung function in some patients with diabetes may be related to other mechanisms, including alterations in the alveolar capillaries and pulmonary arterioles, autonomic neuropathy, and elastic loss secondary to the glycosylation of the pulmonary parenchyma collagen [30].

Asthma and Obesity

With the rising obesity prevalence, the relationship between obesity and asthma, which includes the risk of it being a risk factor for more severe and treatment-resistant asthma [31] is an area of concern and interest [32]. While the two diseases may share a genetic basis [33], obesity may be a potentially modifiable risk factor for asthma [34]. The mechanisms of this relationship may include obesity leading to a reduction in lung compliance and lung volumes, disruption of the ventilation–perfusion relationship, and higher levels of proinflammatory hormones produced in adipose tissue that may worsen airway inflammation [35].

Obesity is associated with low-grade systemic inflammation, characterized by increased levels of inflammatory markers such as Toll-like receptor 4 (TLR4), tumor necrosis factor-alpha (TNF-α), IL-6, IL-1β [36], IL 17, leptin [37], and resistin [38]. Leptin levels are increased in obese adults and children with asthma compared with those without asthma [39]. The levels are also higher in those with uncontrolled asthma compared with controlled asthma [40]. Leptin may also be a risk factor for the development of allergic disease and atopy [41]. In addition, obesity causes metabolic tensions within the cell, leading to stress in the endoplasmic reticulum and overproduction of reactive oxygen
Species, causing damage to mitochondrial components and mitochondrial loss, and contributing to insulin resistance and causing greater activation of inflammatory cells [42]. These inflammatory changes lead to association with multiple other diseases, including dyslipidemia, insulin resistance, hyperinsulinemia, and diabetes [43], with insulin resistance being more strongly related to the risk of asthma in adults than obesity [44].

Interestingly, asthma and polycystic ovarian syndrome (PCOS) have also been found to be related. Whether it is the inflammation involved in both conditions, or the relationship with metabolic syndrome, epidemiological studies have demonstrated that PCOS correlates with asthma. Women with PCOS are prone to develop asthma while patients with asthma tend to exhibit increased susceptibility to metabolic syndrome, impaired fertility, irregular menstruation, and other clinical symptoms similar to PCOS [45]. In addition, obese patients who were considered metabolically unhealthy defined as a BMI of ≥ 30 kg/m² and any one of increased waist circumference, insulin resistance, low physical activity, hyperlipidemia, or hypertension compared with obese without metabolically unhealthy obesity had a higher likelihood of having exacerbations or using emergency department services for their asthma, indicating that there are more factors involved than just BMI alone [46].

Asthma may also coexist with obstructive sleep apnea (OSA), which has been termed “alternative overlap syndrome” [47] and has been considered by some as a possible separate phenotype [48]. Combined upper and lower airway disease is likely a factor in the relationship with obesity, as OSA is clearly more common in obese patients, but often overlooked [49]. OSA seems to be more common with increasing disease severity [50], indicating that it should perhaps be proactively evaluated for in uncontrolled asthmatics [51]. The relationship between other comorbidities such as rhinitis [52] and gastroesophageal reflux disease (GERD) [53] with OSA may be significant factors in poor asthma control in these patients as well [54]. It has also been considered that there may be fatty tissue deposited in both upper and lower airways in those with obesity that could further worsen obstruction [55]. OSA may also complicate asthma owing to specific inflammatory changes of the airways with predominance of neutrophils and C-reactive protein (CRP) as well as the presence of the cytokine interleukin 8 with subsequent changes in the thickness of the basement membrane and remodeling of the airway [56]. Interestingly, continuous positive airway pressure (CPAP, treatment for OSA) therapy for as short of a period of 1 month has been shown to reduce CRP levels [57].

As such, weight loss seems to be a potential therapeutic option for obese patients with asthma as excess weight may both lead to asthma development as well as worsen the clinical manifestations [58].

**Weight Loss and Asthma Improvement**

Multiple studies reviewing the effect of weight loss in obese patients with asthma show an improvement in asthma control, use of asthma medication (both controllers and relievers), dyspnea, exercise tolerance, acute exacerbations of asthma, including hospitalizations due to asthma [59], and lung function [60]. There is some concern, however, that, while weight loss in obese patients with asthma is associated with improvements in level of lung function and airway responsiveness to inhaled methacholine [61], no significant improvements have been observed in exhaled nitric oxide [62] or other markers of eosinophilic airway inflammation [63].

Reduction in inflammation due to weight loss has been postulated, but not completely supported in literature. As such, the cause of improvement may be due to a reduction in mass loading on the respiratory symptoms. Perhaps we are not seeing actual asthma in the overweight or obese patients, but asthma-like symptoms caused by changes in lung mechanics instead of being caused by asthmatic airway inflammation [64]. Another theory is that obese patients with asthma represent a distinct asthma phenotype entirely. One study [65] revealed that obese patients with asthma had an increase in neutrophilic airway inflammation,
while no significant difference in the sputum eosinophil percentage was found between obese and nonobese patients. This may also explain why we see a less than optimal response to our current conventional asthma therapies in obese patients with asthma [27]. Neutrophils are not only the first responders to acute inflammation, but they also help resolve the inflammation. Clinical studies show that chronic respiratory illnesses like asthma and chronic obstructive pulmonary disease (COPD) are associated with systemic and local elevation of neutrophils. Murine studies suggest that airway-infiltrating neutrophils not only help initiate airway inflammation but also prolong the inflammation [66]. Blood serum CRP and fibrinogen levels were higher in obese compared with nonobese people with asthma [67].

Of course, there are different ways to lose weight, which may also be a factor. These can be broken down into surgical, behavioral, and pharmacologically assisted. Studies have looked at these different mechanisms of weight loss in people with asthma and the results of such.

Studies have looked at nonsurgical and nonpharmacologic weight loss. In general, studies showed that weight loss improves asthma control [68, 69]. An 8-week trial of supervised weight reduction with low-energy diet showed a mean weight loss of 14.2 kg, and significant improvement was observed in individuals in the intervention group in forced expiratory volume at one second (FEV1), forced vital capacity (FVC), dyspnea, use of rescue medication, and number of exacerbations, compared with controls [42]. A similar smaller study with the same process with a very-low-calorie diet and a 13.7 kg weight loss showed improvement in peak flow (PEF) variability, morning PEF and FEV1, mid-expiratory flow, airway resistance (Raw), and functional residual capacity [60]. Other trials showed weight loss leading to improvements in FEV1 and asthma control only [70], and similar trials showed also improvements in FEV1, FVC, and total lung capacity, but no significant improvement in airway responsiveness (i.e., airway responsiveness to inhaled methacholine. This suggests that weight loss improves respiratory function independently of the severity of airway responsiveness, rather than by improving asthma perhaps owing to mechanical issues rather than treating inflammation.

Adherence to weight loss diets is consistently low, and one author studied alternate-day low-calorie diets [71]. The weight loss was not very impressive, only 8% of pre-study weight, but the participants showed improvements in both asthma symptoms and lung function (PEF, but not spirometry) as well as in markers of inflammation (including serum tumor necrosis factor-α), and oxidative stress (including 8-isoprostone and nitrotyrosine). This trial suggested that that alternate-day calorie restriction could have beneficial effects on the underlying inflammatory process in obese patients with asthma.

Lastly, while improvements in asthma control can be achieved via weight loss alone, a similar improvement in asthma control can be achieved with a more modest weight loss if there is a corresponding improvement in aerobic capacity [72]. Exercise itself seems to have anti-inflammatory effects. In a study of non-obese patients with asthma, exercise had anti-inflammatory effects in the airways [73] and systemically [74] even in the absence of weight loss. In a study of overweight and obese patients with asthma, an exercise intervention led to a reduction in eosinophilic airway inflammation, even though there was only modest weight loss [75]. Mechanistically, exercise itself may have a potential place as part of anti-inflammatory therapy for asthma.

Bariatric surgery is a very successful weight loss treatment, with data also showing improvement in asthma outcomes. Data from these trials have shown that this treatment when associated with weight loss can reduce emergency department visits and hospital admissions [76], lung function [50, 77, 78], and airway responsiveness [44, 61, 79, 80] in most but not all studies [50], but interestingly this change did not persist in all patients on follow-up [81]. The presence of metabolic syndrome may be a factor in whose control improvements persist, and may negatively affect asthma control, as one trial showed that those with metabolic syndrome at baseline and during follow-up (i.e., their metabolic syndrome did not
resolve with surgery) had the highest risk for losing asthma control at subsequent visits, with the findings statistically significant even when adjusting for weight loss [82].

The effect of bariatric surgery and lung inflammation was measured in a 12-month longitudinal study, comparing obese patients with and without asthma versus obese patients with asthma but no surgical intervention [63]. Findings included an improvement in markers of systemic inflammation, including high-sensitivity CRP, adiponectin, and leptin, in both groups having surgical intervention, but a decrease in mast cell numbers in bronchial biopsies was seen only in the group of patients who underwent bariatric surgery. This study, the first to use bronchial biopsies, showed that weight loss related to bariatric surgery did improve both systemic and airway inflammation. Even this study, however, showed that other markers of inflammation such as TNF-\(\alpha\) and submucosal cell counts of eosinophils and neutrophils were not affected.

Pharmacologic agents to assist in weight loss [83] include medications that assist in weight loss as a side effect, such as topiramate (anti-epileptic), roflumilast (COPD), bupropion and fluoxetine (depression), and methylphenidate (stimulant). In other medications, this is a desirable effect to assist in disease management such as sodium–glucose transport protein 2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor (GLP-1) agonists when used to treat type 2 diabetes mellitus and topiramate when used for migraine prophylaxis and for patients with binge-eating disorder. Other medications are used for weight loss with indications in different parts of the world, including orlistat, bupropion/naltrexone, cethin (an amphetamine), orocaserin, a combination drug phentermine/topiramate, and several different GLP-1 receptor agonists. Data on the effects of these medications on asthma outcomes have been found only with metformin and GLP-1 receptor agonists (compared with other diabetic agents). These will be reviewed below.

GLP-1 Receptor Agonists (RA)A
Background and Anti-inflammatory Effects

Glucagon-like peptide (GLP)-1 is a gut incretin hormone secreted from enteroendocrine cells after food intake that stimulates insulin secretion in a glucose-dependent manner. In addition, GLP-1 inhibits gastric emptying and induces satiety [84, 85]. Although it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) enzyme, its is quickly activated after binding to its receptors found throughout the body tissues. However, it is important to note that the level of GLP-1 is diminished in people with obesity and diabetes. Nevertheless, owing to the numerous GLP-1 receptors expressed in several tissues in the human body, it not surprising that the pleiotropic effects of GLP-1 RA have been identified.

Since 2016, numerous cardiovascular outcome trials on GLP-1 RA have been carried out, examining the cardiovascular effect of GLP-1 RA. These trials demonstrated overwhelmingly positive results regarding major adverse cardiovascular events (MACEs). Smaller analyses showed benefits in renal outcomes, mainly reduction in albuminuria. A more renally dedicated trial examining the effect of GLP-RA on kidney is currently ongoing.

In humans, GLP-1 receptors are expressed in several tissues, including lung tissue. Lungs remarkably contain the highest relative level of GLP-1 receptors in the body [86], and GLP-1 appears in much higher concentrations within bronchoalveolar fluid compared with serum, which may indicate a specific function in the lungs [87]. It is plausible that GLP-1 is produced by pulmonary neuroendocrine cells as GLP-1 is present in human bronchoalveolar lavage fluid samples [88].

GLP-1 is known to modulate inflammation. Nuclear factor-kappa B (NF-kB) is an important transcription factor that plays a key role in the inflammatory process by regulating cytokine activities within the airway. Glucocorticoids’ anti-inflammatory action occurs by inhibiting NF-kB-induced gene transcription, while GLP-1 analogs can inhibit the activation of the NF-kB pathway. In people with T2DM, GLP-1 analogs
have been shown to reduce serum levels of TNF, CRP, and NF-κB through the modulation of the protein kinase A-dependent signalling pathway, while lipopolysaccharide (LPS)-induced macrophage activation was attenuated through the same pathways, which led to a reduction in surface expression of CD11b and CD69 and production of IL-4, IL-8, and IL-13 in eosinophils [89]. The same research team showed lower GLP-1 receptor expression on eosinophils in allergic asthmatic cohorts compared with non-asthmatic patient cohorts, while Th2 cytokine production and markers of eosinophil activation were suppressed with the use of GLP-1 analogs [91]. Liraglutide decreased mucus production, airway inflammation, and proinflammatory cytokine production in one murine study [91]. L-Arginine, which is converted to nitric oxide via nitric oxidase, stimulates the production of GLP-1, and dysregulation of l-arginine in obese patients leads to increased risk of airway inflammation and bronchoconstriction [85]. The production of advanced glycation products (AGEs) increases with prolonged hyperglycemia, dyslipidemia, and oxidative stress, and the binding of AGEs to their receptors (RAGE) can further worsen the inflammatory state. GLP-1 has been shown to attenuate the effect of arginine dysregulation and RAGE activation, which is one of the mechanisms of airway inflammation reduction [85].

GLP-1 RAs further exhibit anti-inflammatory properties that result in reduced concentrations of interleukin-6 and monocyte chemoattractant protein-1, and in the lungs, GLP-1 promotes vasodilation, surfactant production, and bronchodilation via nitric oxide activation [85]. Rogliani et al. used exendin-4, an exendin-based GLP-1 analog, in hypoglycemia-induced bronchial hyperresponsiveness ex vivo, which resulted in bronchodilation that was inhibited by either cAMP–PKA antagonism or GLP-1 RA [90], a result consistent with other findings (Fig. 1).

Potential Role of GLP-1

The GLP-1 receptor is widely distributed throughout the body with multiple biological effects, such as reducing neuroinflammation, promoting nerve growth, improving heart function, suppressing appetite, delaying gastric emptying, regulating blood lipid metabolism, and reducing fat deposition. Studies have also shown that GLP-1 RAs has potential neuroprotective, anti-infectious, cardiovascular protective, and metabolic regulatory effects [91]. The GLP-1 receptor is abundantly found [92] in lung epithelial and endothelial cells [93], suggesting that it has an effect on GLP-1 signaling in pulmonary disease. In the lab, investigators showed a protective role of a GLP 1 agent called exendin-4 against bronchial hyperreactivity. This was mediated by the cAMP–PKA cascade activation, which is similar to the effect induced by b2-agonists [86] (Fig. 2). Therefore, it is possible that this GLP-1 receptor agonist produces a bronchorelaxant effect on human airway smooth muscle, allowing possible reduction of certain agents (beta-agonists) or synergistic with other agents such as antimuscarinic drugs. GLP-1 RA has also in the lab shown inhibition of allergic and viral airway inflammation, decreasing airway eosinophilia, mucus production, and airway hyperresponsiveness [94].

In a retrospective cohort electronic health record study from January 2000 to March 2018 in Massachusets, authors looked at patients with asthma and T2D requiring a step-up of T2D therapy beyond diet and metformin [95]. They compared patients starting on GLP-1 RAs with those starting on SGLT-2 inhibitors, DPP-4 inhibitors, sulfonylurea, and basal insulin. The patients receiving GLP-1 RA had fewer asthma exacerbations and improvement in asthma symptoms than those initiating the alternate agents within 6 months of drug initiation. Asthma exacerbation counts were lower in those patients who started GLP-1 RAs (reference) compared with SGLT-2 inhibitors [incidence rate ratio (IRR), 2.98; 95% confidence interval (CI), 1.30–6.80], DPP-4 inhibitors (IRR, 2.45; 95% CI 1.54–3.89), sulfonylureas (IRR, 1.83; 95% CI 1.20–2.77), and basal insulin (IRR, 2.58; 95% CI 1.72–3.88). In addition, healthcare encounters for asthma symptoms were reduced in those who used GLP-1 RAs. There were no differences in baseline asthma severity across the groups and no differences in routine asthma
care encounters during this time. They adjusted for factors including gender, ethnicity, use of concurrent metformin, seasonality, and smoking status. Interestingly, the result was independent of changes in BMI and HbA1c, showing that, mechanistically, it was related to mechanisms beyond weight loss and improved glycemic control. Unfortunately, this trial did not phenotype patients as T2 high or low, which might limit some of their conclusions for the future utility based on the correct patient population [96].

This was done on background therapy with metformin, which is quite important as metformin has already been shown to potentially have a beneficial effect on asthma. In a retrospective cohort study of Taiwanese patients with concurrent asthma and diabetes from 2001 to 2011 they looked at metformin-prescribed patients 1:2 versus non metformin users corrected for age and gender over 3 years. They found a significant association between metformin use and asthma-related outcomes, including reductions in exacerbations and asthma hospitalizations among patients with metformin use. They postulated an anti-inflammatory mechanism, quoting previous similar findings in animal trials [97, 98], by directly inhibiting TNF-α induced NF-κB resulting in reduction of proinflammatory markers, including IL-6, and also reducing nitric oxide species and reactive oxygen species while reversing eosinophilic infiltration into the lung tissues.

A prospective cohort study compared the effect of metformin as monotherapy versus metformin with additional therapy of either
insulin or GLP-1 RA on lung function in 32 non-asthmatic patients with T2D over 2 years [99]. Compared with the other two cohorts, the GLP-1-RA-treated group improved FEV1, FVC, and maximal expiratory flow rates by 50–75% from baseline.

In a small prospective proof-of-concept trial [100], authors recruited nine diabetic patients with asthma who were given the GLP-1 RA liraglutide. Two of the patients stopped the medication prior to 8 weeks owing to side effects but were kept in the analysis. HbA1c was reduced, and the mean weight loss was 5.6% of baseline. Those who were adherent and had more weight loss did better with respect to asthma control and symptoms, and none of the adherent patients experienced an asthma exacerbation; however, a severe exacerbation did occur in one of the non-adherent patients.

In a study on obese patients with COPD, authors examined the effect of the GLP-1 RA liraglutide (3.0 mg) for 40 weeks on pulmonary measures and the clinical impact of COPD. Liraglutide resulted in significant weight loss after 4 weeks of treatment, which persisted throughout the study. In the liraglutide group, compared with placebo, there was an increase in FVC (both in liters and percentage of expected), diffusing capacity for carbon monoxide (DLCO), and a reduced clinical impact of COPD as assessed by the COPD Assessment Tool (CAT) score. There were, however, no significant differences in FEV1, FEV1/FVC, or 6-min walking test. The authors postulated an anti-inflammatory mechanism on the basis of previous evidence [85]. It is possible that liraglutide-induced activation of GLP-1 receptor signaling decreases the severity of acute exacerbation of COPD, with a possible mechanism of an increase in interferon-gamma production and amelioration of T-cell dysfunction [101]. The authors suggested that liraglutide at 3.0 mg may be an appropriate treatment option in patients with obesity and COPD because it appears to target obesity and pulmonary function [102], with possible anti-inflammatory effects.

Of note, other antihyperglycemic agents used in the management of T2D have been investigated in management of asthma. A meta-analysis of seven trials in patients receiving SGLT-2 inhibitors showed a reduction of asthma risk by 41% (OR 0.59; 95% CI 0.38–0.93) compared with placebo. However, this was predominantly driven by one trial, DECLARE TIMI 58, which included healthier cohorts than other cardiovascular outcome trials (CVOT) involving SGLT-2 inhibitors [103], and this benefit of asthma risk reduction was neutralized when DECLARE TIMI 58 was excluded from the analysis [105]. However, it raises an interesting thought that maybe the benefit of SGLT-2 inhibitors on endothelial function, mediated by nitric oxide, may improve vasodilation of the pulmonary vasculature while reducing insulin resistance, elevated blood glucose, and obesity [105].

Thiazolidinediones (TZD) were expected to improve the asthma outcomes as they reduce insulin resistance by activating PPAR-γ pathways. A rodent model with allergic asthma demonstrated the improved lung reactive oxygen species generation and inflammation, while observational studies also hinted at the link between TZD and reduction in asthma exacerbation [104]. However, three subsequent randomized control trials reported a neutral effect in airway inflammation with both available TZDs, pioglitazone and rosiglitazone.

No positive results were reported for DPP-4 inhibitor and sulfonylurea classes with regard to airway inflammation in a meta-analysis [105].

Tirzepatide, novel dual GIP/GLP-1 receptor agonist, is a new antihyperglycemic agent that was approved by the US Food and Drug Administration (United States) (FDA) in May 2022 that has demonstrated the highest HbA1C and weight reduction as a non-insulin agent. GIP is another incretin hormone, with a similar but not identical function to GLP-1. However, there are no known data on the effect of GIP on airway inflammation as of yet. One could only speculate that tirzepatide will most likely show similar results to GLP-1 RAs in reducing airway inflammation owing to GLP-1-RA component of medication, but its true effect remains to be seen.

Case Study

This 53-year-old nondiabetic woman has given me permission to present her case in this article.
She has been diagnosed with asthma for over 30 years, and both her mother and daughter have asthma. She had been controlled by PRN budesonide/formoterol for several years, barely needing it. She had a non-COVID infectious exacerbation improved with prednisone and macrolide antibiotic. Her symptoms resolved, then recurred, despite treatment with budesonide/formoterol increased to BID and PRN. She had COVID about 9 months prior to the exacerbation, which was managed at home, with her room oxygen saturation reaching levels as low as 93% with full recovery, and not needing antiviral therapy. She did, however, gain about 40 pounds of weight. She was adherent to her medication, had excellent inhaler technique, and had no nasal symptoms, but did have occasional heartburn a few times a week.

Investigations showed a normal chest radiograph/chest X ray (CXR), and spirometry showed moderate obstruction with FEV1 reversibility of 21% (but not back to normal) and even some air-trapping with FVC that improved by 19% with bronchodilator. She was treated with triple therapy indacaterol/mometasone/glycopyrronium by dry powder inhaler, a proton pump inhibitor (PPI) daily on speculation owing to her having some heartburn and to assist in weight loss, and subcutaneous semaglutide (a GLP-1 RA) that was titrated to 1 mg weekly as conventional weight loss strategies of diet and weight loss had not been successful. She lost weight slowly and consistently. Lung function normalized, and her symptoms resolved. She underwent allergy testing, which was positive for house dust mite and mold, but negative for dog (which they owned). Blood eosinophil count was 100, while fractionated exhaled nitric oxide showed a normal level of 11. Repeat spirometry a few months later showed resolution of obstruction, and no further reversibility was demonstrated.

As of her last visit, she had lost 40 pounds of weight and feels “the best she has in years.” Her PPI was discontinued, and her asthma therapy was reduced from triple therapy to moderate-dose ICS/LABA and subsequently to low-dose ICS/LABA, with no recurrence of any asthma or gastroesophageal reflux symptoms. This case brings up the question of why she showed such a great improvement, especially with it continuing along with the PPI being discontinued and the triple therapy being weaned down to just low-dose ICS/LABA. We should consider whether her clinical asthma improvement was due to the weight loss itself, or due to treating the obesity asthma phenotype with GLP-1 RA therapy. It is important to note that her airway obstruction completely resolved on therapy, even without the additional bronchodilator and on a much lower ICS dose, without any change in other airway mechanics or changes in environmental triggers. In addition, she had a fairly low Th2 phenotype, with a low blood eosinophil count (BEC) and fractional exhaled nitric oxide (FENO) even at the height of her symptoms, which may be a more difficult phenotype of asthmatic to treat effectively.

CONCLUSION

Treating asthma optimally requires treatment also of its comorbidities. Classically, these include gastroesophageal reflux and upper airway disease. Obesity should be included in our clinical practice as another important comorbidity to be managed. Weight loss improves asthma outcomes through a variety of potential mechanisms that may include lung mechanics, changes in oxidative stress, and reduction of inflammation. In addition, obese patients with asthma may represent a unique phenotype, often in the low-Th2 group, with current therapeutic options available for patients with low Th2 limited. Small prospective trials of diabetic patients with GLP-1 RAs have shown benefits in improved lung function in non-asthmatic patients and reduction in exacerbations in patients with asthma. A retrospective cohort trial of diabetic patients comparing additional therapies to metformin revealed superiority in asthma exacerbation reduction in those treated with GLP-1 RA versus other diabetic therapies. GLP-1 signaling of the significant numbers of receptors found in the lungs remains a novel target for treatment of chronic airway inflammation in asthma, with further prospective trials clearly needed to clarify the optimal population for benefit.
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**Compliance with Ethics Guidelines.** This article is based on a review of previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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