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REVIEW

Utility of Hypoglycemic Agents to Treat Asthma with Comorbid Obesity

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ABSTRACT

Adults with obesity may develop asthma that is ineffectively controlled by inhaled corticosteroids and long-acting beta-adrenoceptor agonists. Mechanistic and translational studies suggest that metabolic dysregulation that occurs with obesity, particularly hyperglycemia and insulin resistance, contributes to altered immune cell function and low-grade systemic inflammation. Importantly, in these cases, the same proinflammatory cytokines believed to contribute to insulin resistance may also be responsible for airway remodeling and hyperresponsiveness. In the past decade, new research has emerged assessing whether hypoglycemic therapies impact comorbid asthma as reflected by the incidence of asthma, asthma-related emergency department visits, asthma-related hospitalizations, and asthma-related exacerbations. The purpose of this review article is to discuss the mechanism of action, preclinical data, and existing clinical studies regarding the efficacy and safety of hypoglycemic therapies for adults with obesity and comorbid asthma.

Keywords: Body mass index; DPP-4 inhibitors; GLP-1R agonists; Incretins; Insulin; Metformin; SGLT-2 inhibitors; Sulfonylureas; Thiazolidinediones; Type 2 diabetes

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Key Summary Points

Obesity contributes to increased prevalence of comorbid asthma in adults.

Adults with obesity and comorbid asthma exhibit increased asthma symptoms and exacerbation of risk and poorer response to inhaled corticosteroids.

Observational studies of medical therapies approved for type 2 diabetes and/or obesity support the targeting of metabolic pathways for possible beneficial asthma outcomes.

Head-to-head studies and inclusion of asthma endpoints in clinical trials of hypoglycemic therapies are needed for clarification of clinical benefit for adults with obesity and comorbid asthma.

INTRODUCTION

Asthma is classically defined as variable airflow limitation and airway hyperresponsiveness occurring most often in the context of airway inflammation. Clinical evidence indicates that obesity negatively impacts asthma incidence, severity, symptoms, and therapeutic response. Mechanistic and translational studies suggest that the underlying metabolic dysregulation in patients with obesity, particularly hyperglycemia and insulin resistance, contributes to altered immune cell function and low-grade systemic inflammation. Over the past two decades, multiple pharmacologic interventions, targeting a variety of metabolic pathways, have been approved for the treatment of prediabetes, type 2 diabetes mellitus (T2DM), and obesity. Understanding the relevance of these therapeutic advances to asthma clinical outcomes and respiratory function is an essential step towards personalized medicine for high-risk patients with multimorbidity. Unexpectedly, recent studies also suggest that some of these medication classes may directly benefit airway inflammation, airflow limitation, and airway hyperresponsiveness through mechanisms not currently addressed by conventional asthma therapeutics. In this review, we describe the major pharmacologic interventions available for the treatment of metabolic dysregulation and the clinical implications in the context of adult asthma.

ASTHMA IN ADULTS WITH OBESITY: PREVALENCE AND CHALLENGES

Obesity and asthma often coexist through interrelated mechanical, inflammatory, nutritional, and behavioral pathways. In the USA, the National Center for Health Statistics determined that adults with obesity demonstrated higher rates of asthma (11.1%) compared to those classified as overweight (7.8%) or normal weight (7.1%) [1]. From 1999 to 2016, the rate of obesity in adults with asthma trended upwards to 1.75-fold that of the general population without asthma [2]. Patients with obesity and comorbid asthma additionally suffer from increased asthma severity and chronic morbidity, thereby incurring disproportionately large medical costs [3–6]. Long-term treatment options for asthma, the most prominent of which are inhaled corticosteroids (ICS) taken with or without long-acting beta-adrenoceptor agonists (LABA), illicit reduced responses in patients with obesity and comorbid asthma due to rapid medication clearance and poor absorption [7–9]. However, weight loss in individuals with obesity can independently reduce asthma symptoms and protect against a decline in measures of lung function, specifically forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) [10–12]. As a result, recommendations for patients with obesity and comorbid asthma typically involve changes in diet, exercise, or even bariatric surgery to achieve weight loss with secondary remission in asthma symptoms [13, 14].

Obesity and the associated metabolic dysregulation alter the comorbid asthma clinical trajectory. The pathophysiological mechanism

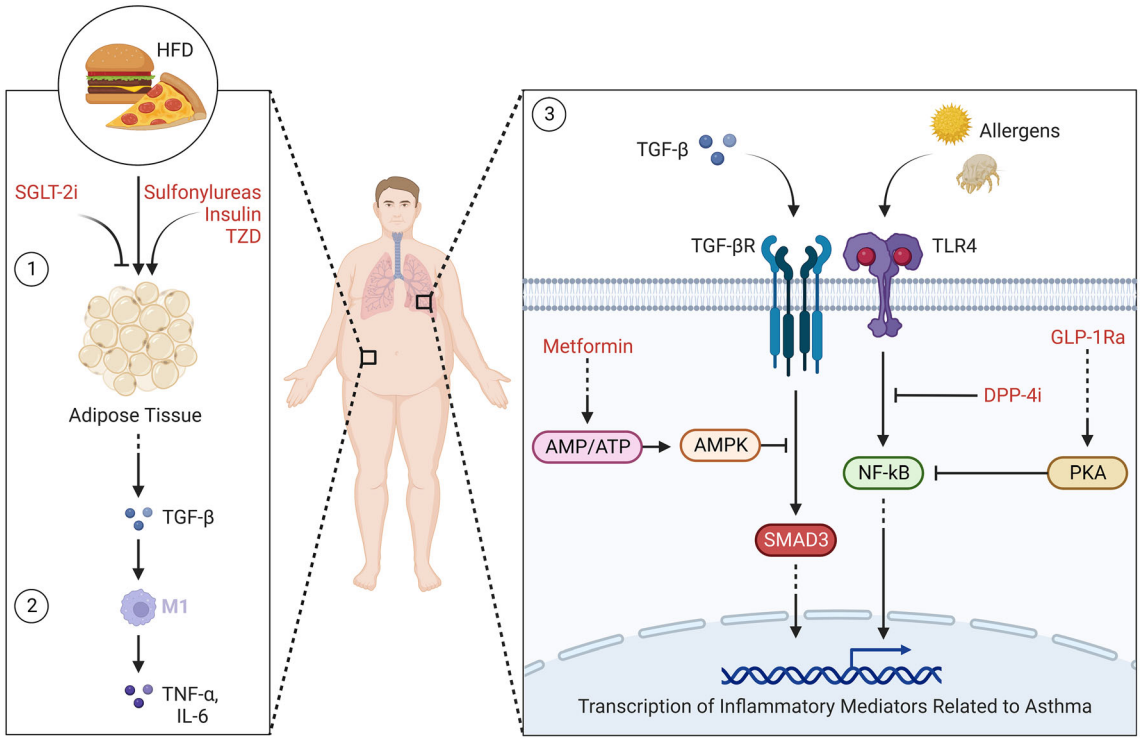

Fig. 1 Proposed mechanisms of action of metabolic pathways in the lung of patients with asthma. This figure depicts the multiple immunological and inflammatory pathways related to asthma that result from metabolic dysfunction in patients with obesity. *1* Accumulated visceral adipose tissue, exacerbated or ameliorated by certain classes of hypoglycemic therapies, can contribute to circulating levels of proinflammatory cytokines, such as TGF-β. *2* These proinflammatory cytokines then activate M1 macrophages characteristic of the type 2-low asthma endotype, which contribute further to the low-grade inflammation. *3* Environmental exposures, including exposure to the common dust mite and mold allergens, result in proinflammatory cytokines upregulating genes in the airway responsible for fibrosis and hyperresponsiveness. Some classes of hypoglycemic therapies directly or indirectly inhibit these pathways. This figure was created with BioRender.com (https://biorender.com/). *HFD* high-fat diet, *SGLT-2i* sodium glucose co-transporter 2 inhibitors, *TZD* thiazolidinediones, *TGF-β* tumor growth factor beta, *TGF-βR* tumor growth factor beta receptor, *TNF-α* tumor necrosis factor alpha, *IL-6* interleukin-6, *TLR4* toll-like receptor 4, *AMP/ATP* adenosine monophosphate/adenosine triphosphate, *AMPK* AMP-activated protein kinase, *SMAD3* mothers against decapentaplegic homolog 3, *NF-κB* nuclear factor-κB, *PKA* protein kinase A, *DPP-4i* dipeptidyl peptidase-4 inhibitors, *GLP-1Ra* glucagon-like peptide-1 receptor agonists

of asthma is largely understood as type (T)2-high inflammation, characterized by interleukin (IL)-4, IL-5, and IL-13 and airway eosinophilia, driving airway hyperresponsiveness (AHR) and airway remodeling and leading to airflow obstruction [15]. As asthma severity increases, T2-low airway inflammation, characterized by airway neutrophilia and inflammasome activation controlled by IL-10, alarmins (e.g., IL-25, IL-33), and tumor growth factor beta (TGF-β) becomes more prevalent [16]. Both classic T2-high and T2-low inflammatory patterns can be observed in obesity-associated asthma. Furthermore, in the context of obesity, accumulated visceral adipose tissue releases TGF-β, which induces M1 macrophages to secrete IL-6 and tumor necrosis factor alpha (TNF-α) (Fig. 1) [17]. Ultimately, the resulting low-grade inflammation causes remodeling and hyperresponsiveness in the airways, increasing the risk of asthma exacerbations, namely, flares in asthma symptoms that lead to an emergency

department (ED) visit, hospitalization, or therapy intensification [18–24]. Obesity increases the risk of impaired fasting glucose and T2DM due to alterations in adipose tissue and β-cell function that altogether causes an inadequate production and response to insulin [25–27]. Increased levels of hemoglobin A1c (HbA1c), a marker for glucose control over a 3-month period used in the diagnosis and monitoring of T2DM, is weakly independently associated with asthma-related hospitalization [28]. Compared to those with normal HbA1c, individuals with HbA1c in the prediabetic/diabetic range have a higher asthma exacerbation rate [29]. Insulin resistance, determined by the homeostatic model assessment of insulin resistance (HOMA-IR) or euglycemic–hyperinsulinemic clamp, is negatively associated with lung function [30, 31]. Furthermore, the downstream effects of insulin resistance may intensify asthma symptoms through hypercontractility, vagally-induced bronchoconstriction, and fibrosis [32–34]. Invasive interventions, such as bariatric surgery, leads to decreased levels of visceral adipose tissue that in turn improves lung function, reduces inflammation, lowers asthma-related exacerbation risk, and decreases the intensity of medication needed to control asthma symptoms [35–39]. However, Forno et al. found that the presence of metabolic syndrome significantly attenuates the effect of bariatric surgery on asthma control [40]. The relative impact of excess fat mass, as in obesity, and metabolic dysregulation, as in insulin resistance and overt T2DM, on airway inflammation and clinical disease in asthma remain an area of active research.

The complex interactions of obesity, metabolic dysregulation, and asthma preclude the establishment of a definitive therapeutic paradigm at this time. Therapies which can address insulin resistance and promote weight loss, while having limited risk for hypoglycemia, may hold the most promise (Fig. 2). There is a growing awareness of the clinical challenges of multimorbidity and polypharmacy facing patients with obesity and comorbid asthma, justifying a renewed approach to personalized medicine in this asthma subpopulation. In the following sections, we review the main therapeutic classes used for the treatment of prediabetes and T2DM in the context of asthma management (Table 1).

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

BIGUANIDES

Most patients initiating hypoglycemic monotherapy are prescribed metformin [41]. Metformin is also approved as an adjunct to diet and exercise for the management of T2DM and routinely used off-label to address insulin resistance in women with polycystic ovarian syndrome and in prediabetes. Metformin reduces gluconeogenesis by inhibiting the mitochondria respiratory chain in hepatocytes, raising the ratio of adenosine monophosphate (AMP)

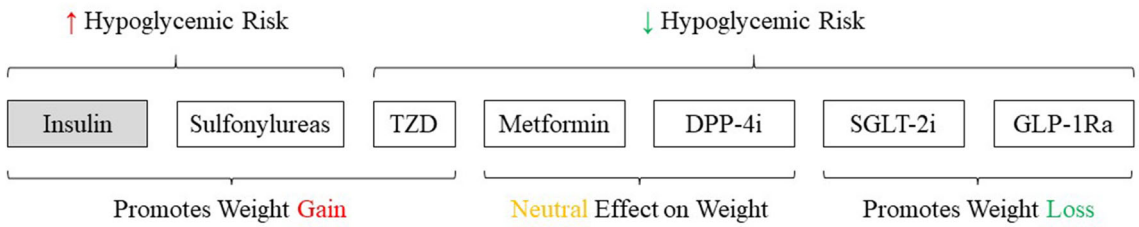

Fig. 2 Impact of therapeutic classes for the treatment of type 2 diabetes mellitus on metabolic parameters relevant in asthma. This figure demonstrates the different effects of multiple classes of hypoglycemic therapies on hypoglycemia, insulin resistance, and weight. Gray shading denotes how insulin is the only hypoglycemic therapy that fails to improve insulin sensitivity. See Fig. 1 caption for abbreviations

Table 1 Studies of type 2 diabetes therapeutics in asthma study populations

First author [reference]	Source	Study design	Sample size (user/non-user)[a]	Cohort diagnosis	Inclusion criteria	Drug class (drug if specified)	Outcome associated with medication use
Single drug studies							
Rinne et al. [75]	US veterans receiving care at Veteran Affairs Medical Centers	Retrospective observational cohort study	2178/10,700	Asthma and diabetes	At least two prescriptions of oral hypoglycemic medications	TZD	Lower risk of asthma exacerbation and oral steroid prescription that strengthened with adherence to diabetes medication
Dixon et al, [77]	University of Vermont and University of Pittsburgh, USA	Placebo-controlled double-blinded clinical trial	12/11	Asthma and obesity	(1) Between ages of 18 and 60 years (2) Absence of active smoking (3) PC_{20} to methacholine < 16 mg/mL (4) Taking stable dose of inhaled corticosteroids for ≥ 4 weeks (5) FEV_1 ≥ 60% predicted	TZD (pioglitazone)	(1) No improvement in median airway reactivity, exhaled nitric oxide, asthma control, or lung function (2) Weight gain
Li et al. [55]	Taiwan National Health Insurance Research Database	Retrospective observational cohort study	444/888	Asthma and diabetes	(1) Adults (age ≥ 18 years) (2) Prescribed ≥ 1 asthma and diabetes medication	Biguanides (metformin)	Lower risk of asthma-related hospitalization and asthma exacerbation

Table 1 continued

First author [reference]	Source	Study design	Sample size (user/non-user)[a]	Cohort diagnosis	Inclusion criteria	Drug class (drug if specified)	Outcome associated with medication use
Colice et al. [92]	Commercial and Medicare Supplemental Databases	Retrospective observational cohort study	3973/7487	Asthma and T2DM	(1) Adults (age ≥ 18 years) (2) At least 1 outpatient pharmacy claim for DPP-4i or non-DPP-4i oral hypoglycemic medications (except for metformin and insulin)	DDP-4i	No improvement in risk-domain asthma control, overall asthma control, treatment stability, and severe asthma exacerbation rates
Wu et al. [56]	IBM MarketScan Research Databases	Retrospective observational cohort study	11,960/11,960	Asthma and T2DM	(1) Adults (aged ≥ 18 years) (2) Enrolled in a health plan for ≥ 1 year that submitted prescription claims	Biguanides (metformin)	Lower hazard of asthma exacerbation, asthma-related ED visits, and asthma-related hospitalization without differences in corticosteroid use
Wu et al. [57]	Genetic Epidemiology of COPD (COPDGene) Study	Retrospective observational cohort study	39/471	Asthma-COPD overlap diagnosed before the age of 40 years	(1) Non-Hispanic white or African American (2) Adults (age Between 45 and 80 years) (3) ≥ 10 pack-year smoking history	Biguanides (metformin)	(1) Lower rate of total and severe exacerbations and improved quality of life (2) No improvement in lung function and physical functional ability

Table 1 continued

First author [reference]	Source	Study design	Sample size (user/non-user)[a]	Cohort diagnosis	Inclusion criteria	Drug class (drug if specified)	Outcome associated with medication use
Wu et al. [58]	John Hopkins Electronic Health Record	Retrospective observational cohort study	698/698	Asthma and T2DM	(1) Adults (age $\geq$ 18 years) (2) HbA1c $\geq$ 6.5 or taking diabetes medications after identification of asthma (3) $\geq$ 1 active outpatient medication at index date (4) At least 1 additional contact with the healthcare system	Biguanides (metformin)	Varied upon analysis: Lower hazard of asthma-related ED visits (time-independent) and lower hazard of asthma-related hospitalizations (time-dependent)
Sood et al. [76]	US Veterans receiving care at Veteran Affairs Medical Centers	Retrospective observational cohort study	NA	Obesity, diabetes, and/or hypertension	BMI $\geq$ 25 kg/m^2	TZD	(1) Lower risk of incident asthma strengthened by concurrent ACEi usage (2) Higher risk of incident asthma with concurrent ARB usage
Comparator drug studies							
Chen et al. [64]	Taiwan National Health Insurance Research Database	Retrospective observational cohort study	304, 891, 499, 179/1982	Diabetes	Diagnosed with diabetes prior to diagnosis of asthma	Insulin, biguanides (metformin), sulfonylurea, TZD	(1) Higher risk of incident asthma among insulin users (2) Lower risk of incident asthma among metformin (3) Neither TZD nor sulfonylureas significantly modified the risk of incident asthma

Table 1 continued

First author [reference]	Source	Study design	Sample size (user/non-user)[a]	Cohort diagnosis	Inclusion criteria	Drug class (drug if specified)	Outcome associated with medication use
Rayner et al. [65]	Royal College of General Practitioners Research and Surveillance Center Dataset	Retrospective observational cohort study	16,258, 4159, 3300/8800	T2DM	(1) Adults (age ≥ 18 years) (2) Without a baseline diagnosis of asthma, COPD, or type 1diabetes	Biguanides (metformin), sulfonylurea, insulin	(1) Lower risk of incident asthma among metformin and sulfonylureas users (2) Higher risk of incident asthma among insulin users
Foer et al. [113]	Partners Healthcare Research and Patient Data Repository	Retrospective observational cohort study	448, 112, 435, 2253, 2692	Asthma and T2DM	Adults (age ≥ 18 years)	GLP-1Ra, SGLT-2i, DPP-4i, sulfonylurea, insulin	Lower risk of asthma exacerbation and asthma symptoms relative to those on SGLT-2i, DPP-4i, sulfonylureas, or basal insulin
Albogami et al. [114]	IBM MarketScan Research Databases	Retrospective observational cohort study	4150, 12,540	T2DM and respiratory disorders	Ages ≥ 17 years	GLP-1Ra, DDP-4i	Lower incident rate of respiratory disorders hospitalizations and exacerbations relative to those on DPP-4i

This table organizes studies assessing comorbid asthma-related outcomes in patients with obesity and/or type 2 diabetes by whether a single drug or multiple drugs were investigated

ACEi Angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *DPP-4i* dipeptidyl peptidase-4 inhibitors, *ED* emergency department, FEV_1 forced expiratory volume in the first second, *GLP-1Ra* glucagon-like peptide-1 receptor agonists, *HbA1c* hemoglobin A1c, *NA* not applicable due to missing information, PC_{20} provocation concentration causing a 20% fall in FEV1, *SGLT-2i* sodium glucose co-transporter 2 inhibitors, *T2DM* type 2 diabetes mellitus, *TZD* thiazolidinediones

[a]The sample sizes of users of hypoglycemic drugs are separated by commas in comparator studies in the order listed in the drug classes column while the sample size of nonusers of hypoglycemic drugs is separated by a slash

to adenosine triphosphate (ATP) ratio and activating AMP-activated protein kinase (AMPK) [42]. In patients with metabolic dysregulation, reduced AMPK activity led to increased inflammatory gene expression [43]. Notably, AMPK also plays a crucial role in preserving respiratory function, as studies in animal models suggest AMPK suppresses TGF-β-induced proliferation of airway smooth muscle cells and AHR caused by hypoxia-inducible factor/vascular endothelial growth factor (HIF/VEGF) interaction [44, 45]. By indirectly upregulating AMPK expression, metformin demonstrates highly efficacious and tolerable anti-inflammatory properties systemically and in lung tissue in murine models [46–49].

Metformin use in patients with obesity and comorbid asthma is linked to the improvement of both chronic conditions. In a study involving temporarily induced insulin resistance through treatment of non-esterified fatty acid (NEFA), metformin improved extrahepatic glucose utilization in patients with T2DM potentially by promoting microvascular perfusion [50, 51]. However, two randomized clinical trials showed that other hypoglycemic therapies alone or in combination with metformin led to superior glycemic control compared to metformin by itself [52, 53]. While multiple studies show metformin yields insignificantly or modest weight loss, the U.S. Food and Drug Administration (FDA) does not recognize metformin as a weight loss agent [54]. Importantly, many large retrospective observational cohort studies examining metformin usage in adults with asthma provided evidence of superior asthma-related outcomes. Both Li et al. and Wu et al. used a claims-based cohort and arrived at the similar conclusion that adults with asthma and comorbid diabetes who took metformin demonstrated decreased rates of asthma exacerbations, asthma-related ED visits, and asthma-related hospitalizations [55–57]. Wu et al. later identified adults with asthma-chronic obstructive pulmonary disease (COPD) overlap within the COPDGene database and found metformin initiation improved quality of life as assessed by the St. George's Respiratory Questionnaire [58]. Prospective controlled studies in asthma, with and without comorbid obesity, are needed to establish the utility of metformin.

INSULIN

By improving glucose control, insulin substantially reduces the risk of diabetes-related endpoints, diabetes-related death, and all-cause mortality, compared to conventional dietary interventions in patients with T2DM [59]. Administering insulin can lower blood glucose level in a dose-dependent manner albeit with notable adverse effects [60]. Two basal insulin analogs, glargine and detemir, cause modest weight gain of 2 kg per 1% reduction in HbA1c, with weight gain worsened by twice-daily dosing as compared to once-daily dosing [61]. While hypoglycemia is more commonly reported by patients with type 1 diabetes mellitus, 46.5% of insulin users with T2DM reported hypoglycemic events at an average 2.5 severe hypoglycemic events/patient-year [62]. In a prospective cohort study of patients with T2DM without comorbid asthma or COPD, insulin initiation exacerbated the methacholine-induced decline in FEV_1 in the first 60 days and serum total immunoglobulin E at 1 year [63]. Multiple retrospective observational cohort studies have identified associations between insulin usage and asthma onset in patients with diabetes. In one study, patients with T2DM who had ≥ 3 prescriptions of insulin per year were more than twice as likely to be subsequently diagnosed with asthma [64]. Similarly, Reynar et al. found that among adults diagnosed with T2DM, insulin usage, but not duration of therapy, glycemic control, or T2DM complications, increased the risk of incident asthma [65]. The addition of insulin to the treatment regime for T2DM in the context of asthma is unlikely to change from current T2DM guidelines where it is added as a last-line chronic agent.

THIAZOLIDINEDIONES

Widely prescribed in the early 1990s, thiazolidinediones (TZD) have largely declined in popularity over the past two decades over

concerns of side effects, including weight gain, skeletal fractures, and edema [66–68]. Rosiglitazone and pioglitazone may also increase the risk for heart failure and bladder cancer, respectively [69, 70]. TZD help control levels of excessive serum-free fatty acids by ligating to the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ) and promoting the ability of adipose tissue to store fat [71, 72]. By addressing the underlying adipose tissue dysfunction that occurs during obesity, TZD showed potential for having anti-inflammatory properties with low hypoglycemic risk. In cultured human airway smooth muscle cells, troglitazone dose-dependently reduced the release of IL-6 via a pathway distinct from AMPK and PPARγ [73]. However, a systematic review found that usage of TZD across many clinical trials did not significantly affect IL-6 levels [74].

The authors of a few studies have argued in favor of TZD for protection against asthma in patients with obesity and comorbid T2DM. Two large retrospective observational cohort studies utilizing data from the U.S. Veteran Affairs Medical Centers found that TZD lowered the risk of incident asthma, asthma exacerbation, and oral steroid prescriptions [75, 76]. These effects were strengthened by adherence to TZD and concurrent usage of angiotensin-converting enzyme inhibitors. However, a pilot randomized controlled trial (RCT) of pioglitazone in patients with poorly controlled asthma with comorbid obesity was prematurely discontinued due to new safety concerns around the risk for bladder cancer [77]. Additionally, the significant weight gain observed in the treatment group had the potential for harm without improving asthma control or lung function. In a second RCT of pioglitazone in severe asthma, patients in the pioglitazone arm showed both no improvement in the primary clinical endpoint of the asthma quality of life questionnaire score and a high rate of adverse effects [78]. Systemic TDZ are unlikely to advance as a therapeutic intervention for asthma due to these safety concerns and the lack of clinical benefit. The impact of local delivery of TZD to the airway and in adults with asthma without comorbid obesity remain unexplored.

SULFONYLUREAS

After metformin initiation, sulfonylureas are commonly used as second-line therapy to lower levels of HbA1c and blood glucose during the fasting and post-prandial periods [79]. Sulfonylureas raise plasma insulin concentration by binding to receptors on the cell membranes of β-pancreatic cells. This interaction blocks the inflow of potassium into the cytosol and subsequent depolarization, triggering the diffusion of calcium that contracts actomyosin responsible for the exocytosis of insulin [80]. However, adding on and switching to sulfonylureas may increase the risk of myocardial infarction, mortality, and severe hypoglycemia compared to other hypoglycemic agents [81, 82]. One retrospective observational cohort study found sulfonylureas provided modest protection in adults with T2DM against incident asthma, statistically equivalent to that of metformin initiation [65]. Cardiovascular and hypoglycemic risk limit the use of sulfonylureas in T2DM, independent of asthma comorbidity, and a strong rationale for clinical benefit would need to be observed to warrant their further study in the asthma context.

DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Dipeptidyl peptidase-4 inhibitors (DPP-4i) may be considered over sulfonylureas as second-line therapy after metformin because of their reduced hypoglycemic risk and neutral effect on weight [83, 84]. Glucagon-like peptide-1 (GLP-1) stimulates insulin secretion from pancreatic β-cells in hyperglycemic conditions but is cleaved by dipeptidyl peptidase-4 (DPP-4), an adipokine released in excessive amounts by adipose tissue in patients with obesity [85, 86]. By preventing inactivation of GLP-1, DPP-4i has been found to significantly improve β-cell function and glycemic control, albeit its effects are attenuated in patients with high levels of insulin resistance [87, 88]. Studies employing in vitro models of human bronchial epithelial cells have indicated that DPP-4i blocks pathways contributing to oxidative stress and

fibrosis [89, 90]. Saxagliptin has been shown to mitigate oxidative stress in ovalbumin (OVA)-sensitized mice by modulation of toll-like receptor 4 (TLR4) and nuclear factor-κB (NF-κB) signaling [91]. However, a retrospective observational matched cohort study showed that adults with asthma who utilized DPP-4i showed no improvement in asthma control, treatment stability, and asthma exacerbation compared to their counterparts on other hypoglycemic medications [92]. A recent network meta-analysis further established that DPP-4i did not reduce the risk of incident asthma relative to placebo [93]. Clinical data are currently lacking to support their preferential use in the context of comorbid asthma.

SODIUM GLUCOSE CO-TRANSPORTER 2 CHANNEL INHIBITORS

In the past decade, the U.S. FDA approved a new class of drugs for improving glucose control in adults with T2DM: sodium-glucose co-transporter 2 channel (SGLT-2) inhibitors (SGLT-2i) [94]. In the kidneys, SGLT-2 are responsible for reabsorption of 90–97% of filtered glucose [95]. By blocking SGLT-2, SGLT-2i induce glucosuria, thereby reducing signs of chronic hyperglycemia, as indicated by HbA1c levels and insulin sensitivity. The authors of an in vitro transcriptomics experiment assessing the progression of diabetic kidney disease in human proximal tubular cells concluded that the one of the SGLT-2i currently available, canagliflozin, reverses inflammation by decreasing the levels of TNF receptor 1, IL-6, matrix metalloproteinase 7, and fibronectin 1 compared to the sulfonylurea glimepiride [96]. The mechanism underlying the anti-inflammatory properties of SGLT-2i could be a downstream effect of its ability to lower uric acid and insulin production [97]. A network analysis pooling nine clinical trials of SGLT-2i evaluating cardiorenal outcomes in patients with T2DM, heart failure, and/or chronic kidney disease reported that SGLT-2i reduced the occurrence of asthma serious adverse events compared to placebo [98]. Wang et al. used a similar approach to identify 19 clinical trials and found that SGLT-2i decreased the risk of asthma, based on asthma-related adverse events reported in the studies, compared to GLP-1 receptor agonists (GLP-1Ra) and DPP-4i [93]. However, the validity of both meta-analyses is limited by the very low frequency of asthma outcomes in both the treatment and placebo groups. Adequately powered studies of SGLT-2i use in asthma populations with sufficient (e.g., at higher risk of) asthma-related events and with prespecified asthma outcomes are needed.

GLUCAGON LIKE PEPTIDE-1 RECEPTOR AGONISTS

Since 2005, GLP-1Ra have emerged as a highly effective drug class for glycemic control that also reduce the risk of cardiovascular events and promote weight loss [99]. GLP-1Ra improve pancreatic β-cell function by promoting cell proliferation, stimulating insulin secretion, and inhibiting glucagon release [100]. Additionally, GLP-1Ra limit weight gain by suppressing food intake through the induction of satiety and delayed gastric emptying. The authors of a randomized clinical trial that enrolled adults with obesity concluded that 68 weeks of once-weekly semaglutide 2.4 mg resulted in a mean change in body of − 14.9% compared to − 2.4% in adults on placebo [101]. GLP-1Ra potentially mediates multiple inflammatory pathways involved in the pathophysiology of comorbid asthma in patients with obesity [102]. Preclinical experiments have shown that GLP-1Ra decreased expression of proinflammatory cytokines, such as TNF-α, through protein kinase A-dependent inactivation of NF-κB (Fig. 1) [103–105]. Through inhibiting the release of IL-33, GLP-1Ra administered in murine models attenuated airway eosinophilia and neutrophilia, the release of T2 cytokines from type 2 innate lymphoid cells (ILC2), mucus production, and AHR following exposure to fungal allergens and viral antigens [106–108]. Interestingly, GLP-1Ra given to OVA-sensitized mice also depressed the activity of oligomerization domain-like receptor protein (NLRP)3, which induces airway inflammation and AHR in

obesity by upregulating levels of IL-17 secretion by ILC3 via secretion of IL-1β [109–111].

In multiple studies, GLP-1Ra use was associated with improvements in asthma outcomes in adults with T2DM and comorbid asthma. The first preliminary uncontrolled study of nine patients treated with a GLP-1Ra found that 1 year of a GLP-1Ra improved asthma symptoms and reduced asthma exacerbation rate in those with weight loss in excess of the population median [112]. In a new user, active comparator study design using data available in the electronic health record, adults with T2DM and comorbid asthma who initiated a GLP-1Ra for treatment intensification for T2DM experienced the lowest risk of asthma exacerbation in the following 6 months compared to those initiating sulfonylureas, SGLT-2i, or DPP-4 inhibitors [113]. A claims-based analysis comparing users of GLP-1Ra and DPP-4i in patients with T2DM and comorbid chronic lower respiratory disease (CLRD)—a term encompassing asthma and COPD—similarly found that GLP-1Ra led to reduced incidence of CLRD-related hospitalizations and exacerbations [114]. Although tangential to asthma, a randomized clinical trial which recruited patients with T2DM revealed that liraglutide reduced serum levels of surfactant protein D which independently predicted improvements in FVC [115]. Additionally in a prospective cohort of 32 adults with T2DM but without co-existing obstructive lung disease, the addition of a GLP-1Ra to metformin as treatment improved lung function (FEV_1 and FVC) over metformin alone or metformin + insulin [116]. GLP-1Ra are an active area of research in clinical and translational asthma studies, and a prospective clinical trial of the GLP-1Ra semaglutide in adults with asthma and comorbid obesity is forthcoming [117].

FUTURE DIRECTIONS

The majority of studies examining asthma-related outcomes in adults with obesity and/or comorbid diabetes taking hypoglycemic agents are large retrospective observational cohort studies. To strengthen the observed associations and move findings into practice requires additional investigation. First, prospective studies in adults with asthma and comorbid obesity stratified by the extent of metabolic dysfunction or weight loss can help determine whether hypoglycemic agents exhibit independent, beneficial effects in the airway, as suggested by preclinical studies. Second, head-to-head studies comparing hypoglycemic agents in adults with obesity and comorbid asthma should consider endpoints beyond asthma-related exacerbations, such as levels of circulating and airway inflammation markers that could help inform response to therapy or identify asthma endotypes to target.

The area of study reviewed in this paper continues to evolve as new hypoglycemic agents as well as non-pharmacologic interventions advance. Two recent phase 3 multicenter randomized trials in adults with obesity showed that tirzepatide, a novel dual gastric inhibitory peptide\GLP-1R agonist, caused substantial weight loss in patients who failed to lose weight via dietary changes and noninferior and superior glycemic control compared to semaglutide in those with comorbid T2DM [118, 119]. Limited data are currently available on the impact of tirzepatide on comorbidities seen in patients with obesity, such as asthma. Hypoglycemic therapies should also be compared to non-pharmacologic interventions, such as bariatric surgery, to develop rational approaches to the use of these interventions in patients with obesity and comorbid asthma and to identify who may benefit most from each approach. In doing so, clinicians and researchers may more fully expand the growing armamentarium of personalized medicine for patients with obesity and comorbid asthma.

CONCLUSION

The current therapeutic paradigm for adults with obesity and comorbid asthma requires a balancing act between improving clinically meaningful asthma-related outcomes, avoiding weight gain, minimizing hypoglycemia, and preventing unintended severe adverse events. An expanding volume of observational evidence suggests that certain classes of

hypoglycemic agents could be used to address both chronic conditions by targeting the underlying metabolic dysregulation. However, until randomized clinical trials of these pharmacologic tools for obesity and metabolic dysfunction evaluate asthma outcomes as a primary endpoint, the costly management of comorbid asthma in adults with obesity will still heavily rely on the paradigm of inhaled ICS with or without LABA.

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