

Review

Not peer-reviewed version

Unraveling the Link Between Insulin Resistance and Bronchial Asthma

[Konstantinos Bartzokas](#) , Andriana I Papaioannou , [Fotios Drakopanagiotakis](#) , [Evanthia Gouveri](#) , [Nikolaos Papanas](#) , [Paschalis Steiropoulos](#) *

Posted Date: 15 January 2024

doi: 10.20944/preprints202401.1135.v1

Keywords: asthma; insulin resistance; antidiabetic drugs; metabolic dysfunction; obesity



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Review

Unraveling the Link Between Insulin Resistance and Bronchial Asthma

Konstantinos Bartziokas ¹, Andriana I Papaioannou ², Fotios Drakopanagiotakis ³, Evanthia Gouveri ⁴, Nikolaos Papanas ⁴ and Paschalis Steiropoulos ^{3*}

¹ Pulmonologist, 42132 Trikala, Greece; bartziokas@gmail.com

² 1st University Department of Respiratory Medicine, "Sotiria" Hospital, National and Kapodistrian University of Athens, 15772 Athens, Greece; papaioannouandrianna@gmail.com

³ Department of Pneumology, Medical School, Democritus University of Thrace, 68100 Alexandroupolis, Greece; fdrakopanagiotakis@gmail.com, steiropoulos@yahoo.com

⁴ Diabetes Centre, 2nd Department of Internal Medicine, Democritus University of Thrace, 68100, Alexandroupolis, Greece; vangouv@yahoo.gr, papanasnikos@yahoo.gr

* Correspondence: Prof. Paschalis Steiropoulos; steiropoulos@yahoo.com

Abstract: Evidence from large epidemiological studies has shown that obesity may predispose to increased Th2 inflammation and increase the odds of developing asthma. On the other hand, there is growing evidence suggesting that metabolic dysregulation that occurs with obesity, and more specifically hyperglycemia and insulin resistance, may modify immune cell function and in some degree systemic inflammation. Insulin resistance seldom occurs on its own, and in most cases constitutes a clinical component of metabolic syndrome, along with central obesity and dyslipidemia. Despite that, in some cases, hyperinsulinemia associated with insulin resistance has been proven a stronger risk factor than body mass in developing asthma. This finding has been supported by recent experimental studies showing that insulin resistance may contribute to airway remodeling, promotion of airway smooth muscle (ASM) contractility and proliferation, increase of airway hyper-responsiveness and release of pro-inflammatory mediators from adipose tissue. All these effects indicate the potential impact of hyperinsulinemia on airway structure and function, suggesting the presence of a specific asthma phenotype with insulin resistance. Epidemiologic studies have found that individuals with severe and uncontrolled asthma have a higher prevalence of glycemic dysfunction, whereas longitudinal studies have linked glycemic dysfunction to an increased risk of asthma exacerbations. Since the components of metabolic syndrome interact with one another so much, it is challenging to identify each one's specific role in asthma. This is why, over the last decade, additional studies have been conducted to determine whether treatment of type 2 diabetes mellitus affects comorbid asthma as shown by the incidence of asthma, asthma control and asthma-related exacerbations. The purpose of this review is to present the mechanism of action, and existing preclinical and clinical data, regarding the effect of insulin resistance in asthma.

Keywords: asthma; insulin resistance; antidiabetic drugs; metabolic dysfunction; obesity

1. Introduction

Asthma is one of the most common respiratory disorders worldwide [1]. Chronic eosinophilic bronchitis with T helper 2 (Th2) inflammation, bronchial smooth muscle hyperplasia, easy epithelium shedding, mucus plug formation in the bronchi, and thickening of the subepithelial basement membrane are its hallmark pathologic features [1]. Due to its broad diagnostic standards, which include varying expiratory airflow limitation and respiratory symptoms, asthma is a heterogeneous disease composed of numerous pathologic mechanisms (endotypes) and higher order groups with shared clinical features (phenotypes) [2]. Although several asthma phenotypes have been described, including allergic and non-allergic asthma, occupational and aspirin-induced asthma, the pathologic characteristics of these phenotypes are very similar, while type 2 inflammation by Th2 and group 2 innate lymphoid (ILC2) cells is their crucial component [2]. Regarding severe uncontrolled asthma phenotypes, recently developed monoclonal antibody treatments have highlighted the importance of

type 2 inflammation [3]. Despite the differences in design of different studies, it is clear that a significant minority of patients with severe uncontrolled asthma have a lack of atopy and type 2 inflammation, emphasizing the significance of non-allergic triggers to these patients [4,5].

Dysglycemia, glycemic dysfunction, and glucose dysmetabolism, (also referred to as disorders of glucose metabolism) have been implicated as potential triggers of asthma exacerbation and drivers of severe asthma [6,7]. Compared to individuals with Th2 inflammation, patients with asthma and metabolic dysfunction have additional pathogenic and pathologic characteristics [7]. Often presented as metabolic syndrome, metabolic dysfunction has a number of significant clinical characteristics, such as central obesity, insulin resistance/glucose intolerance, dyslipidemia, and in certain cases, vitamin D (VitD) deficiency [8,9].

It is commonly known that asthma treatment in obese patients can be challenging, partly because of the patients' poor response to inhaled corticosteroids [10,11]. Treatment of insulin resistance has favorable effects on asthma management [12]. Additionally, metabolic dysfunction appears to be the primary cause of asthma exacerbation, according to a cohort analysis of asthmatic patients who were prone to exacerbations [13]. These characteristics highlight the association between metabolic dysfunction and asthma phenotype, as well as the significance of metabolic dysfunction in the pathophysiology of asthma. The impact of obesity and metabolic dysfunction on asthma is becoming increasingly apparent as these diseases' prevalence rises worldwide.

In this context, the aim of this review was to summarize current data on the deleterious role of insulin resistance in asthma, along with suggested mechanisms of asthma irritation.

2. Insulin Resistance

The most comprehensive definition of "insulin resistance" was formulated by Petersen and Shulman [14] as a "*maladaptive in the setting of chronic overnutrition*". Even though its molecular causes are not entirely known, improper lipid accumulation in the liver is considered as a major factor that contributes to decreased cellular sensitivity to insulin. To preserve glucose homeostasis, pancreatic b-cells produce more insulin, which results in a period of clinically silent hyperinsulinemia with normal blood glucose levels [6].

With time, blood glucose levels rise in tandem with reductions in insulin secretion as this compensatory hyperinsulinemia starts to falter [15]. This period can be identified by elevated glycated hemoglobin A1c (HbA_{1c}), which is a measure of the average blood glucose levels over the previous 3 months, elevated fasting glucose (also named impaired fasting glucose, or IFG), or an inadequate ability to completely offset hyperglycemic increases as a result of a glucose load (also named impaired glucose tolerance or IGT). Elevated IFG, IGT, or HbA_{1c} are useful to diagnose prediabetes [16]. Crucially, the human body still secretes more insulin during the prediabetic state, and eventually, there is a reduction in insulin secretion that coincides with overt hyperglycemia and pancreatic failure. The diagnosis of diabetes is based on blood glucose or HbA_{1c} levels [17].

Data from the Third National Health and Nutrition Examination Survey (NHANES III) have shown that one-third of non-diabetic adults in the United States (US) experience hyperinsulinemia associated with insulin resistance [18], whereas 12-43% of US adults have prediabetes. In the US, 11.3% of population of all ages (more than 37 million people), had diabetes in 2019 [19]. Taken together, this data suggests that insulin resistance, prediabetes and diabetes are widespread and inter-related. Metabolic syndrome that includes obesity, hypertension, dyslipidemia, and hyperglycemic tendencies is closely linked to obesity (specifically abdominal obesity), while insulin resistance and hyperinsulinemia are the main molecular markers of this syndrome [20]. Indeed, large epidemiological studies [21,22] have shown that the main obesity-associated asthma risk was attributed to insulin resistance, and even maternal obesity, raises the incidence of childhood asthma, in susceptible children, pointing to systemic causes [23]. In the Korean Health and Genome Study (a population-based study of 10,038 Korean adults 40 to 69 years of age) [24], metabolic syndrome was associated with asthma-like symptoms.

There is a strong connection between more severe and uncontrolled asthma and metabolic syndrome [25], which are often related with increased airway hyper-responsiveness, oxidative stress,

regulation of systemic and pulmonary inflammation, and macrophage activation [26,27,28]. Modifications to nutrition and microbiome, immunity, inflammation and biophysical lung function associated with obesity may also likely have an impact on asthma, regardless metabolic pathways [9,29]. Particularly, obesity-induced insulin resistance seems to precede macrophage accumulation and inflammation in adipose tissue [30], and has been linked to elevated inflammatory markers in serum and adipose tissue among patients with severe asthma [29]. On the other hand, sputum and serum expression of interleukin 6, which is recognized to have a role in the development of insulin resistance, have been associated with more severe asthma and airway obstruction [31,32].

3. Insulin Resistance and Asthma Pathophysiology: A Missing Link

The degree of insulin resistance and the amount of circulating insulin are strongly correlated in most patients with prediabetes and insulin resistance. As a result, the lung and other peripheral organs that retain insulin sensitivity are susceptible to high levels of circulating insulin [25]. Studies have shown the presence of insulin receptors in the developing lung [33], but while the lungs' extent of insulin sensitivity is unknown, it is assumed that (like most other tissues) hyperinsulinemia, is accompanied by reduced insulin-like growth factor binding proteins (IGFBP-1 and -3) and increased free insulin-like growth factor (IGF-1) [34,35]. Both insulin and IGF-1 have significant impact on cell proliferation and differentiation through several mechanisms of action including increased fibrosis, increased epithelium to mucus transition, as well as increased airway smooth muscle (ASM) mass and contractility. Some of these are associated with asthma phenotypes.

Insulin causes a hypercontractile phenotype of bovine ASM, similar to that seen in asthma, by increasing the production of β 1-containing laminins through a phosphoinositide-3 kinase (PI-3K)/Akt-dependent signaling pathway [36]. Recent observations in humans [36] have shown that inhaled insulin can cause an abrupt loss in lung function due to airway smooth muscle contraction, suggesting that hyperinsulinemia may increase airway smooth muscle bulk or contraction. Intranasal insulin administration in mice, resulted in increased collagen deposition in the lungs, as well as increased airway hyper-responsiveness [37]. Furthermore, lungs of mice treated with insulin showed PI3K/Akt mediated activation of β -catenin, a positive regulator of epithelial mesenchymal transition and fibrosis, suggesting that hyperinsulinemia may have negative impacts on airway structure and function.

A key mechanism involved in many biological processes, including cell proliferation, morphogenesis, and development, is the Wnt/ β -catenin signaling pathway [38]. Several human abnormalities, such as malignancies and inflammatory, fibrotic, and metabolic disorders, have been linked to aberrant Wnt/ β -catenin signaling [39]. Studies have illustrated that blocking Wnt/ β -catenin signaling decreases pulmonary fibrosis in a murine model [40]. Wnt/ β -catenin signaling pathway plays crucial role in pulmonary arterial hypertension, in which vascular smooth muscle cell proliferation is a fundamental feature [41]. Given that smooth muscle hyperplasia and subepithelial fibrosis are the hallmarks of airway remodeling, we can speculate that Wnt/ β -catenin signaling plays a role in the process of airway remodeling in asthma. In the lung tissue of mice with chronic asthma, the use of a particular siRNA which blocks β -catenin expression, resulted in airway remodeling and inflammation, reduction of subepithelial fibrosis and collagen accumulation, and downregulation of transforming growth factor- β production [42]. Furthermore, suppression of β -catenin in a model of chronic asthma prevented smooth muscle hyperplasia through downregulation of the tenascin C/platelet-derived growth factor receptor pathway, indicating that this pathway is abundantly expressed and controls the process of airway remodeling. Hence, insulin is thought to be involved in β -catenin-mediated unfavorable airway remodeling since inhibiting this protein has been demonstrated to block the development of ASM hyperplasia, mucus metaplasia, and subepithelial fibrosis in chronic asthma [43].

In patients with severe persistent asthma, remodeling of the airway wall is a characteristic of chronic airway inflammation and could be a major factor in airway hyper-responsiveness and lung function loss [44]. Both changes in extracellular matrix (ECM) [45] and increased mass of airway smooth muscle (ASM) [46] are characteristics of airway wall remodeling in these patients. Laminins

are ECM proteins commonly found in basement membranes with an increased expression being observed in the airways of patients with asthma compared with healthy controls [47]. Using bovine tracheal smooth muscle, Dekkers et al. [36] showed a pivotal role for laminins in the establishment of an ASM phenotype that is hypercontractile and hypoproliferative after insulin exposure. Thus, increased ASM contractility and contractile protein expression may be related to increased laminin synthesis by ASM in asthma. Moreover, the same study showed that eight days administration of insulin causes an elevation in the expression of particular markers of the contractile phenotype in bovine tracheal smooth muscle cells and strips [48]. This was followed by a decrease in mitogenic responses and the installation of a functionally hypercontractile phenotype [49].

Additionally, it has been observed that high-fat-diet (HFD)-induced obesity increased the expression of TGF- β 1 and insulin resistance in the lungs, which causes perivascular and peribronchial pulmonary fibrosis and aggravated airway hyper-responsiveness (AHR) to inhaled aerosolized methacholine (MCh) in mice [50].

Intranasal insulin enhanced the expression of TGF- β 1 in the bronchial epithelium and caused lung fibrosis. HFD-induced AHR, lung fibrosis, and goblet cell hyperplasia were reduced by the anti-TGF- β 1 antibody. Regarding airway hyper-responsiveness, insulin inhibits M2 muscarinic receptors in parasympathetic nerves in the trachea of humans and rats, which leads to an increase in acetylcholine release and an increase in airway contraction [51]. Loss of inhibitory M2 muscarinic receptor function on parasympathetic nerves and enhanced vagally mediated bronchoconstriction in obesity are strongly related [51]. These findings may explain why obese people are more likely to experience asthma exacerbations since hyperinsulinemia is more common and predominant in obese people. They also imply that anticholinergic medications may be useful in treating this type of asthma. Furthermore, insulin-exposed open ring guinea pig tracheal preparations induce ASM contraction via PI3-kinase and Rho kinase-dependent mechanisms mediated by contractile prostaglandin synthesis [52]. Xu et al. found [53] that insulin treatment decreased the β -agonist responsiveness of primary human ASM cells and obese mice via phosphorylating phosphodiesterase 4D and upregulating its downstream activity. In contrast, a recent study by Ferreira et al. [54] demonstrated that insulin deficiency correlated with decreased lung concentrations of ERK1/2, JNK, and STAT3. It also prevented the development of allergic inflammation, eosinophilic pulmonary infiltration, and airway hyper-responsiveness in a mouse model of asthma [54].

Delving even deeper into the pathophysiology of asthma, it is worth mentioning that mast cells are essential for the onset and progression of inflammatory and acute type allergic reactions. Lessman et al. [55] showed that insulin and IGF-1 increased cell survival via the PI3-kinase pathway in rabbit bone-marrow-derived mast cells. These effects may play a role in the inverse link between atopic diseases, such as allergies and asthma, and type 1 diabetes mellitus, which is characterized by low insulin levels. Insulin-mediated stimulation of PI3-kinase and ERK pathways prevented human bronchial epithelial cells apoptosis, which may facilitate airway remodeling [56]. Accordingly, insulin is important in the pathogenesis of apoptosis-driven lung diseases (such as asthma and chronic obstructive pulmonary disease) and provide evidence for a possible novel protective role of insulin.

The lungs are not sterile, but they have a far lower bacterial load compared with other mucosal surfaces. This is partly because of strict control over the availability of nutrients, including glucose. Normally, the airway surface liquid (ASL) has up to 12 times lower glucose levels compared with plasma [57]. Two mechanisms maintain this low concentration: glucose transporters that take up the glucose from the blood, and tight junctions, which block it from entering the airway. Keeping glucose levels low may be a homeostatic strategy that prevents bacteria from growing by depriving them of an essential nutrient [58]. A higher risk of bacterial lung infection arises when these processes fail with resultant glucose increase, particularly in individuals with underlying lung disease, such as asthma [59]. In line with this, high glucose levels increase the likelihood of respiratory tract bacterial colonization in critically ill patients [59].

In the event of chronic hyperglycemia, advanced glycation end-products (AGEs) are actively generated and accumulate in the bloodstream and in different organs [60]. By various mechanisms, AGEs also promote the expression of AGE receptors and have a crucial role in the development of

vascular complications in diabetes. Initially, the multiligand receptor known as the receptor for advanced glycation end products (RAGE) was suggested as a potential mediator in diabetes [61]. However, it was later discovered that membrane RAGE (mRAGE) signaling is pro-inflammatory, while soluble RAGE (sRAGE), a secreted form of RAGE, is generally anti-inflammatory due to its ability to scavenge pro-inflammatory ligands [61]. Milutinovic et al. [62] showed that RAGE plays a pivotal role in the disease processes that lead to pulmonary eosinophilia, mucus hypersecretion, airway remodeling, and hyper-responsiveness of the airways in a model of dust mite-induced asthma/allergic airway disease. The absence of RAGE abolished airway hypersensitivity (resistance, tissue damping, and elastance), eosinophilic inflammation, and airway remodeling and reduced the expression of IL-5 and IL-13 protein and mRNA in the lung [62].

Finally, insulin resistance, hyperglycemia, or both has been linked as a cause of accelerated decline in respiratory function, a condition that has been reported as "diabetic lung" [63]. The term "diabetic lung" includes several abnormalities of the respiratory function concerning lung volume, pulmonary diffusing capacity, control of ventilation, bronchomotor tone, and neuroadrenergic bronchial innervation. Although the exact pathogenetic mechanisms by which insulin resistance, hyperglycemia, and diabetes mellitus may affect respiratory function are not yet fully understood, it is speculated that increase in lung collagen and elastin [64], as well as the occurrence of subclinical nodular fibrosis, in addition to physiological impacts on the function of the respiratory muscles are responsible for this effect [65].

The suggested mechanisms of insulin resistance in asthma are shown in Table 1.

Table 1. Suggested mechanisms of insulin resistance in asthma.

Enhanced Airway Remodeling
Increased collagen deposition in the lungs
Increased epithelium to mucus transition
Increased fibrosis
Increased airway smooth muscle mass
Increased expression of TGF- β 1
Increased Airway Smooth Muscle (ASM) contractility
Increased airway hyper-responsiveness
Loss of inhibitory M2 muscarinic receptor function
Enhanced vagally mediated bronchoconstriction
Lung function impairment
Reduced Forced Expiratory Volume in the 1 st sec (FEV ₁)
Reduced Forced vital capacity (FVC)
Reduced Forced expiratory flow over the middle half of the FVC (FEF _{25-75%})
Increase the risk of respiratory tract bacterial colonization
Release of pro-inflammatory mediators from adipose tissue
Increased IL-6
Increased TNF- α
Increased Th2-inflammation

4. Epidemiological-Observational Studies

Diabetes and disorders of glucose metabolism have been associated with reduced diffusing capacity and restrictive spirometry in subpopulations free from any pulmonary disease. This is based on 40 studies evaluating lung function data of 3,182 patients with diabetes [66]. However, no study has clearly clarified whether hyperglycemia, and consequently diabetes mellitus, increases the risk of asthma or vice versa [67]. There appears to be a bidirectional independent relationship between diabetes mellitus and asthma [67].

One of the first studies evaluating this issue was conducted in Denmark [21] and showed that insulin resistance was associated with a higher risk of manifesting asthma-like symptoms, thus

supporting the theory that asthma and obesity may be linked through inflammatory processes also implicated in insulin resistance.

A few years later, Mueller et al. [68], using data from the Singapore Chinese Health Study, also observed a positive association between self-reported, physician-diagnosed asthma and risk of developing type 2 diabetes. In agreement with the two aforementioned studies, the Nord-Trøndelag Health Study (HUNT) examining prospectively 23191 adults aged 19-55 years, without asthma at baseline, found that metabolic syndrome was associated with increased risk of incident asthma, indicating that physicians may take metabolic syndrome into account as a predictor of future risk of asthma [69]. The above observation is also seen in children: an Australian study illustrated signs of insulin resistance in 43% of allergic asthmatic children 6-17 years of age [70].

In addition to the aforementioned epidemiological population based-studies, studies employing electronic and administrative health records, similarly reported that the risk of asthma is higher in subjects with type 2 diabetes compared with non-diabetic individuals, suggesting that these 2 diseases are related [71,72]. Nevertheless, one of the major limitations in all these studies is that incident asthma was defined by self-report or through diagnostic codes and not objectively confirmed.

One step forward, Cardet et al. [73] hypothesized that insulin resistance is an effect modifier of the relationship between obesity and asthma in adults. A history of physician-diagnosed current asthma and insulin resistance were obtained from 12,421 individuals, aged 18-85 years, using the large National Health and Nutrition Examination Survey from 2003-2012. In logistic regression analysis, increased insulin resistance increases in obese individuals increased the likelihood of asthma [73]. This was not the case for other components of the metabolic syndrome [73]. Therefore, it is possible that a subgroup of obese individuals with asthma may be identified by their insulin resistance, and agents targeting insulin resistance may also improve asthma control in this subgroup [73]. This was confirmed recently, in another cross-sectional study of 1276 adults from the NHANES 2009-2012 database [74]. In this analysis, waist-to-hip ratio and insulin resistance independently predicted impaired pulmonary function in overweight/obese asthmatic adults [74]. Evaluations were based on forced expiratory volume in the 1st second (FEV₁), forced vital capacity (FVC), and forced expiratory flow over the middle half of the FVC (FEF_{25-75%}).

Accordingly, the association between insulin resistance, diabetes, and prevalent asthma is bidirectional. Other studies including patients with asthma have also reported a positive correlation between disorders of glucose metabolism and asthma morbidity. According to a recent longitudinal analysis of the Severe Asthma Research Program cohort, higher incidence of diabetes, hypertension, and obesity has been associated with a higher risk of asthma exacerbation [13]. In a cross-sectional analysis using data from ERICA (Study of Cardiovascular Risk in Adolescents, Portuguese acronym ERICA), a multicenter, school-based countrywide study in a complex sample of adolescents aged 12-17 years, metabolic syndrome and insulin resistance were significantly associated with severe asthma in Brazilian adolescents [75].

In an attempt to ascertain the relationship between pre-diabetes/diabetes and asthma exacerbations in an obese asthma cohort, Wu et al. [76] conducted a retrospective cohort of 5,722 individuals with obese asthma in United States, aged 18-64, from a claims-based health care database covering 2010-2015. It is worth underlining, that in the current study, the investigators used HbA_{1c} instead of a historical or self-reported diagnosis of diabetes, and pre-diabetes defined as 5.7% ≤ HbA_{1c} < 6.4%, while diabetes was defined as HbA_{1c} ≥ 6.5% [76]. Compared to patients with normal HbA_{1c}, those in the pre-diabetes range experienced a 27% and those in the diabetes range experienced a 33% higher asthma exacerbation rate, respectively. Yang et al. [12] evaluated the relationship between asthma-related hospitalizations, lung function and HbA_{1c}, in a cross-sectional analysis of 47,606 adults with asthma but not diabetes mellitus from the UK Biobank. Both HbA_{1c} per se and an HbA_{1c} in the pre-diabetic or diabetic range were associated with ≥1 asthma hospitalization. Both HbA_{1c} per se and a HbA_{1c} in the prediabetic/diabetic range were significantly and inversely associated with FEV₁ and FVC [12].

Other studies have also found that prediabetes or diabetes is associated with asthma exacerbations [77,78]. Although non-significant after adjustment for covariates, diabetes has been linked to asthma exacerbations [77]. Individuals with exacerbation-prone asthma were more likely to self-report a diagnosis of diabetes mellitus than individuals without exacerbation-prone asthma, according to a cross-sectional study of data from 709 participants in the US-based Severe Asthma Research Program (SARP)-3 cohort [77]. Conversely, even after controlling for smoking status, overweight or obesity, and other potential confounders, a study of 130,547 patients (aged 12-80 years) in two UK databases found that a diagnosis of type 1 or type 2 diabetes was significantly associated with 1.53 times increased odds of hospitalizations related to asthma within the following year [78].

Insulin resistance and glucose dysregulation have been further associated with worse lung function in people with and without asthma. After adjustment for body-mass index, waist circumference, smoking, and other covariates, a multivariable analysis of 15,792 United States adults in the Atherosclerosis Risk in Communities (ARIC) Study showed that % predicted of FEV₁ and % predicted of FVC were 2.4% and 3.6% lower, respectively, in adults with diabetes than in those without diabetes [79]. Conversely, in a U.S. nationwide survey study of 4,257 adults without diabetes there was a significant non-linear inverse association between elevated HbA_{1c} and FEV₁, FVC, and FEV₁/FVC ratio, after adjusting for body-mass index and waist-to-hip ratio [80]. Unfortunately, none of those two studies considered potential effects of respiratory comorbidities, such as asthma, on glucose metabolism.

Furthermore, a cross-sectional study of 1429 adolescents aged 12-17 years in the 2007-2010 National Health and Nutrition Examination Survey in the United States [80] concluded that insulin resistance and metabolic syndrome were associated with impaired pulmonary function in overweight/obese adolescents. In another cross-sectional study of diabetic and non-diabetic adults [81], a 1% absolute increase in HbA_{1c} was associated with a -52 mL difference in FVC and a -25 mL difference in FEV₁ in women, and a -128 mL difference in FVC and a -73 mL difference in FEV₁ in men, showing an inverse association between glycemic measures and lung function. The findings of an additional cross-sectional observational cohort study of non-smokers African American adults from the Jackson Heart Study were also similar [82]. Women and men with diabetes had lower FEV₁ and FVC than those with normal glucose tolerance, but there was no significant difference in lung function between women or men with impaired glucose tolerance and those with normal glucose tolerance [82].

Ultimately, data from Colombian Diabetes Association Center in Bogotá [83], showed that patients with type 2 diabetes and inadequate glucose control, had lower FEV₁ (-75.4 mL) and FVC (-121 mL) mean residuals, and higher FEV₁/FVC (0.013%) residuals than those with adequate control, as well as increased levels of all inflammatory markers.

In the light of all this data, we can assume that insulin resistance and metabolic syndrome are strongly related with asthma prevalence and may predict impairment of lung function. However, the underlying mechanisms remain unclear. In an attempt to answer this query, 168 Hispanic and African American adolescents (13-18 years) from Children's Hospital in Montefiore were divided into groups of 42 obese subjects with asthma, 42 normal-weight subjects with asthma, 40 obese subjects without asthma, and 44 healthy control subjects [28]. Insulin resistance and dyslipidemia were associated with non-atopic systemic inflammation, and lung function deficits in children with obesity-related asthma [28].

5. Current Antidiabetic Drugs and Asthma

If diabetes and insulin resistance aggravate asthma, it makes sense that treating these conditions could have a positive therapeutic impact, provided that the mechanism causing lung damage is reversible. In addition to their effects on glucose management, many antidiabetic drugs have additional actions that can also affect asthma.

According to in vivo and in vitro studies of the last decade, metformin exerts anti-inflammatory effects in airways [84,85]. Metformin has been shown to reverse lung tissue eosinophilic infiltration and decrease amounts of pro-inflammatory cytokines, as well as reactive oxygen species, and nitric

oxide species in mouse asthma models [85]. Adenosine monophosphate-activated protein kinase (AMPK) is thought to be the likely key mechanism by which metformin has an anti-inflammatory effect on the airway [85]. Metformin has been observed to activate AMPK, and in a dose-dependent manner inhibit tumor necrosis factor (TNF)- α -induced NF- κ B activation and TNF- α -induced I κ B kinase activity [86]. Additionally, this agent appears to attenuate TNF- α -induced gene expression of various pro-inflammatory and cell adhesion molecules (such as vascular cell adhesion molecule-1, E-selectin, intercellular adhesion molecule-1, and monocyte chemoattractant protein-1) in human umbilical vein endothelial cells (HUVECs) [86]. AMPK activity also reduces oxidative stress and contributes to the inhibition of TNF- α -induced inflammatory signaling and nuclear factor- κ B-mediated inducible nitric oxide synthase expression [85]. In male mice fed for 10 weeks with a high-fat diet (HFD) to induce obesity, Calixto et al. [84] showed that metformin reduced the exacerbation of allergic eosinophilic inflammation [84]. Given that metformin is recommended as a first-line treatment for diabetes [87], it may be a new therapeutic option for these patients. Indeed, in a US cohort of individuals with asthma and diabetes, metformin was associated with a lower hazard of asthma-related emergency department visits and hospitalizations [88].

In an 11-year (2001-2011) retrospective cohort study using the Taiwan National Health Insurance Research Database [89], 1332 patients with concurrent asthma and diabetes, were followed for 3 years for asthma-related outcomes. Compared with non-users, metformin users had a lower risk of asthma-related hospitalization and asthma exacerbation [89]. Very recently, Wu TD et al. [90] identified 1749 patients with asthma and diabetes using the Johns Hopkins electronic health record from April 2013 to May 2018. Metformin use, independently of glycemic control and obesity, was associated with lower hazard of asthma-related emergency department visits and hospitalizations [90]. Unfortunately, there is no data on the beneficial role of metformin from prospective controlled studies in asthma, with and without obesity.

Glucagon-like peptide 1 (GLP-1) is a gut-derived hormone that enhances insulin sensitivity and increases pancreatic insulin production in response to oral food intake [91]. Its receptor exists in the lung and immune cells and may mediate several inflammatory pathways implicated in the pathogenesis of obesity-related asthma [92]. Preclinical studies have demonstrated that GLP-1 inhibited the production of pro-inflammatory cytokines, including TNF- α , by inactivating NF- κ B in a protein kinase A-dependent manner [93,94]. Moreover, GLP-1 receptor agonists (GLP-1RAs) suppress RAGE expression, and thus reduce inflammation and bronchoconstriction [95]. Furthermore, the GLP-1RA liraglutide reduced mucus hypersecretion and airway inflammation in a mouse model of allergic asthma [96]. In addition, in mice models, GLP-1RAs reduced release of T2 cytokines from type 2 innate lymphoid cells (ILC2), as well as mucus production after exposure to fungal allergens and viral antigens [97,98,99]. Interestingly, in isolated human airways, GLP-1R activation reduced contractile tone, and reduced lipopolysaccharide-stimulated eosinophil activation [100,101].

GLP-1RAs have been associated with improvements in asthma outcomes in adults with diabetes mellitus and asthma. In the first preliminary uncontrolled study, 9 participants receiving a GLP-1RA for one year improved asthma symptoms and decreased asthma exacerbations [102]. An electronic health records-based new user, active-comparator, retrospective cohort study of patients with type 2 diabetes and asthma showed that patients on GLP-1RAs for type 2 diabetes had fewer asthma exacerbations compared with other antidiabetic agents (sodium-glucose cotransporter-2 inhibitors [SGLT-2is], dipeptidyl peptidase inhibitors [DPP-4is], sulfonylureas, or basal insulin) [103].

Another new-user active-comparator analysis using a national claims database (2005-2017) also showed that patients with diabetes and chronic lower respiratory disease (CLRD) (a medical term that includes both COPD and asthma) who started GLP-1RA had fewer CLRD exacerbations in comparison with those starting DPP-4is [104]. In diabetes, a randomized clinical trial reported that liraglutide decreased serum surfactant protein D, which independently predicted improvements in FVC [105]. In a prospective cohort of 32 adults with diabetes but without obstructive lung disease, addition of a GLP-1RA to metformin improved lung function (FEV1 and FVC) over metformin alone or metformin plus insulin [106].

Sulfonylureas are frequently used as second-line antidiabetic therapy [107]. Sulfonylureas attach to receptors on the cell membranes of pancreatic beta cells and increase insulin secretion. Their main untoward effect is hypoglycemia [108,109]. A retrospective cohort study using a representative UK primary care database showed that sulphonylureas were associated with reduced risk of incident asthma [110].

DPP-4is are preferable to sulfonylureas as second-line therapy after metformin initiation, due to their neutral effect on weight and the absence of hypoglycemia [111, 112, 113]. Very recently, studies utilizing in vitro models of human bronchial epithelial cells have demonstrated that DPP-4is inhibit pathways leading to fibrosis [114] and oxidative stress [115]. Nonetheless, a retrospective observational matched cohort study showed that treatment with DPP-4i did not improve asthma control, treatment stability or asthma exacerbations [116]. This has been confirmed in a network meta-analysis [117].

SGLT-2is promote glycosuria [118]. An in vitro transcriptomics experiment in human proximal tubular cells showed that the SGLT-2i canagliflozin decreased TNF receptor 1, IL-6, matrix metalloproteinase 7 and fibronectin 1 during 2 years of follow-up, as compared with the sulfonylurea glimepiride [119].

In 2021, 9 large randomized controlled trials (RCTs) were included in a fixed-effects meta-analysis to evaluate the relationship between -2is inhibitors and occurrence of 9 types of non-infectious respiratory disorders [120]. SGLT-2is reduced the occurrence of asthma serious adverse events compared to placebo. Another meta-analysis with a similar design concluded SGLT-2is reduced the risk of asthma in comparison with GLP-1RAs and DPP-4is [117]. Despite that, the extremely low incidence of asthma outcomes in both the treatment and placebo groups limits the validity of both meta-analyses.

Thiazolidinediones (TZDs) are another class of antidiabetic agents. They bind to the gamma isoform of the peroxisome proliferator-activated receptor (PPAR γ) and reduce insulin resistance and ectopic fat accumulation [121,122]. So far, the results of studies regarding the anti-inflammatory effect of TZDs on asthma are controversial. In cultured human airway smooth muscle cells, troglitazone reduced IL-6 in a dose-dependent manner [123], but a systematic review concluded TZDs did not significantly affect IL-6 levels [124]. A large retrospective observational study of diabetic Veterans who asthma and were taking oral antidiabetic agents [125] showed TZDs were associated with significant reductions in the risk of asthma exacerbation and oral steroid prescription. Use of angiotensin converting enzyme inhibitors (ACE-is) and/or TZDs was also associated with a lower risk for incident asthma in overweight/obese patients with diabetes mellitus and/or hypertension, in another retrospective observational longitudinal data analysis, of 77,278 Veterans with incident asthma [126].

Conversely, a 12-week, randomized, placebo-controlled, double-blind trial found no difference in exhaled nitric oxide, asthma control or lung function between treatment groups [127]. Interestingly, patients receiving pioglitazone gained significantly more weight than those receiving placebo [127]. The study was prematurely discontinued due to new safety concerns on the risk for bladder cancer with pioglitazone [127]. Finally, a RCT of pioglitazone in severe asthma found no beneficial effect on asthma quality of life, as well as many untoward effects [128]. Thus, TDZs do not appear to hold for asthma.

The potential effects of current classes of hypoglycemic therapies in pathophysiology of asthma are shown in Table 2.

Table 2. Potential effects of current classes of antidiabetics in pathophysiology of Asthma.

Antidiabetic agent	Potential beneficial effects on asthma	Putative mechanisms
Metformin	YES	Reverse lung tissue eosinophilic infiltration ↓ Proinflammatory cytokines ↓ Reactive Oxygen Species

		↓ Nitric Oxide Species ↓ TNF- α ↓ Cell adhesion molecules ↓ Allergic eosinophilic inflammation
GLP-1	YES	↓ Proinflammatory cytokines ↓ TNF- α Suppress receptors of advanced glycation end-products (RAGE) expression ↓ Bronchoconstriction ↓ T2 cytokines ↓ Mucus hypersecretion ↓ Airway hyperresponsiveness (AHR) ↓ IL-33 ↓ Contractile tone
Dipeptidyl peptidase-4 inhibitors (DPP-4i)	UNCERTAIN	↓ Oxidative stress ↓ Lung fibrosis
Inhibitor of the sodium-glucose co-transporter 2 channel (SGLT-2)	YES	↓ TNF receptor 1 ↓ IL-6 ↓ Matrix metalloproteinase 7 ↓ Fibronectin 1
Thiazolidinediones (TZD)	NO	↓ IL-6 *
Sulfonylureas	UNCERTAIN	

*A systematic review concluded that TZD does not significantly affect IL-6 levels.

5. Conclusions

Obesity, insulin resistance or glucose intolerance, dyslipidemia, and other key clinical features of metabolic dysfunction—typically manifested as metabolic syndrome—have been found to be possible risk factors for severe and uncontrolled asthma. More specifically, disorders of glucose metabolism, ranging from clinically silent insulin resistance through degrees of hyperglycemia defining prediabetes and diabetes, can precipitate changes in the lung consistent with asthma through pathways principally involving insulin excess. Recent experimental studies have shown that insulin resistance may contribute to an increase of systemic inflammation, modulation of immune function, effects on airway remodeling, promotion of airway smooth muscle (ASM) contractility and proliferation and increase of airway hyper-responsiveness. Evidence from observational studies also supports clinically relevant associations between glycemic dysregulation and asthma outcomes. A growing volume of epidemiologic evidence indicates that by focusing on the underlying glycemic dysregulation, specific types of hypoglycemic drugs may be able to treat both chronic diseases. To better understand the influence and the role of insulin resistance in asthma, more research is required, and novel antidiabetic drugs pertaining to asthma should be investigated.

Author Contributions: Conceptualization, P.S.; methodology, K.B.; data curation, K.B.; writing—original draft preparation, K.B., A.I.P.; writing—review and editing, F.D., E.G., N.P.; supervision, P.S.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: K.B., A.I.P., F.D., E.G. and P.S. declare no conflicts of interest. N.P. has been an advisory board member of AstraZeneca, Boehringer Ingelheim, MSD, Novo Nordisk, Pfizer, Takeda and TrigoCare International; has participated in sponsored studies by AstraZeneca, Eli Lilly, GSK, MSD, Novo Nordisk, Novartis and Sanofi-Aventis; has received honoraria as a speaker for AstraZeneca, Boehringer Ingelheim, Eli

Lilly, Elpen, MSD, Mylan, Novo Nordisk, Pfizer, Sanofi-Aventis and Vianex; and has attended conferences sponsored by TrigoCare International, Eli Lilly, Galenica, Novo Nordisk, Pfizer and Sanofi-Aventis.

References

- To, T.; Stanojevic, S.; Moores, G.; Gershon, A.S.; Bateman, E.D.; Cruz, A.A.; Boulet, L.-P. Global Asthma Prevalence in Adults: Findings from the Cross-Sectional World Health Survey. *BMC Public Health* **2012**, *12*, 204.
- 2023 GINA Main Report Available online: <https://ginasthma.org/2023-gina-main-report/> (accessed on 12 December 2023).
- Papaioannou, A.I.; Fouka, E.; Bartziokas, K.; Kallieri, M.; Vontetsianos, A.; Porpodis, K.; Rovina, N.; Loukides, S.; Bakas, P. Defining Response to Therapy with Biologics in Severe Asthma: From Global Evaluation to Super Response and Remission. *Expert Rev. Respir. Med.* **2023**, *17*, 481–493.
- Moore, W.C.; Meyers, D.A.; Wenzel, S.E.; Teague, W.G.; Li, H.; Li, X.; D'Agostino, R., Jr; Castro, M.; Curran-Everett, D.; Fitzpatrick, A.M.; et al. Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program. *Am. J. Respir. Crit. Care Med.* **2010**, *181*, 315–323.
- Loza, M.J.; Djukanovic, R.; Chung, K.F.; Horowitz, D.; Ma, K.; Branigan, P.; Barnathan, E.S.; Susulic, V.S.; Silkoff, P.E.; Sterk, P.J.; et al. Validated and Longitudinally Stable Asthma Phenotypes Based on Cluster Analysis of the ADEPT Study. *Respir. Res.* **2016**, *17*, 165.
- Wu, T.D. Diabetes, Insulin Resistance, and Asthma: A Review of Potential Links. *Curr. Opin. Pulm. Med.* **2021**, *27*, 29–36.
- Park, J.-W. Asthma Phenotype with Metabolic Dysfunction. *Yonsei Med. J.* **2022**, *63*, 1–7.
- Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z. The Metabolic Syndrome. *Lancet* **2005**, *365*, 1415–1428.
- Peters, U.; Dixon, A.E.; Forno, E. Obesity and Asthma. *J. Allergy Clin. Immunol.* **2018**, *141*, 1169–1179.
- Liu, S.; Verma, M.; Michalec, L.; Liu, W.; Sripada, A.; Rollins, D.; Good, J.; Ito, Y.; Chu, H.; Gorska, M.M.; et al. Steroid Resistance of Airway Type 2 Innate Lymphoid Cells from Patients with Severe Asthma: The Role of Thymic Stromal Lymphopoietin. *J. Allergy Clin. Immunol.* **2018**, *141*, 257–268.e6.
- Chambers, E.S.; Nanzer, A.M.; Pfeffer, P.E.; Richards, D.F.; Timms, P.M.; Martineau, A.R.; Griffiths, C.J.; Corrigan, C.J.; Hawrylowicz, C.M. Distinct Endotypes of Steroid-Resistant Asthma Characterized by IL-17A(high) and IFN- γ (high) Immunophenotypes: Potential Benefits of Calcitriol. *J. Allergy Clin. Immunol.* **2015**, *136*, 628–637.e4.
- Yang, G.; Han, Y.-Y.; Forno, E.; Yan, Q.; Rosser, F.; Chen, W.; Celedón, J.C. Glycated Hemoglobin A, Lung Function, and Hospitalizations Among Adults with Asthma. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 3409–3415.e1.
- Peters, M.C.; Mauger, D.; Ross, K.R.; Phillips, B.; Gaston, B.; Cardet, J.C.; Israel, E.; Levy, B.D.; Phipatanakul, W.; Jarjour, N.N.; et al. Evidence for Exacerbation-Prone Asthma and Predictive Biomarkers of Exacerbation Frequency. *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 973–982.
- Petersen, M.C.; Shulman, G.I. Mechanisms of Insulin Action and Insulin Resistance. *Physiol. Rev.* **2018**, *98*, 2133–2223.
- Zaccardi, F.; Webb, D.R.; Yates, T.; Davies, M.J. Pathophysiology of Type 1 and Type 2 Diabetes Mellitus: A 90-Year Perspective. *Postgrad. Med. J.* **2016**, *92*, 63–69.
- American Diabetes Association 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* **2020**, *43*, S14–S31.
- American Diabetes Association Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* **2010**, *33* Suppl 1, S62–S69.
- Li, C.; Ford, E.S.; McGuire, L.C.; Mokdad, A.H.; Little, R.R.; Reaven, G.M. Trends in Hyperinsulinemia among Nondiabetic Adults in the U.S. *Diabetes Care* **2006**, *29*, 2396–2402.
- National Diabetes Statistics Report 2022 Available online: <https://repository.gheli.harvard.edu/repository/11854/> (accessed on 12 December 2023).
- Terzano, C.; Morano, S.; Ceccarelli, D.; Conti, V.; Paone, G.; Petroianni, A.; Graziani, E.; Carnovale, A.; Fallarino, M.; Gatti, A.; et al. Effect of Insulin on Airway Responsiveness in Patients with Type 2 Diabetes Mellitus: A Cohort Study. *J. Asthma* **2009**, *46*, 703–707.
- Thuesen, B.H.; Husemoen, L.L.N.; Hersoug, L.-G.; Pisinger, C.; Linneberg, A. Insulin Resistance as a Predictor of Incident Asthma-like Symptoms in Adults. *Clin. Exp. Allergy* **2009**, *39*, 700–707.
- Appleton, S.L.; Adams, R.J.; Wilson, D.H.; Taylor, A.W.; Ruffin, R.E.; North West Adelaide Health Study Team Central Obesity Is Associated with Nonatopic but Not Atopic Asthma in a Representative Population Sample. *J. Allergy Clin. Immunol.* **2006**, *118*, 1284–1291.
- Scholtens, S.; Wijga, A.H.; Brunekreef, B.; Kerkhof, M.; Postma, D.S.; Oldenwening, M.; de Jongste, J.C.; Smit, H.A. Maternal Overweight before Pregnancy and Asthma in Offspring Followed for 8 Years. *Int. J. Obes.* **2010**, *34*, 606–613.
- Lee, E.J.; In, K.H.; Ha, E.S.; Lee, K.J.; Hur, G.Y.; Kang, E.H.; Jung, K.H.; Lee, S.Y.; Kim, J.H.; Lee, S.Y.; et al. Asthma-like Symptoms Are Increased in the Metabolic Syndrome. *J. Asthma* **2009**, *46*, 339–342.

25. Agrawal, A.; Mabalirajan, U.; Ahmad, T.; Ghosh, B. Emerging Interface between Metabolic Syndrome and Asthma. *Am. J. Respir. Cell Mol. Biol.* **2011**, *44*, 270–275.
26. Scichilone, N.; Rizzo, M.; Benfante, A.; Catania, R.; Giglio, R.V.; Nikolic, D.; Montalto, G.; Bellia, V. Serum Low Density Lipoprotein Subclasses in Asthma. *Respir. Med.* **2013**, *107*, 1866–1872.
27. Rasmussen, F.; Hancox, R.J.; Nair, P.; Hansen, H.S.; Siersted, H.C.; Nybo, M. Associations between Airway Hyperresponsiveness, Obesity and Lipoproteins in a Longitudinal Cohort. *Clin. Respir. J.* **2013**, *7*, 268–275.
28. Rastogi, D.; Fraser, S.; Oh, J.; Huber, A.M.; Schulman, Y.; Bhagtani, R.H.; Khan, Z.S.; Tesfa, L.; Hall, C.B.; Macian, F. Inflammation, Metabolic Dysregulation, and Pulmonary Function among Obese Urban Adolescents with Asthma. *Am. J. Respir. Crit. Care Med.* **2015**, *191*, 149–160.
29. Sideleva, O.; Suratt, B.T.; Black, K.E.; Tharp, W.G.; Pratley, R.E.; Forgiione, P.; Dienez, O.; Irvin, C.G.; Dixon, A.E. Obesity and Asthma: An Inflammatory Disease of Adipose Tissue Not the Airway. *Am. J. Respir. Crit. Care Med.* **2012**, *186*, 598–605.
30. Shimobayashi, M.; Albert, V.; Woelnerhanssen, B.; Frei, I.C.; Weissenberger, D.; Meyer-Gerspach, A.C.; Clement, N.; Moes, S.; Colombi, M.; Meier, J.A.; et al. Insulin Resistance Causes Inflammation in Adipose Tissue. *J. Clin. Invest.* **2018**, *128*, 1538–1550.
31. Peters, M.C.; McGrath, K.W.; Hawkins, G.A.; Hastie, A.T.; Levy, B.D.; Israel, E.; Phillips, B.R.; Mauger, D.T.; Comhair, S.A.; Erzurum, S.C.; et al. Plasma Interleukin-6 Concentrations, Metabolic Dysfunction, and Asthma Severity: A Cross-Sectional Analysis of Two Cohorts. *Lancet Respir Med* **2016**, *4*, 574–584.
32. Neveu, W.A.; Allard, J.L.; Raymond, D.M.; Bourassa, L.M.; Burns, S.M.; Bunn, J.Y.; Irvin, C.G.; Kaminsky, D.A.; Rincon, M. Elevation of IL-6 in the Allergic Asthmatic Airway Is Independent of Inflammation but Associates with Loss of Central Airway Function. *Respir. Res.* **2010**, *11*, 28.
33. Baffi, C.W.; Wood, L.; Winnica, D.; Strollo, P.J., Jr; Gladwin, M.T.; Que, L.G.; Holguin, F. Metabolic Syndrome and the Lung. *Chest* **2016**, *149*, 1525–1534.
34. Attia, N.; Tamborlane, W.V.; Heptulla, R.; Maggs, D.; Grozman, A.; Sherwin, R.S.; Caprio, S. The Metabolic Syndrome and Insulin-like Growth Factor I Regulation in Adolescent Obesity. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 1467–1471.
35. Singh, S.; Prakash, Y.S.; Linneberg, A.; Agrawal, A. Insulin and the Lung: Connecting Asthma and Metabolic Syndrome. *J. Allergy* **2013**, *2013*, 627384.
36. Dekkers, B.G.J.; Schaafsma, D.; Tran, T.; Zaagsma, J.; Meurs, H. Insulin-Induced Laminin Expression Promotes a Hypercontractile Airway Smooth Muscle Phenotype. *Am. J. Respir. Cell Mol. Biol.* **2009**, *41*, 494–504.
37. Singh, S.; Bodas, M.; Bhatraju, N.K.; Pattnaik, B.; Gheware, A.; Parameswaran, P.K.; Thompson, M.; Freeman, M.; Mabalirajan, U.; Gosens, R.; et al. Hyperinsulinemia Adversely Affects Lung Structure and Function. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2016**, *310*, L837–L845.
38. MacDonald, B.T.; Tamai, K.; He, X. Wnt/beta-Catenin Signaling: Components, Mechanisms, and Diseases. *Dev. Cell* **2009**, *17*, 9–26.
39. George, S.J. Wnt Pathway: A New Role in Regulation of Inflammation. *Arterioscler. Thromb. Vasc. Biol.* **2008**, *28*, 400–402.
40. Henderson, W.R., Jr; Chi, E.Y.; Ye, X.; Nguyen, C.; Tien, Y.-T.; Zhou, B.; Borok, Z.; Knight, D.A.; Kahn, M. Inhibition of Wnt/beta-catenin/CREB Binding Protein (CBP) Signaling Reverses Pulmonary Fibrosis. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 14309–14314.
41. de Jesus Perez, V.; Yuan, K.; Alastalo, T.-P.; Spiekeroetter, E.; Rabinovitch, M. Targeting the Wnt Signaling Pathways in Pulmonary Arterial Hypertension. *Drug Discov. Today* **2014**, *19*, 1270–1276.
42. Kwak, H.J.; Park, D.W.; Seo, J.-Y.; Moon, J.-Y.; Kim, T.H.; Sohn, J.W.; Shin, D.H.; Yoon, H.J.; Park, S.S.; Kim, S.-H. The Wnt/ β -Catenin Signaling Pathway Regulates the Development of Airway Remodeling in Patients with Asthma. *Exp. Mol. Med.* **2015**, *47*, e198.
43. Kumawat, K.; Koopmans, T.; Gosens, R. β -Catenin as a Regulator and Therapeutic Target for Asthmatic Airway Remodeling. *Expert Opin. Ther. Targets* **2014**, *18*, 1023–1034.
44. Bousquet, J.; Jeffery, P.K.; Busse, W.W.; Johnson, M.; Vignola, A.M. Asthma. From Bronchoconstriction to Airways Inflammation and Remodeling. *Am. J. Respir. Crit. Care Med.* **2000**, *161*, 1720–1745.
45. Fernandes, D.J.; Bonacci, J.V.; Stewart, A.G. Extracellular Matrix, Integrins, and Mesenchymal Cell Function in the Airways. *Curr. Drug Targets* **2006**, *7*, 567–577.
46. Ebina, M.; Takahashi, T.; Chiba, T.; Motomiya, M. Cellular Hypertrophy and Hyperplasia of Airway Smooth Muscles Underlying Bronchial Asthma. A 3-D Morphometric Study. *Am. Rev. Respir. Dis.* **1993**, *148*, 720–726.
47. Altraja, A.; Laitinen, A.; Virtanen, I.; Kämpe, M.; Simonsson, B.G.; Karlsson, S.E.; Håkansson, L.; Venge, P.; Sillastu, H.; Laitinen, L.A. Expression of Laminins in the Airways in Various Types of Asthmatic Patients: A Morphometric Study. *Am. J. Respir. Cell Mol. Biol.* **1996**, *15*, 482–488.
48. Schaafsma, D.; McNeill, K.D.; Stelmack, G.L.; Gosens, R.; Baarsma, H.A.; Dekkers, B.G.J.; Frohwerk, E.; Penninks, J.-M.; Sharma, P.; Ens, K.M.; et al. Insulin Increases the Expression of Contractile Phenotypic Markers in Airway Smooth Muscle. *Am. J. Physiol. Cell Physiol.* **2007**, *293*, C429–C439.

49. Gosens, R.; Nelemans, S.A.; Hiemstra, M.; Grootte Bromhaar, M.M.; Meurs, H.; Zaagsma, J. Insulin Induces a Hypercontractile Airway Smooth Muscle Phenotype. *Eur. J. Pharmacol.* **2003**, *481*, 125–131.
50. Park, Y.H.; Oh, E.Y.; Han, H.; Yang, M.; Park, H.J.; Park, K.H.; Lee, J.-H.; Park, J.-W. Insulin Resistance Mediates High-Fat Diet-Induced Pulmonary Fibrosis and Airway Hyperresponsiveness through the TGF- β 1 Pathway. *Exp. Mol. Med.* **2019**, *51*, 1–12.
51. Nie, Z.; Jacoby, D.B.; Fryer, A.D. Hyperinsulinemia Potentiates Airway Responsiveness to Parasympathetic Nerve Stimulation in Obese Rats. *Am. J. Respir. Cell Mol. Biol.* **2014**, *51*, 251–261.
52. Schaafsma, D.; Gosens, R.; Ris, J.M.; Zaagsma, J.; Meurs, H.; Nelemans, S.A. Insulin Induces Airway Smooth Muscle Contraction. *Br. J. Pharmacol.* **2007**, *150*, 136–142.
53. Xu, R.; Gopireddy, R.R.; Wu, Y.; Wu, L.; Tao, X.; Shao, J.; Wang, W.; Li, L.; Jovanovic, A.; Xu, B.; et al. Hyperinsulinemia Promotes Heterologous Desensitization of β Adrenergic Receptor in Airway Smooth Muscle in Obesity. *FASEB J.* **2020**, *34*, 3996–4008.
54. Ferreira, S.S.; Oliveira, M.A.; Tsujita, M.; Nunes, F.P.B.; Casagrande, F.B.; Gomes, E.; Russo, M.; Tavares de Lima, W.; Martins, J.O. Insulin Modulates the Immune Cell Phenotype in Pulmonary Allergic Inflammation and Increases Pulmonary Resistance in Diabetic Mice. *Front. Immunol.* **2020**, *11*, 84.
55. Lessmann, E.; Grochoway, G.; Weingarten, L.; Giesemann, T.; Aktories, K.; Leitges, M.; Krystal, G.; Huber, M. Insulin and Insulin-like Growth Factor-1 Promote Mast Cell Survival via Activation of the Phosphatidylinositol-3-Kinase Pathway. *Exp. Hematol.* **2006**, *34*, 1532–1541.
56. Numata, T.; Araya, J.; Fujii, S.; Hara, H.; Takasaka, N.; Kojima, J.; Minagawa, S.; Yumino, Y.; Kawaishi, M.; Hirano, J.; et al. Insulin-Dependent Phosphatidylinositol 3-kinase/Akt and ERK Signaling Pathways Inhibit TLR3-Mediated Human Bronchial Epithelial Cell Apoptosis. *J. Immunol.* **2011**, *187*, 510–519.
57. Tregoning, J.S.; Mallia, P. Modulating Airway Glucose to Reduce Respiratory Infections. *Expert Rev. Respir. Med.* **2019**, *13*, 121–124.
58. Baker, E.H.; Baines, D.L. Airway Glucose Homeostasis: A New Target in the Prevention and Treatment of Pulmonary Infection. *Chest* **2018**, *153*, 507–514.
59. Gill, S.K.; Hui, K.; Farne, H.; Garnett, J.P.; Baines, D.L.; Moore, L.S.P.; Holmes, A.H.; Filloux, A.; Tregoning, J.S. Increased Airway Glucose Increases Airway Bacterial Load in Hyperglycaemia. *Sci. Rep.* **2016**, *6*, 27636.
60. Rhee, S.Y.; Kim, Y.S. The Role of Advanced Glycation End Products in Diabetic Vascular Complications. *Diabetes Metab. J.* **2018**, *42*, 188–195.
61. Ramasamy, R.; Yan, S.F.; Schmidt, A.M. RAGE: Therapeutic Target and Biomarker of the Inflammatory Response—the Evidence Mounts. *J. Leukoc. Biol.* **2009**, *86*, 505–512.
62. Milutinovic, P.S.; Alcorn, J.F.; Englert, J.M.; Crum, L.T.; Oury, T.D. The Receptor for Advanced Glycation End Products Is a Central Mediator of Asthma Pathogenesis. *Am. J. Pathol.* **2012**, *181*, 1215–1225.
63. Pitocco, D.; Fuso, L.; Conte, E.G.; Zaccardi, F.; Condoluci, C.; Scavone, G.; Incalzi, R.A.; Ghirlanda, G. The Diabetic Lung—a New Target Organ? *Rev. Diabet. Stud.* **2012**, *9*, 23–35.
64. Ofulue, A.F.; Thurlbeck, W.M. Experimental Diabetes and the Lung. II. In Vivo Connective Tissue Metabolism. *Am. Rev. Respir. Dis.* **1988**, *138*, 284–289.
65. Kida, K.; Utsuyama, M.; Takizawa, T.; Thurlbeck, W.M. Changes in Lung Morphologic Features and Elasticity Caused by Streptozotocin-Induced Diabetes Mellitus in Growing Rats. *Am. Rev. Respir. Dis.* **1983**, *128*, 125–131.
66. van den Borst, B.; Gosker, H.R.; Zeegers, M.P.; Schols, A.M.W.J. Pulmonary Function in Diabetes: A Metaanalysis. *Chest* **2010**, *138*, 393–406.
67. Rayner, L.; McGovern, A.; Creagh-Brown, B.; Woodmansey, C.; de Lusignan, S. Type 2 Diabetes and Asthma: Systematic Review of the Bidirectional Relationship. *Curr. Diabetes Rev.* **2019**, *15*, 118–126.
68. Mueller, N.T.; Koh, W.-P.; Odegaard, A.O.; Gross, M.D.; Yuan, J.-M.; Pereira, M.A. Asthma and the Risk of Type 2 Diabetes in the Singapore Chinese Health Study. *Diabetes Res. Clin. Pract.* **2013**, *99*, 192–199.
69. Brumpton, B.M.; Camargo, C.A., Jr; Romundstad, P.R.; Langhammer, A.; Chen, Y.; Mai, X.-M. Metabolic Syndrome and Incidence of Asthma in Adults: The HUNT Study. *Eur. Respir. J.* **2013**, *42*, 1495–1502.
70. Arshi, M.; Cardinal, J.; Hill, R.J.; Davies, P.S.W.; Wainwright, C. Asthma and Insulin Resistance in Children. *Respirology* **2010**, *15*, 779–784.
71. Thomsen, S.F.; Duffy, D.L.; Kyvik, K.O.; Skytthe, A.; Backer, V. Risk of Asthma in Adult Twins with Type 2 Diabetes and Increased Body Mass Index. *Allergy* **2011**, *66*, 562–568.
72. Ehrlich, S.F.; Quesenberry, C.P., Jr; Van Den Eeden, S.K.; Shan, J.; Ferrara, A. Patients Diagnosed with Diabetes Are at Increased Risk for Asthma, Chronic Obstructive Pulmonary Disease, Pulmonary Fibrosis, and Pneumonia but Not Lung Cancer. *Diabetes Care* **2010**, *33*, 55–60.
73. Cardet, J.C.; Ash, S.; Kusa, T.; Camargo, C.A., Jr; Israel, E. Insulin Resistance Modifies the Association between Obesity and Current Asthma in Adults. *Eur. Respir. J.* **2016**, *48*, 403–410.
74. Sadeghimakki, R.; McCarthy, H.D. Interactive Effects of Adiposity and Insulin Resistance on the Impaired Lung Function in Asthmatic Adults: Cross-Sectional Analysis of NHANES Data. *Ann. Hum. Biol.* **2019**, *46*, 56–62.

75. Kuschnir, F.C.; Felix, M.M.R.; Caetano Kuschnir, M.C.; Bloch, K.V.; Azevedo de Oliveira Costa Jordão, E.; Solé, D.; Ledo Alves da Cunha, A.J.; Szklo, M. Severe Asthma Is Associated with Metabolic Syndrome in Brazilian Adolescents. *J. Allergy Clin. Immunol.* **2018**, *141*, 1947–1949.e4.
76. Wu, T.D.; Brigham, E.P.; Keet, C.A.; Brown, T.T.; Hansel, N.N.; McCormack, M.C. Association Between Prediabetes/Diabetes and Asthma Exacerbations in a Claims-Based Obese Asthma Cohort. *J. Allergy Clin. Immunol. Pract.* **2019**, *7*, 1868–1873.e5.
77. Denlinger, L.C.; Phillips, B.R.; Ramratnam, S.; Ross, K.; Bhakta, N.R.; Cardet, J.C.; Castro, M.; Peters, S.P.; Phipatanakul, W.; Aujla, S.; et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 302–313.
78. Price, D.; Wilson, A.M.; Chisholm, A.; Rigazio, A.; Burden, A.; Thomas, M.; King, C. Predicting Frequent Asthma Exacerbations Using Blood Eosinophil Count and Other Patient Data Routinely Available in Clinical Practice. *J. Asthma Allergy* **2016**, *9*, 1–12.
79. Yeh, H.-C.; Punjabi, N.M.; Wang, N.-Y.; Pankow, J.S.; Duncan, B.B.; Cox, C.E.; Selvin, E.; Brancati, F.L. Cross-Sectional and Prospective Study of Lung Function in Adults with Type 2 Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* **2008**, *31*, 741–746.
80. Forno, E.; Han, Y.-Y.; Muzumdar, R.H.; Celedón, J.C. Insulin Resistance, Metabolic Syndrome, and Lung Function in US Adolescents with and without Asthma. *J. Allergy Clin. Immunol.* **2015**, *136*, 304–311.e8.
81. Kabeya, Y.; Kato, K.; Tomita, M.; Katsuki, T.; Oikawa, Y.; Shimada, A. Association of Glycemic Status with Impaired Lung Function among Recipients of a Health Screening Program: A Cross-Sectional Study in Japanese Adults. *J. Epidemiol.* **2014**, *24*, 410–416.
82. Hickson, D.A.; Burchfiel, C.M.; Liu, J.; Petrini, M.F.; Harrison, K.; White, W.B.; Sarpong, D.F. Diabetes, Impaired Glucose Tolerance, and Metabolic Biomarkers in Individuals with Normal Glucose Tolerance Are Inversely Associated with Lung Function: The Jackson Heart Study. *Lung* **2011**, *189*, 311–321.
83. Dennis, R.J.; Maldonado, D.; Rojas, M.X.; Aschner, P.; Rondón, M.; Charry, L.; Casas, A. Inadequate Glucose Control in Type 2 Diabetes Is Associated with Impaired Lung Function and Systemic Inflammation: A Cross-Sectional Study. *BMC Pulm. Med.* **2010**, *10*, 38.
84. Calixto, M.C.; Lintomen, L.; André, D.M.; Leiria, L.O.; Ferreira, D.; Lellis-Santos, C.; Anhô, G.F.; Bordin, S.; Landgraf, R.G.; Antunes, E. Metformin Attenuates the Exacerbation of the Allergic Eosinophilic Inflammation in High Fat-Diet-Induced Obesity in Mice. *PLoS One* **2013**, *8*, e76786.
85. Park, C.S.; Bang, B.-R.; Kwon, H.-S.; Moon, K.-A.; Kim, T.-B.; Lee, K.-Y.; Moon, H.-B.; Cho, Y.S. Metformin Reduces Airway Inflammation and Remodeling via Activation of AMP-Activated Protein Kinase. *Biochem. Pharmacol.* **2012**, *84*, 1660–1670.
86. Hattori, Y.; Suzuki, K.; Hattori, S.; Kasai, K. Metformin Inhibits Cytokine-Induced Nuclear Factor kappaB Activation via AMP-Activated Protein Kinase Activation in Vascular Endothelial Cells. *Hypertension* **2006**, *47*, 1183–1188.
87. Executive Summary: Standards of Medical Care in Diabetes—2013. *Diabetes Care* **2012**, *36*, S4–S10.
88. Wu, T.D.; Keet, C.A.; Fawzy, A.; Segal, J.B.; Brigham, E.P.; McCormack, M.C. Association of Metformin Initiation and Risk of Asthma Exacerbation. A Claims-Based Cohort Study. *Ann. Am. Thorac. Soc.* **2019**, *16*, 1527–1533.
89. Li, C.-Y.; Erickson, S.R.; Wu, C.-H. Metformin Use and Asthma Outcomes among Patients with Concurrent Asthma and Diabetes. *Respirology* **2016**, *21*, 1210–1218.
90. Wu, T.D.; Fawzy, A.; Akenroye, A.; Keet, C.; Hansel, N.N.; McCormack, M.C. Metformin Use and Risk of Asthma Exacerbation Among Asthma Patients with Glycemic Dysfunction. *J. Allergy Clin. Immunol. Pract.* **2021**, *9*, 4014–4020.e4.
91. Pabreja, K.; Mohd, M.A.; Koole, C.; Wootten, D.; Furness, S.G.B. Molecular Mechanisms Underlying Physiological and Receptor Pleiotropic Effects Mediated by GLP-1R Activation. *Br. J. Pharmacol.* **2014**, *171*, 1114–1128.
92. Bendotti, G.; Montefusco, L.; Lunati, M.E.; Uselli, V.; Pastore, I.; Lazzaroni, E.; Assi, E.; Seelam, A.J.; El Essawy, B.; Jang, J.; et al. The Anti-Inflammatory and Immunological Properties of GLP-1 Receptor Agonists. *Pharmacol. Res.* **2022**, *182*, 106320.
93. Li, Z.; Li, S.; Wang, N.; Xue, P.; Li, Y. Liraglutide, a Glucagon-like Peptide-1 Receptor Agonist, Suppresses Osteoclastogenesis through the Inhibition of NF-κB and MAPK Pathways via GLP-1R. *Biomed. Pharmacother.* **2020**, *130*, 110523.
94. Baker, R.G.; Hayden, M.S.; Ghosh, S. NF-κB, Inflammation, and Metabolic Disease. *Cell Metab.* **2011**, *13*, 11–22.
95. Nguyen, D.-V.; Linderholm, A.; Haczku, A.; Kenyon, N. Glucagon-like Peptide 1: A Potential Anti-Inflammatory Pathway in Obesity-Related Asthma. *Pharmacol. Ther.* **2017**, *180*, 139–143.
96. Zhu, T.; Wu, X.-L.; Zhang, W.; Xiao, M. Glucagon Like Peptide-1 (GLP-1) Modulates OVA-Induced Airway Inflammation and Mucus Secretion Involving a Protein Kinase A (PKA)-Dependent Nuclear Factor-κB (NF-κB) Signaling Pathway in Mice. *Int. J. Mol. Sci.* **2015**, *16*, 20195–20211.

97. Toki, S.; Goleniewska, K.; Reiss, S.; Zhang, J.; Bloodworth, M.H.; Stier, M.T.; Zhou, W.; Newcomb, D.C.; Ware, L.B.; Stanwood, G.D.; et al. Glucagon-like Peptide 1 Signaling Inhibits Allergen-Induced Lung IL-33 Release and Reduces Group 2 Innate Lymphoid Cell Cytokine Production in Vivo. *J. Allergy Clin. Immunol.* **2018**, *142*, 1515–1528.e8.
98. Bloodworth, M.H.; Rusznak, M.; Pfister, C.C.; Zhang, J.; Bastarache, L.; Calvillo, S.A.; Chappell, J.D.; Boyd, K.L.; Toki, S.; Newcomb, D.C.; et al. Glucagon-like Peptide 1 Receptor Signaling Attenuates Respiratory Syncytial Virus-Induced Type 2 Responses and Immunopathology. *J. Allergy Clin. Immunol.* **2018**, *142*, 683–687.e12.
99. Toki, S.; Newcomb, D.C.; Printz, R.L.; Cahill, K.N.; Boyd, K.L.; Niswender, K.D.; Peebles, R.S., Jr Glucagon-like Peptide-1 Receptor Agonist Inhibits Aeroallergen-Induced Activation of ILC2 and Neutrophilic Airway Inflammation in Obese Mice. *Allergy* **2021**, *76*, 3433–3445.
100. Rogliani, P.; Calzetta, L.; Capuani, B.; Facciolo, F.; Cazzola, M.; Lauro, D.; Matera, M.G. Glucagon-Like Peptide 1 Receptor: A Novel Pharmacological Target for Treating Human Bronchial Hyperresponsiveness. *Am. J. Respir. Cell Mol. Biol.* **2016**, *55*, 804–814.
101. Mitchell, P.D.; Salter, B.M.; Oliveria, J.P.; El-Gammal, A.; Tworek, D.; Smith, S.G.; Sehmi, R.; Gauvreau, G.M.; Butler, M.; O'Byrne, P.M. Glucagon-like Peptide-1 Receptor Expression on Human Eosinophils and Its Regulation of Eosinophil Activation. *Clin. Exp. Allergy* **2017**, *47*, 331–338.
102. Khan, F.; Mat, A.; Hogan, A.E.; Kent, B.D.; Eigenheer, S.; Corrigan, M.A.; O'Shea, D.; Butler, M.W. Preliminary Asthma-Related Outcomes Following Glucagon-like Peptide 1 Agonist Therapy. *QJM* **2017**, *110*, 853–854.
103. Foer, D.; Beeler, P.E.; Cui, J.; Karlson, E.W.; Bates, D.W.; Cahill, K.N. Asthma Exacerbations in Patients with Type 2 Diabetes and Asthma on Glucagon-like Peptide-1 Receptor Agonists. *Am. J. Respir. Crit. Care Med.* **2021**, *203*, 831–840.
104. Albogami, Y.; Cusi, K.; Daniels, M.J.; Wei, Y.-J.J.; Winterstein, A.G. Glucagon-Like Peptide 1 Receptor Agonists and Chronic Lower Respiratory Disease Exacerbations Among Patients With Type 2 Diabetes. *Diabetes Care* **2021**, *44*, 1344–1352.
105. López-Cano, C.; Ciudin, A.; Sánchez, E.; Tinahones, F.J.; Barbé, F.; Dalmases, M.; García-Ramírez, M.; Soto, A.; Gaeta, A.M.; Pellitero, S.; et al. Liraglutide Improves Forced Vital Capacity in Individuals With Type 2 Diabetes: Data From the Randomized Crossover LIRALUNG Study. *Diabetes* **2022**, *71*, 315–320.
106. Rogliani, P.; Matera, M.G.; Calzetta, L.; Hanania, N.A.; Page, C.; Rossi, I.; Andreadi, A.; Galli, A.; Coppola, A.; Cazzola, M.; et al. Long-Term Observational Study on the Impact of GLP-1R Agonists on Lung Function in Diabetic Patients. *Respir. Med.* **2019**, *154*, 86–92.
107. Kudaravalli, J.; Vijayalakshmi, G.; Kiran Kishore, K. Safety and Efficacy of Sulfonylurea Drugs in Type 2 Diabetes Mellitus. *Apollo Med.* **2013**, *10*, 165–168.
108. Hougen, I.; Whitlock, R.H.; Komenda, P.; Rigatto, C.; Clemens, K.K.; Tangri, N. Safety of Add-on Sulfonylurea Therapy in Patients with Type 2 Diabetes Using Metformin: A Population-Based Real-World Study. *BMJ Open Diabetes Res Care* **2021**, *9*, doi:10.1136/bmjdr-2021-002352.
109. Douros, A.; Dell'Aniello, S.; Yu, O.H.Y.; Fillion, K.B.; Azoulay, L.; Suissa, S. Sulfonylureas as Second Line Drugs in Type 2 Diabetes and the Risk of Cardiovascular and Hypoglycaemic Events: Population Based Cohort Study. *BMJ* **2018**, *362*, k2693.
110. Rayner, L.H.; McGovern, A.; Sherlock, J.; Gatenby, P.; Correa, A.; Creagh-Brown, B.; deLusignan, S. The Impact of Therapy on the Risk of Asthma in Type 2 Diabetes. *Clin. Respir. J.* **2019**, *13*, 299–305.
111. GRADE Study Research Group; Nathan, D.M.; Lachin, J.M.; Balasubramanyam, A.; Burch, H.B.; Buse, J.B.; Butera, N.M.; Cohen, R.M.; Crandall, J.P.; Kahn, S.E.; et al. Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. *N. Engl. J. Med.* **2022**, *387*, 1063–1074.
112. Lee, Y.-S.; Jun, H.-S. Anti-Diabetic Actions of Glucagon-like Peptide-1 on Pancreatic Beta-Cells. *Metabolism* **2014**, *63*, 9–19.
113. Lyu, X.; Zhu, X.; Zhao, B.; Du, L.; Chen, D.; Wang, C.; Liu, G.; Ran, X. Effects of Dipeptidyl Peptidase-4 Inhibitors on Beta-Cell Function and Insulin Resistance in Type 2 Diabetes: Meta-Analysis of Randomized Controlled Trials. *Sci. Rep.* **2017**, *7*, 44865.
114. Sun, J.; Chu, S.; Lu, M.; Pan, Q.; Li, D.; Zheng, S.; Ma, L. The Roles of Dipeptidyl Peptidase-4 and Its Inhibitors in the Regulation of Airway Epithelial-Mesenchymal Transition. *Exp. Lung Res.* **2020**, *46*, 163–173.
115. Ma, L.; Chang, E.; Ruan, X.; Zhang, B.; Tang, F.; Zhang, J. The Protective Effects of Omarigliptin against Lipopolysaccharide (LPS)- Induced Inflammatory Response and Expression of Mucin 5AC (MUC5AC) in Human Bronchial Epithelial Cells. *Mol. Immunol.* **2022**, *141*, 108–115.
116. Colice, G.; Price, D.; Gerhardsson de Verdier, M.; Rabon-Stith, K.; Ambrose, C.; Cappell, K.; Irwin, D.E.; Juneau, P.; Vlahiotis, A. The Effect of DPP-4 Inhibitors on Asthma Control: An Administrative Database Study to Evaluate a Potential Pathophysiological Relationship. *Pragmat Obs Res* **2017**, *8*, 231–240.

117. Wang, A.; Tang, H.; Zhang, N.; Feng, X. Association between Novel Glucose-Lowering Drugs and Risk of Asthma: A Network Meta-Analysis of Cardiorenal Outcome Trials. *Diabetes Res. Clin. Pract.* **2022**, *183*, 109080.
118. Story of Discovery: SGLT2 Inhibitors: Harnessing the Kidneys to Help Treat Diabetes Available online: <https://www.niddk.nih.gov/news/archive/2016/story-discovery-sgl2-inhibitors-harnessing-kidneys-help-treat-diabetes> (accessed on 20 December 2023).
119. Heerspink, H.J.L.; Perco, P.; Mulder, S.; Leierer, J.; Hansen, M.K.; Heinzel, A.; Mayer, G. Canagliflozin Reduces Inflammation and Fibrosis Biomarkers: A Potential Mechanism of Action for Beneficial Effects of SGLT2 Inhibitors in Diabetic Kidney Disease. *Diabetologia* **2019**, *62*, 1154–1166.
120. Qiu, M.; Ding, L.-L.; Zhan, Z.-L.; Liu, S.-Y. Use of SGLT2 Inhibitors and Occurrence of Noninfectious Respiratory Disorders: A Meta-Analysis of Large Randomized Trials of SGLT2 Inhibitors. *Endocrine* **2021**, *73*, 31–36.
121. Boden, G.; Cheung, P.; Mozzoli, M.; Fried, S.K. Effect of Thiazolidinediones on Glucose and Fatty Acid Metabolism in Patients with Type 2 Diabetes. *Metabolism* **2003**, *52*, 753–759.
122. Soccio, R.E.; Chen, E.R.; Lazar, M.A. Thiazolidinediones and the Promise of Insulin Sensitization in Type 2 Diabetes. *Cell Metab.* **2014**, *20*, 573–591.
123. Zhu, M.; Flynt, L.; Ghosh, S.; Mellema, M.; Banerjee, A.; Williams, E.; Panettieri, R.A., Jr; Shore, S.A. Anti-Inflammatory Effects of Thiazolidinediones in Human Airway Smooth Muscle Cells. *Am. J. Respir. Cell Mol. Biol.* **2011**, *45*, 111–119.
124. Chen, R.; Yan, J.; Liu, P.; Wang, Z. Effects of Thiazolidinedione Therapy on Inflammatory Markers of Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *PLoS One* **2015**, *10*, e0123703.
125. Rinne, S.T.; Feemster, L.C.; Collins, B.F.; Au, D.H.; Perkins, M.; Bryson, C.L.; O’Riordan, T.G.; Liu, C.-F. Thiazolidinediones and the Risk of Asthma Exacerbation among Patients with Diabetes: A Cohort Study. *Allergy Asthma Clin. Immunol.* **2014**, *10*, 34.
126. Sood, A.; Qualls, C.; Murata, A.; Kroth, P.J.; Mao, J.; Schade, D.S.; Murata, G. Potential for Repurposing Oral Hypertension/diabetes Drugs to Decrease Asthma Risk in Obesity. *J. Asthma* **2023**, *60*, 802–810.
127. Dixon, A.E.; Subramanian, M.; DeSarno, M.; Black, K.; Lane, L.; Holguin, F. A Pilot Randomized Controlled Trial of Pioglitazone for the Treatment of Poorly Controlled Asthma in Obesity. *Respir. Res.* **2015**, *16*, 143.
128. Kaler, M.; Barochia, A.V.; Weir, N.A.; Cuento, R.A.; Stylianou, M.; Roth, M.J.; Filie, A.C.; Vaughey, E.C.; Nathan, S.D.; Levine, S.J. A Randomized, Placebo-Controlled, Double-Blinded, Crossover Trial of Pioglitazone for Severe Asthma. *J. Allergy Clin. Immunol.* **2017**, *140*, 1716–1718.

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.