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REVIEW

Diabetes and Lung Disease: An Underestimated Relationship

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■ Abstract

BACKGROUND: Diabetes mellitus is a systemic disorder associated with inflammation and oxidative stress which may target many organs such as the kidney, retina, and the vascular system. The pathophysiology, mechanisms, and consequences of diabetes on these organs have been studied widely. However, no work has been done on the concept of the lung as a target organ for diabetes and its implications for lung diseases. **AIM**: In this review, we aimed to investigate the effects of diabetes and hypoglycemic agent on lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, pulmonary hypertension, and lung cancer. We also reviewed the potential mechanisms by which these effects may affect lung disease patients. **RESULTS**: Our results suggest that diabetes can affect the severity and clinical course of several lung diseases. **CONCLUSIONS**: Although the diabetes-lung association is epidemiologically and clinically well-established, especially in asthma, the underlying mechanism and pathophysiology are not been fully understood. Several mechanisms have been suggested, mainly associated with the pro-inflammatory and proliferative properties of diabetes, but also in relation to micro- and macrovascular effects of diabetes on the pulmonary vasculature. Also, hypoglycemic drugs may influence lung diseases in different ways. For example, metformin was considered a potential therapeutic agent in lung diseases, while insulin was shown to exacerbate lung diseases; this suggests that their effects extend beyond their hypoglycemic properties.

Keywords: diabetes · asthma · chronic obstructive pulmonary disease · COPD · idiopathic pulmonary fibrosis · pulmonary hypertension · lung cancer · hypoglycemic drugs

1. Introduction

Diabetes mellitus is a systemic disorder characterized by a chronic hyperglycemic state that is associated with inflammation and oxidative stress. This leads to micro- and macrovascular damage to many organs, especially the kidney, retina, and cardiovascular system [1-4]. The clinical basis and molecular mechanisms associated with the diabetic micro- and macrovascular damage to these organs have been investigated widely. However, there is a lack of evidence and research regarding the lung as a target for diabetic damage. This is because the clinical significance of such damage is unknown, mainly due to the extensive physiological reserve of the lung.

The lung has a complicated alveolar-capillary network which may be targeted by diabetic microvascular damage, suggesting its involvement in diabetes. Diabetic patients frequently report respiratory symptoms [5] and are at increased risk of several pulmonary diseases [6].

Hyperglycemia has been shown to lead to interstitial fibrosis [7] and alveolar capillary microangiopathy [8]; it is associated with both restrictive and obstructive lung function impairment, including reduction in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), lung dif-

fusing capacity (DLco) [9-10], and lung elastic recoil [11]. It has also been shown to cause mucus overproduction in the airway, contributing to morbidity and mortality in many lung diseases.

The molecular basis for the diabetes-lung association has yet to be fully investigated and understood. However, several molecular mechanisms have been suggested; they involve mainly pro-inflammatory pathways and vascular inflammation. One such mechanism is the receptor for advanced glycation end-products (RAGE) which is expressed in the lung and promotes vascular inflammation in diabetic patients [13]. Another is interleukin 6, a biomarker of inflammation and metabolic dysfunction, which has been suggested as a severity predictor in lung diseases [14]. Interestingly, little evidence suggests a beneficial role of hypoglycemic agents on lung function and inflammation [15].

In this review, we aim to discuss the effects of diabetes and hypoglycemic agents on lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH), and lung cancer, and we review the potential mechanisms by which they may affect lung disease patients.

Abbreviations:

ABCA1	adenosine triphosphate-binding cassette, subfamily A, member 1
ADPN	adiponectin
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
DLco	lung diffusing capacity
EMT	epithelial to mesenchymal transition
eNOS	endothelial nitric oxide synthase
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GERD	gastroesophageal reflux disease
GLP-1	glucagon-like peptide 1 agonists
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	hazard ration
HRCT	high-resolution computed tomography
ILGF-1	insulin-like growth factor 1
IL-6	interleukin 6
IPF	idiopathic pulmonary fibrosis
MCP-1	monocyte chemoattractant protein
MMP-9	matrix metalloprotinase 9
NADPH	nicotinamide adenine dinucleotide phosphate
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NO	nitric oxide
NOD	non-obese diabetic
PDGF	platelet-derived growth factor
PH	pulmonary hypertension
PPARγ	peroxisome proliferator-activated receptor gamma
RAGE	receptor for advanced glycation end-products
RV	right ventricular
SGLT2	sodium-glucose cotransporter 2
SV	stroke volume
TGF-β1	transforming growth factor beta 1
TNF	tumor necrosis factor
UIP	usual interstitial pneumonia

2. Asthma and diabetes

2.1 Background

Asthma is a heterogeneous disease mainly characterized by airway hyperresponsiveness, which leads to bronchoconstriction and chronic inflammation. This causes proliferation and extracellular matrix deposition, eventually leading to the destruction of the airway wall structure and airway remodeling. Asthma manifests mainly by two phenotypes, distinguished by their inflammatory responses [16]:

1. Th2-predominant inflammation, typically atopic, which leads to early-onset asthma that responds well to steroids.
2. Adult-onset asthma that typically occurs in non-atopic patients with Th1-predominance, which is more closely related to metabolic and inflammatory processes such as diabetes [17].

Table 1 provides an overview of lung diseases in diabetic patients.

2.2 Epidemiology

Earlier studies reported an inverse relationship between atopy and diabetes mellitus [18]. Type 1 diabetes was associated with a lower incidence of asthma, which was due to the anti-inflammatory properties of insulin [19]. In contrast, later studies found high levels of asthma in countries with a high level of type 1 diabetes [20].

The association between type 2 diabetes and asthma has been investigated in more detail. Type 2 diabetes has been shown to cause airway hyperresponsiveness in humans [21], with an association between insulin resistance and increased risk of asthma-like symptoms [22]. The risk of asthma in diabetic patients is over twice that of non-diabetics (hazard ratio (HR) of 2.2) [6]. A higher prevalence of asthma has been found in hospitalized patients with type 2 diabetes, independent of other comorbid conditions [23]. In one study, it was shown that asthma symptoms preceded the diagnosis of diabetes by a few years, regardless of glucocorticoid treatment [24]. Likewise, uncontrolled

Table 1. Lung diseases in diabetic patients

Lung disease	Epidemiology	Clinical presentation	Proposed mechanisms	Molecular basis
Asthma	• High prevalence with a 2.2 risk [6, 20].	• More severe asthma [27]. • Higher exacerbation rate [28]. • Higher number of emergency department visits [29]. • Higher sputum secretion [12, 30]. • Increased long-term mortality [31].	• Chronic airway inflammation [34]. • Airway hyper responsiveness [24, 35, 36]. • Sputum overproduction [30, 42].	• RAGE signaling pathway [13, 41, 42]. • Th2 predominance [38]. • Increased IL-6 [39, 40]. • Induction of MCP-1 [41] and MMP-9 [30, 42].
COPD	• Slightly more prevalent than in the general population, [44]. • Inconsistent epidemiologic data.	• More severe phenotype (GOLD 3-4). • Worse outcome, including lung function [50], hospitalization, and mortality [48].	• Smoking-related comorbidities [49]. • Obesity: reduced oxidative capacity and hypoxia [51]. • Decreased thoracic and septum compliance. • Systemic inflammation [53-55].	• IL-6, TNF alpha [53]. • CRP [54]. • Circulating ADPN [53-55].
IPF	• Higher prevalence. • Variable epidemiologic data [61, 62].	• UIP pattern more common. • Higher incidences of cardiovascular diseases and malignancies [60, 63].	• Shared risk factors: • age, tobacco use [62]. • GERD [64, 65].	• Unknown. •
Pulmonary hypertension	• Higher incidence of diabetes in PH [66]. • Higher prevalence of idiopathic and venous PH [69].	• More severe symptoms [70]. • Worse hemodynamic parameters including RV SV [72]. • Reduced survival in diabetes and PH patients (HR of 1.7) [73]	• Accelerated RV failure [74]. • Collagen production [75- 77]. • RV ischemia [78]. • Increased endothelial dysfunction in pulmonary vessels [79, 80].	• PDGF activation [75] . • Upregulation of microRNA miR-29 family [76]. • Endothelin-1 induction and • NADPH oxidase-derived superoxide production [77]. • Inhibition of eNOS [79, 80]. • Upregulation of ILGF-1 [81]. • Decrease of PPARγ activity [82].
Lung cancer	• Conflicting evidence on risk [83, 86, 86].	• Poor glycemic control. • Decreased lung cancer survival [93]. • Higher risk for radiation pneumonitis. • More invasive metastatic lung cancer and local recurrence [93].	• Acceleration of tumor metastasis and progression [96]. • Increased cancer cell proliferation	• Oxidative stress induction [96]. • Enhancement of EMT [93]. • TGF-1β1/PI3K/Akt signaling pathway [97]. • Fibroblast growth factor 2 [98]. • WNT/β-catenin signaling pathway [99].

Legend: ADPN - adiponectin, COPD - chronic obstructive pulmonary disease, CRP – C-reactive protein, EMT - epithelial to mesenchymal transition, eNOS - endothelial nitric oxide synthase, GERD - gastro-esophageal reflux disease, IL-6 - interleukin 6, ILGF-1 - insulin-like growth factor, IPF - idiopathic pulmonary fibrosis, MCP-1 - monocyte chemoattractant protein, MMP-9 - matrix metalloprotinase 9, PDGF – platelet-derived growth factor, PH - pulmonary hypertension, PPARγ - peroxisome proliferator-activated receptor gamma, RAGE - receptor for advanced glycation end-products, RV - right ventricular, SV - stroke volume, TNF - tumor necrosis factor, UIP - usual interstitial pneumonia.

diabetes has been associated with a higher risk of asthma, and poor glycemic control has been related to increased asthma risk [25]. In contrast, a large prospective study found no significant statistical relationship among women with asthma [26], suggesting that the diabetes-asthma association is still not sufficiently well established.

2.3 Clinical presentation

Diabetes in asthma patients is an important comorbidity, causing more severe asthma [27] with a higher exacerbations rate [28] and more frequent emergency department visits [29]. Diabetes was also shown to induce sputum hypersecretion [12, 30]. Moreover, diabetes in the context of asthma exacerbation was shown to impact long-term mortality [31].

2.4 Mechanisms

Chronic inflammation and pro-inflammatory cytokines may emerge in the pathogenesis of both diabetes mellitus [32] and asthma [33]. It has been shown that diabetes is a pro-inflammatory state associated with airway inflammation [34]. Studies on type 2 diabetes have shown that it causes airway hyperresponsiveness in human airway smooth muscle cells *in vitro* [35], in diabetic animal models [36], and in humans [25]. Therefore, the most investigated pathway in the pathogenesis of the diabetes-asthma association is chronic inflammation such as RAGE.

RAGE signaling has been shown to be highly expressed in the lung and to induce chronic airway and vascular inflammation [13, 37]. RAGE has a regulatory role in T-cell proliferation and differentiation of both Th1 and Th2 cells [38]. Diabetes-prone non-obese diabetic (NOD) mice have been shown to give rise to enhanced Th2-mediated responses and contribute to a Th2-predominant asthma phenotype. Increased systemic interleukin 6 as an inflammatory and metabolic dysfunction biomarker in diabetes has been associated with more severe asthma [39, 40]. In this context, monocyte chemoattratant protein (MCP) 1, which recruits monocytes to inflammation sites, has been shown to play a significant role in diabetic patients with asthma via airway remodeling and predicts a poorer prognosis [41].

Matrix metallopreinase (MMP) 9 mediates sputum overproduction secondary to airway epithelial barrier dysfunction caused by hyperglycemia, especially during exacerbation, and cause airway inflammation in airway epithelial cells [30, 42].

2.5 Summary

The diabetes-asthma association is well-established epidemiologically and clinically. Diabetes is a risk factor for more severe and complicated asthma. The main pathogenesis of this association is inflammation and pro-inflammatory cytokines. However, the pathogenesis has yet to be fully understood and more research is necessary to establish a strong biological basis.

3. Chronic obstructive pulmonary disease (COPD) and diabetes

3.1 Introduction

COPD is a preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, which are often secondary to significant exposure to noxious particles or gases [43]. It is currently the fourth leading cause of death worldwide.

It has been increasingly recognized that the presence of common factors in COPD and in other chronic extra-pulmonary diseases, such as diabetes mellitus, together with the frequent coexistence of these conditions in the same adult individual, supports the hypothesis of common processes sharing their pathogeneses within the same patient [44].

3.2 Epidemiology

Metabolic syndrome has been recognized as one of the most relevant clinical comorbidities associated with COPD patients [45]. However, the link between COPD and diabetes is much less clear. Diabetes is more prevalent in COPD than in the general population. Prevalence estimates of diabetes among COPD patients range between 10.1-23.0% [46, 47].

3.3 Clinical presentation

The risk of diabetes in COPD patients has been found to be higher in more severe phenotypes (level 3-4 according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline). This risk was independent of BMI, smoking, and other confounding factors. Moreover, the presence of diabetes among those with COPD has been shown to be associated with worse outcomes, such as mortality and hospitalization [48].

3.4 Mechanisms

The mechanisms by which diabetes influences lung function have not yet been fully determined. The correlation between COPD and diabetes may depend on several mutual risk factors and physiological alterations.

COPD patients are primarily former or active smokers. Smoking may lead to concomitant comorbidity, but it is increasingly evident that patients with COPD also have a high burden of comorbidity independent of smoking [49]. In the large COPD Gene cohort, diabetes subjects with a history of smoking had worse lung function even if they had no established diagnosis of COPD [50].

Recently, there has been increasing interest in the relationship between obesity and COPD, although the nature of this association remains unknown. It has been proposed that reduced oxidative capacity and systemic hypoxia may play a role in the pathogenesis of COPD in obese patients [51]. The potential interaction between impaired adipose tissue function, systemic inflammation, and COPD may provide insight into the pathogenesis and reversibility of the systemic pathology in the disease. The effects of obesity on respiratory function depend on the mass and anatomical distribution of the excessive adipose tissue in the thorax and abdomen [52]. Thus, another potential explanation is that increased abdominal obesity directly affects thoracic and diaphragm (septum?) compliance, which impairs lung function.

COPD is associated with a chronic systemic inflammatory condition. Insulin resistance has been found to be related to interleukin 6 (IL-6) and tumor necrosis factor alpha soluble receptor in non-hypoxemic COPD patients [53]. Moreover, elevated serum levels of C-reactive protein (CRP) have also been associated with impaired pulmonary function [54]. Increased visceral fat has been identified as the main factor increasing CRP concentration [55]. Another mechanism associated with COPD is circulating adiponectin (ADPN), which has been inversely associated with disease severity in patients with COPD. Studies assessing the relationship between ADPN and lung function in subjects from the general population have shown diverging results. It is noteworthy that there was no association between ADPN and lung function after adjustment for covariates related to adiposity [56].

3.5 Summary

The association between COPD and diabetes has not been fully established epidemiologically and clinically. However, it is strongly suggested that continuously elevated levels of inflammatory mediators, reflecting the enhanced inflammatory state seen in COPD, may contribute to the development of diabetes. Whilst a converse relation is not suggested; the presence of diabetes alone is not considered a risk factor for COPD, and has not been found to contribute to its development in studies regarding COPD pathogenesis.

4. Idiopathic pulmonary fibrosis (IPF) and diabetes

4.1 Introduction

IPF is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults. It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis [57]. No significant extra-pulmonary manifestation has been recognized so far. Thus, it is assumed to be limited to the lung.

4.2 Epidemiology

The incidence of IPF is estimated to be between 4 to 11 cases per 100,000 persons per year, and is more common in males. It increases with older age, typically occurring in the sixth and seventh decade. The majority of patients have a history of cigarette smoking [58, 59]. Although considered a single-organ disease (affecting only the lung), many studies suggest that there is an association between IPF and diabetes [60, 61]. In a nationwide Korean survey performed in the years 2003-2007, which retrospectively analyzed 1,685 patients using the interstitial lung disease (ILD) registry, 17.8% of the patients with IPF also had diabetes [60].

Case-control analyses performed in Japan, Mexico, and the U.K. estimated the prevalence of type 2 diabetes among individuals with IPF to be 10-33%, which was significantly higher than that of matched control populations [62].

4.3 Clinical presentation

Many comorbid conditions are known to occur in IPF, including coronary artery disease, pulmonary hypertension, gastroesophageal reflux, and diabetes [63]. It remains unclear whether the presence of diabetes influences survival in patients with IPF. However, IPF patients with diabetes are more likely to have the usual interstitial pneumo-

nia (UIP) patterns on high-resolution computed tomography (HRCT), including reticular and honeycomb patterns, than are those without diabetes. Furthermore, significantly higher incidences of hypertension, cardiovascular diseases, and other malignancies (except lung cancer) have been found in IPF patients with diabetes than in IPF patients without diabetes [60].

4.4 Mechanisms

Since the incidence of IPF increases with age, it is possible that age and lifestyle-related diseases, including diabetes, may be a risk factor affecting either the initiation or progression of IPF. In a case-controlled study, the adjusted odds ratios for cigarette smoking and diabetes were 5.40 (95% CI: 2.30-12.66) and 4.06 (95% CI: 1.80-9.15) [62]. Another potential link between IPF and diabetes is based on the higher prevalence of gastroesophageal reflux disease (GERD) in both conditions. Patients with diabetes are at greater risk of GERD than those without diabetes. [64]. Several studies suggest that GERD is a risk factor for IPF because of its presumed association with microaspiration. Abnormal GERD is common in patients with IPF [65].

4.5 Summary

It has yet to be defined whether diabetes is associated with IPF. However, mounting evidence suggests at least an epidemiologic connection with these conditions and a trend towards a more severe disease state.

5. Pulmonary hypertension (PH) and diabetes

5.1 Introduction

PH is an abnormally elevated pressure in the pulmonary vasculature that may cause right heart failure and death. The micro- and macrovascular damage caused by diabetes may affect the pulmonary vasculature, suggesting that diabetes may play a role in the development and exacerbation of pulmonary hypertension. It has been shown that the incidence of diabetes in PH patients is higher than in the general population, suggesting a connection between the two diseases [66]. However, the clinical significance is unknown, mostly because of the extensive reserve within the pulmonary capillary bed.

5.2 Epidemiology

It has not yet been established whether pulmonary hypertension is the consequence of diabetes or its cause. It has been shown that PH patients have more glucose intolerance [67], and that diabetic patients were more likely to have idiopathic pulmonary hypertension [68] (24% compared to 10%), and to have venous rather than arterial pulmonary hypertension [69].

5.3 Clinical presentation

Symptoms of PH patients and physical performance measured by a 6-minute walk test were worse in diabetic than in non-diabetic patients [70]. In patients with COPD and diabetes, PH was more severe than in patients with COPD only [71]. Moreover, hemodynamic parameters such as right atrial pressure and mean pulmonary capillary wedge pressure were higher in diabetic patients than in non-diabetics, with a trend towards lower response to nitric oxide (NO) in diabetic patients [69]. It was shown that right ventricular stroke volume, which is associated with PH prognosis and survival, was reduced in patients with diabetes and PH [72]. Consequently, survival among PH patients with diabetes was lower than that of patients without diabetes (hazard ratio of 1.7) [73]. It was also obvious that well-controlled diabetes (HbA1c less than 5.7) in PH patients was associated with greater survival [74].

5.4 Mechanisms

Although mechanisms that contribute to the development of pulmonary hypertension have been widely studied, the effect of diabetes on pulmonary vasculature is less well understood. It has been shown that diabetes influences PH by causing accelerated right heart failure [74]. Diabetes has been shown to accelerate fibrosis of the right heart via platelet-derived growth factor (PDGF) activation, which causes an increase in the transforming growth factor beta 1 (TGF-β1) gene, thus modulating both human mesangial cells and matrix [75]. Another mechanism is via upregulation of the microRNA miR-29 family, which causes collagen production by cardiac fibroblasts [76]. Moreover, hyperglycemia has been shown to induce endothelin-1 in the right ventricle, and to cause fibrosis [77].

It has also been suggested that right ventricle ischemia plays a role in PH patients with diabetes, which is mostly due to the role of diabetes in the general promotion of ischemia [78]. However, there have been no specific studies on the role of diabe-

tes in ischemia of pulmonary vasculature. Animal studies suggest that diabetes may have a direct effect on pulmonary vasculature. It has been found that pulmonary arteries from diabetic rats are less responsive to vasodilatation, because of increased endothelial dysfunction via enhanced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived superoxide production and inhibition of endothelial nitric oxide synthase (eNOS) [79, 80].

Diabetes has also been shown to increase arterial smooth muscle cell proliferation via upregulation of insulin-like growth factor 1 (ILGF-1) [81]. Also, the anti-proliferative role of peroxisome proliferator-activated receptor gamma (PPARγ) was decreased in diabetes, while its effect was enhanced with the PPARγ activator rosiglitazone [82].

5.5 Summary

Diabetes and pulmonary hypertension are strongly associated. Diabetic microvascular and macrovascular injuries may affect pulmonary vasculature by increasing its susceptibility to the development and progression of pulmonary hypertension, and may play a role in patient prognosis and survival.

6. Lung cancer and diabetes

6.1 Introduction

Recent studies suggest an association between diabetes and lung cancer, providing epidemiological and clinical support for the hypothesis that diabetes is a risk factor for lung cancer [90]. Diabetes may influence lung cancer progression and outcome, and may serve as a poor prognostic factor for lung cancer [83].

6.2 Epidemiology

Type 1 diabetes is regarded to be associated with an increased risk of lung cancer [84], despite several conflicting retrospective studies on lung cancer prognosis among diabetic patients [85, 86]. On the basis of two large cohorts from Shanghai, it was reported that the risk of lung cancer was observed in both men and women, with a HR of 0.87 and 0.92, respectively [87]. However, a recent large prospective study provided evidence that pre-existing diabetes is associated with poor survival among women with cancer [88], and it is considered a negative prognostic factor in lung cancer [89].

6.3 Clinical presentation

Proper glycemic control for lung cancer patients is required to induce antineoplastic effects and increase survival (HZ of 0.62) [90]. Diabetic patients have been shown to be more vulnerable to radiation [91]. Diabetes has also been shown to be a risk factor for radiation pneumonitis in lung cancer patients who receive radiotherapy [92]. A multicenter study found that diabetic patients with lung cancer may have a more invasive metastatic lung cancer with greater local recurrence [93].

On the contrary, several studies found that diabetes does not impact overall survival in lung cancer [94], and may even be associated with longer survival rates [85]. Furthermore, another study found that diabetes may play a protective role against lung metastasis [95], suggesting that the role of diabetes in lung cancer needs further clarification.

6.4 Mechanisms

Diabetes may influence cancer progression and prognosis via several mechanisms. It has been shown to accelerate tumor metastasis and tumor progression in a lung cancer animal model via hyperglycemia-induced oxidative stress. This effect is reversible when removing systemic hydrogen peroxide [96]. Diabetes has been shown to increase cancer invasiveness via enhancement of epithelial to mesenchymal transition (EMT), which plays a key role in local tumor recurrence and metastasis in non-small cell lung cancer [93], and via an increased metastasis-associated protein expression secondary to oxidative stress and increased upregulation of TGF-1β1/PI3K/Akt signaling pathway [97].

Consequently, it has been shown that hyperglycemia enhances cell proliferation via fibroblast growth factor 2, and that hyperglycemia may alter endothelial cell function and promote basement membrane changes. It may also promote cancer cell proliferation [98] via metabolic remodeling, resulting in WNT/β-catenin signaling pathway enhancement, thus promoting proliferation, survival, and senescence bypass [99].

6.5 Summary

Epidemiological and clinical data support an association between diabetes and lung cancer. The pre-existence of diabetes in lung cancer is assumed to aggravate lung cancer, although this remains unclear.

7. Lung diseases and hypoglycemic agents

7.1 Introduction

The diabetes-lung association hypothesis has been studied in combination with the effect of hypoglycemic drugs on the lungs (**Table 2**). Interestingly, hypoglycemic drugs seem to have a role beyond their contribution to diabetes control; they also act as a modulator of airway glucose homeostasis, leading to lung disease exacerbation or prevention [100].

7.2 Metformin

The most common oral antidiabetic drug and most investigated in lung diseases is metformin, mainly because of its antidiabetic, antioxidant, and anti-inflammatory properties.

The role of metformin in lung cancer is constantly under debate. In a meta-analysis of the association between hypoglycemic agents and lung cancer prognosis, metformin was the only drug shown to improve survival outcomes [101], especially in non-small cell lung cancer [102]. It has also been shown to have anticancer effects beyond its role as a drug for diabetes [103], such as a protective agent for both radiation-induced pulmonary injury [104] and chemotherapy pneumonitis [105]. In contrast, a recent large cohort study concluded that, unlike breast and liver cancer, there is no evidence of an antitumor efficacy of metformin on lung cancer [106]. Thus, the protective role of metformin on lung cancer is still unknown.

In lung infections, metformin has been shown to promote macrophage bactericidal activity and improve survival [107, 108]; and it may serve both as a means of protection against pulmonary tuberculosis and as a therapy for improving the effectiveness of anti-tuberculous drugs [109]. In idiopathic pulmonary fibrosis, metformin attenuated lung fibrosis via inhibition of fibrosis marker expression, and it has been proposed as an anti-fibrotic modality [110, 111]. Metformin use in asthmatic patients has been associated with a significant reduction in asthma exacerbations and hospitalization [112]. In COPD, metformin seems to have a protective role on lung inflammatory response during the development of emphysema [113]. However, it had no effect on COPD exacerbations [15].

To conclude, metformin has a beneficial role in various lung diseases independent of its antidiabetic role, and it may be considered as a potential therapeutic agent for clinical use in lung disease. However, its role in lung cancer prevention remains unknown.

7.3 Insulin

In contrast to metformin, insulin is known to have oncogenic activity, and it is associated with non-small cell lung cancer development [114]. Insulin-like growth factor receptor 1 (IGF-1) is associated with lung cancer development and metastasis [115] and an acquired resistance to chemotherapy [116].

Insulin has been shown to modify mast cell phenotype and increase its activity *in vitro* [117], along with increasing hyperresponsiveness, bronchoconstriction [118, 119], and airway inflammation [19]. Insulin modulates T-cell differentiation by promoting a shift towards Th2 type response, which is the main disease pathway in asthma [120]. A recent study in a Taiwanese cohort demonstrated that insulin may increase the risk of asthma [121]. Although very little is known regarding the association between insulin and IPF, it has been suggested that insulin growth factor binding proteins may be a key factor responsible for IPF initiation [122].

In conclusion, we assume that insulin affects the lung by causing airway inflammation, exacerbating lung disease, and playing a role in lung cancer development.

7.4 PPAR-γ agonists

Several studies suggest that PPAR-γ agonists reduce airway inflammation [123] and decrease mucus secretion [124]. It has been shown that pioglitazone diminishes alveolar and interstitial neutrophil influx and reduces lung inflammation and injury both *in vitro* [125] and in animal models and that it attenuates lung ischemia reperfusion injury via inhibition of pro-inflammatory cytokines [126]. Pioglitazone has been shown to have a beneficial effect on fibrotic processes of the lung, suggesting that it may serve as an anti-fibrotic agent in IPF and in bleomycin-induced lung injury [127, 128].

Rosiglitazone, another PPAR-γ agonist, demonstrated beneficial effects on lung function and airway inflammation in a rat model of asthma [129]. However, this effect was not achieved in human studies *in vivo* [130].

Regarding lung cancer, PPAR-γ agonists have demonstrated anti-tumor and anti-proliferative properties [131, 132] and might offer therapeutic effects in lung cancer [133].

Table 2. Hypoglycemic agents and lung diseases

Hypoglycemic agent	Effect on lung
Metformin	Improved survival in lung cancer [101]. Protective against radiation- and chemotherapy-induced lung injury [104, 105]. Improved survival in lung infections [107, 108]. Lung fibrosis attenuation [110, 111]. Reduced risk of exacerbations in asthma exacerbation, but not in COPD [15, 112].
Insulin	Higher prevalence of lung cancer and metastasis [114, 115]. Higher resistance of lung cancer to chemotherapy [116]. Higher risk of asthma and airway hyperresponsiveness [120].
PPARγ agonists	Reduced airway inflammation and mucus production [123, 124]. Beneficial effect on lung fibrosis in IPF and in bleomycin-induced lung injury [127, 128]. Anti-tumor and anti-proliferative effect [131, 132].
DDP-4 inhibitors	Mediated allergic airway inflammation [134].
Sulfonylurea and sulfonylurea-like drugs	Glibenclamide has a protective role in asthma development [129]. A protective role against eosinophil-associated diseases [140].
GLP-1 agonists	Decreased COPD exacerbations and reduced mortality [143]. Reduced airway inflammation [144, 145].
SGLT-2 inhibitors	May induce pulmonary artery smooth muscle cell relaxation [148].

Legend: COPD - chronic obstructive pulmonary disease, DPP-4 - dipeptidyl peptidase 4, GLP-1 - glucagon-like peptide 1, IPF - idiopathic pulmonary fibrosis, PPARγ - peroxisome proliferator-activated receptor gamma, SGLT2 - sodium-glucose cotransporter 2.

7.5 DPP-4 inhibitors

These drugs were shown *in vitro* and in an animal model to mediate allergic airway inflammation and regulate common immunological pathways in asthma via CD26 [134]. However, no association between DPP-4 use and asthma control was found [135].

7.6 Sulfonylurea and sulfonylurea-like drugs

Although a large-scale study showed that insulin secretagogues increased the risk of overall cancer [136], a recent meta-analysis showed that sulfonylurea use was not associated with risk of lung cancer [137]. In another study, sulfonylurea use was proposed in combination with chemotherapy for resistant lung cancer cells [138]. Glibenclamide has been shown to play an important protective role in asthma development via airway muscle relaxation in mice [139], and glyburide inhibited cytokine-mediated eosinophil survival and superoxide production, suggesting that it could be used to treat eosinophil-associated disease, such as asthma [140].

7.7 Glucagon-like peptide 1 agonists (GLP-1)

The GLP-1 receptor is found in human lung tissue [141], suggesting that the lung may be a target for GLP-1 agonists. GLP-1 augments surfactant production in rats [142] and was shown to be a potential therapy in the treatment of obstructive pulmonary disease by decreasing severity of acute exacerbations and reducing mortality in an animal model of obstructive lung disease [143]. The mechanism is still unknown, but it has been suggested that GLP-1 may have anti-inflammatory effects via downregulation of inflammatory cytokines, such as TNFα and NF-κB [144, 145], and via airway smooth muscle cell proliferation and migration mediated by adenosine triphosphate-binding cassette, subfamily A, member 1 (ABCA1) [146]. However, the effect of GLP-1 agonists on human lungs has not yet been investigated, and clinical data are lacking.

7.8 Inhibitors of sodium-glucose cotransporter 2 (SGLT2)

These are a new class of oral anti-diabetic drugs with increasing evidence of a beneficial role in cardiovascular diseases [147]. Little is known about their effects on the lung. A recent *in vitro* study suggested that SGLT2 may induce human pulmonary artery smooth muscle cell relaxation in an NO-dependent manner [148]. However, their role in pulmonary vasculature and lung diseases has yet to be investigated.

8. Conclusion

Diabetes mellitus is one of the most thoroughly investigated systemic diseases worldwide, and is considered a part of the metabolic syndrome epi-

demic. Although it has been shown to affect almost every organ in the body, the lung is one of the most neglected target organs of diabetes, presumably because its clinical relevance is undetermined. Thus, the diabetes-lung association is considered a newly investigated concept. In fact, most pulmonology literature does not address diabetes as an influencing factor for lung diseases.

Emerging evidence suggests that diabetes and the widely used hypoglycemic drugs may affect the pathogenesis, development, and progression of several lung diseases and their prognosis and clinical outcome, suggesting that diabetes should be considered as a relevant factor in the clinical approach to lung disease patients. The pro-inflammatory, proliferative, and oxidative properties of hyperglycemia have been shown to have an important role in affecting pulmonary vasculature, airways, and lung parenchyma.

The evidence reviewed in this article supports further investigation in this field. More studies are needed to evaluate and reinforce the biological and clinical associations between diabetes and lung disease, and thus more research is justified. After all, why should the lung be a neglected organ within this systemic and epidemic disease?

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