Diabetic lung disease: fact or fiction?

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Abstract
Diabetes mellitus is a chronic, progressive, incompletely understood metabolic disorder whose prevalence has been increasing steadily worldwide. Even though little attention has been paid to lung disorders in the context of diabetes, its prevalence has recently been challenged by newer studies of disease development. In this review, we summarize and discuss the role of diabetes mellitus involved in the progression of pulmonary diseases, with the main focus on pulmonary fibrosis, which represents a chronic and progressive disease with high mortality and limited therapeutic options.

Keywords Diabetes mellitus · Pulmonary disease · Lung · Fibrosis

Abbreviations
ALI acute lung injury
ARDS acute respiratory distress syndrome
AGE advanced glycation end product
ASMs airway smooth muscle cells
ASL airway surface liquid
CO carbon monoxide
COPD chronic obstructive pulmonary disease
CTGF connective tissue growth factor
CFRD cystic fibrosis-related diabetes
dm diabetes mellitus
EMT epithelial-mesenchymal transition
ECM extracellular matrix
FEV1 forced expiratory volume in one second
IPF idiopathic pulmonary fibrosis
IL interleukin

1 Introduction

Diabetes mellitus (DM) along with its associated complications is a global health problem that has expanded over the past several decades [1]. According to the current information from the World Health Organization, 8.5% (442 million persons) of the worldwide adult population had DM in 2014, which nearly doubled since 1980 (4.7%) [2]. The International Diabetes Federation has estimated that the number of diabetic patients worldwide will rise to 592 million in 2035 [3]. Large population-based studies reported 3.7 million deaths due to DM and its associated complications in 2012 [2]. DM is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impaired insulin secretion, defective insulin action or both [4]. The disease
can be classified into the following general categories: 1. type 1 diabetes mellitus (T1DM) (due to autoimmune pancreatic β-cell loss, leading to absolute insulin deficiency); 2. type 2 diabetes mellitus (T2DM) (due to dysfunctional pancreatic β-cells and insulin resistance, leading to progressively impaired glucose regulation); 3. gestational DM (a condition diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation); 4. specific types of DM due to other causes, e.g., monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes [4, 5]. T1DM, also known as autoimmune diabetes, is a chronic disease that is not preventable and that has no available cure. Affected patients depend on lifelong insulin substitution due to pancreatic β-cell destruction by islet-targeting autoantibodies that results in absolute insulin deficiency. Usually, the symptomatic onset is during childhood or adolescence however, symptoms can sometimes develop much later (latent autoimmune diabetes of adults). The underlying pathophysiology is characterized by the persistent presence of two or more autoantibodies, and the progression depends on the age at first antibody detection (the younger the individual, the faster the progression), the number of antibodies (the more antibodies present, the faster the progression), antibody specificity (the more specific the antibody, the faster the progression), and antibody titer (the higher the titer, the faster the progression). Genetic linkage studies have identified polymorphic variations in the class II genes encoding HLA-DR and HLA-DQ as well as one or more additional genes within the HLA region that increase the genetic risk for T1DM [6]. The progression of the disease can be divided into three stages depending on the absence or presence of hyperglycemia and hyperglycemia-associated symptoms (such as polyuria, polydipsia, recurrent infections, sudden weight loss and diabetic ketoacidosis) [4]. T2DM, which is much more common than T1DM (accounting for 90% of all DM disorders worldwide), is primarily a problem of progressively impaired glucose regulation due to a combination of dysfunctional pancreatic β-cells and insulin resistance. T2DM patients comprise a heterogeneous group. In most patients, alimentary obesity and physical inactivity significantly contribute to the increasing prevalence of T2DM diagnoses; however, some patients have a normal body weight but develop T2DM over time. Various pharmacologic approaches, all of which control glycemia, can be considered for patients with T2DM. First-line therapy is based on metformin unless specific contraindications such as renal impairment occurs. The molecular mechanism of metformin is incompletely understood but involves inhibiting the mitochondrial respiratory chain (complex I) and activating 5’-AMP-activated protein kinase, which mainly affects lipid metabolism [7, 8]. All other glucose-lowering therapies such as sulfonylureas, glucagon-like-peptide-1 analogues, dipeptidyl peptidase IV inhibitors, sodium-glucose-transporter-2–inhibitors and peroxisome proliferator-activated receptor gamma agonists are considered second-line agents for addition to metformin if glycemic targets are not reached. Most of these drugs directly or indirectly target organs involved in T2DM development, including the pancreas (β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue. The common problem of untreated diabetes subtypes is an increasing risk of long-term complications. These long-term complications are subdivided into neurological, microvascular and macrovascular complications. Microvascular complications manifest as nephropathy and retinopathy leading to kidney failure and blindness. Macrovascular complications include not only coronary heart disease but also cerebrovascular disease and peripheral artery disease [4, 5], that the latter even to the point of amputation. These complications are the main focus of ongoing studies, and the overall goal of the available therapies is to reduce or avoid these health-threatening problems. In addition to these complications, different pulmonary abnormalities, such as pronounced decrements in lung function, have been reported in patients with DM [9]. In this context, increasing attention has been given to recognizing pulmonary dysfunction and the underlying etiology as a complication of DM [9]. Our review focuses on the effects of DM on the pulmonary system with an overview of the association between DM and lung disorders, mainly pulmonary fibrosis, and suggestions for future research on the lung as a target organ for DM.

2 Pathophysiology of lung dysfunction in patients with DM

The pathophysiology of pulmonary symptoms in DM (Fig. 1) is complex and multifactorial and not completely understood. The currently known underlying mechanisms for lung dysfunction in patients with DM include hyperglycemia [10] (Fig. 2), hyperinsulinemia [11] (Fig. 3), autonomic neuropathy [12], oxidative stress [13], micro/macronangiopathy of alveolar capillaries and pulmonary arterioles [14, 15], glycosylation of tissue proteins [16, 17], collagen and elastin changes [18, 19], alteration of connective tissue [20, 21], surfactant dysfunction [22, 23] and malfunction of respiratory muscles [24, 25].

In 1976, Schuyler et al. for the first time reported a reduction in lung elastic recoil in T1DM patients [26]. Subsequently, several longitudinal studies (with 3–7 years of follow-up) revealed an accelerated decline in lung function in patients with T1DM or T2DM, mainly in cases with inadequate glycemic control [27–31]. The findings of these studies showed that the reduction in the lung function of diabetic patients characterized by low forced expiratory volume in one second is two to three times faster than that of normal nonsmoking subjects (71 ml/year reduction compared to an
expected decline in healthy nonsmokers of 25–30 ml/year) [27–31]. In line with the reduction in forced expiratory volume in one second (FEV1) is two to three times faster than that of normal nonsmoking subjects. Reduced forced vital capacity and lung dynamic compliance, peripheral airway obstruction as well as reduced pulmonary diffusing capacity for carbon monoxide (CO) has been reported in diabetic patients. Pulmonary autonomic neuropathy in diabetic patients, results in an impaired ventilatory response to hypoxia. In diabetic patients, sympathetic neuropathy impairs pulmonary function, resulting in ventilatory response abnormalities to central and peripheral stimuli. In this line, parasympathetic neuropathy may cause an increase in airway caliber at baseline. Pulmonary autonomic neuropathy reduces mucociliary clearance and prone the lung to the infections. Reduced respiratory muscle strength due to defective muscle metabolism and neuropathy of the phrenic nerve promote respiratory muscle dysfunction in diabetic patients.

Fig. 1 Respiratory tract abnormalities in patients with diabetes mellitus. Several functional abnormalities in the respiratory tract are proven in patients with diabetes mellitus. Reduced lung function of diabetic patients characterized by low forced expiratory volume in one second (FEV1) is two to three times faster than that of normal nonsmoking subjects. Reduced forced vital capacity and lung dynamic compliance, peripheral airway obstruction as well as reduced pulmonary diffusing capacity for carbon monoxide (CO) has been reported in diabetic patients. Pulmonary autonomic neuropathy in diabetic patients, results in an impaired ventilatory response to hypoxia. In diabetic patients, sympathetic neuropathy impairs pulmonary function, resulting in ventilatory response abnormalities to central and peripheral stimuli. In this line, parasympathetic neuropathy may cause an increase in airway caliber at baseline. Pulmonary autonomic neuropathy reduces mucociliary clearance and prone the lung to the infections. Reduced respiratory muscle strength due to defective muscle metabolism and neuropathy of the phrenic nerve promote respiratory muscle dysfunction in diabetic patients.

Fig. 2 Schematic representation of hyperglycemia-induced lung diseases. Hyperglycemia promotes airway hyperresponsiveness via the Rho-associated protein kinase (Rock) pathway. Hyperglycemia accelerates lung fibrosis through the activation of signal transducer and activator of transcription 3 (STAT3), connective tissue growth factor (CTGF) and transforming growth factor beta (TGFβ). Hyperglycemia increases cancer cell growth, chronic inflammation, inflammatory cytokine release and oxidative stress through activation of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB) pathway and NADPH oxidase (NOX) as well as the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Higher glucose concentrations in airway surface liquid (ASL) and lung immune cell dysfunction due to hyperglycemia promote a susceptibility to pulmonary infections.
mucociliary clearance, might explain the vulnerability of diabetic patients to lung infections [44, 45].

Recent studies have suggested a reduction in respiratory muscle strength in T1DM and T2DM mainly because of defective muscle metabolism [25, 46, 47]. The endurance of the respiratory muscles is reduced in diabetic patients, and this deficit is inversely correlated to the degree of metabolic control, as indicated by the HbA1c (glycated hemoglobin) level [25]. Neuropathy of the phrenic nerve alters bronchial reactivity, promoting respiratory muscle dysfunction in diabetic patients [48]. Respiratory muscle disorders, due to defective muscle metabolism or phrenic neuropathy, reduce lung volumes and accelerate lung restrictive complications in diabetic patients [45–48]. Cardiopulmonary exercise tests have revealed that maximal workload, maximal oxygen consumption and maximal heart rate are all severely reduced in diabetic patients, which explains the limitation of physical exercise capacity in these patients [49, 50].

Furthermore, systemic chronic inflammation associated with oxidative stress and loss of antioxidant capacity may cause lung endothelial dysfunction and thickening of the lung interstitium in patients with DM [13, 51, 52]. A large capillary network in the lung (surface area = 140 m²), characterized by a great microvascular reserve, is the main protective mechanism against DM-induced pulmonary complications. Because of the large pulmonary reserve, micro- and macrovascular dysfunctions due to diabetes develop later in the lung than in other organs. However, the association of DM with primary pulmonary disease may cause severe loss of lung microvascular reserve with an increased risk of pulmonary abnormalities [53, 54]. The association of DM and pulmonary diseases, considering susceptibility, prevalence, progression and severity, will be discussed in the following chapter of this review.

### 3 DM and lung cancer

Previous studies have shown a positive correlation between DM and colorectal, breast, endometrial, kidney and pancreatic cancer [55–58]. Hyperinsulinemia (either endogenous due to insulin resistance in T2DM or exogenous due to administered insulin in T1DM) may increase cell survival and proliferation related to insulin and insulin-like growth factor [59–61]. Concomitant to hyperinsulinemia, hyperglycemia may promote cancer cell growth, pro/antiinflammatory cytokine imbalance, chronic inflammation, oxidative stress and anticancer immunity suppression [13, 62] (Fig. 2). Although DM and lung cancer share similar risk factors, including age, smoking and alcohol, studies assessing the causative association of DM and lung cancer have yielded conflicting results [62–66]. A large retrospective study from the United Kingdom showed a lower cancer incidence rate in a diabetic population than in the general healthy population [66]. The authors assumed that the difference may be partly due to the reduced life expectancy of individuals with DM compared with that of the general population, resulting in a lower chance to develop lung cancer [66]. However, a meta-analysis of observational studies from Lee et al. (2013) showed a higher incidence of lung cancer in diabetic women [67]. The correlation of DM and lung cancer did not reach a significant level for male patients in this study [67]. Dankner et al. (2018) recently showed a mildly higher risk for lung cancer in diabetic patients with poor glycemic

[Fig. 3] Schematic representation of insulin effects on the lung. Insulin inhibits surfactant protein A (SP-A) and surfactant protein D (SP-D) production via a phosphoinositide-3-kinases (PI3K) pathway. Insulin inhibits the proliferation of T helper cell type 1 (Th1) and shifts T cells towards a T helper cell type 2 (Th2)-type response. Insulin promotes mast cell survival, degranulation and histamine release via a PI3K pathway and activates pulmonary inflammatory macrophages. Insulin proliferates and contracts airway smooth muscle cells (ASMs) via mitogen-activated protein kinase (MAPK), Rho kinase and PI3K pathways. Insulin increases the deposition of extracellular matrix (ECM) in the lung and promotes epithelial-mesenchymal transition (EMT) and fibrosis via the PI3K/protein kinase B β-catenin pathway.
control [68]. Analyses of the survival rate of patients with both lung cancer and DM compared with that in lung cancer patients without DM have yielded conflicting results [69–74]. Some studies have shown an increase [69, 70], some studies have shown a decrease [71, 72], and other studies have reported no significant change [73, 74] in the survival rate of patients suffering from both lung cancer and DM compared with that in lung cancer patients without DM. A lower rate of metastasis in lung cancer patients with DM has been reported in some studies [70, 73]. The antineoplastic effects of some antidiabetic medications, especially metformin, have been suggested to partially correlate with a reduced incidence and progression of lung cancer in diabetic patients [75–77]. However, the underlying biological mechanisms are not clear, and the results of these studies are still contradictory [75–80]. Further well-designed prospective population-based studies with high-quality databases are needed to compare the incidence of lung cancers between individuals with high circulating insulin levels and/or hyperglycemia with or without diabetes and nondiabetic individuals with normal insulin sensitivity and/or normoglycemia. To reduce heterogeneity across studies, common risk factors such as type and duration of DM, body weight, physical activity, age, sex, ethnicity, diet, therapy, degree of glycemic control, tobacco smoke and alcohol consumption need to be considered in these investigations.

4 DM and lung infection

A wide range of neutrophil and macrophage functions, including chemotaxis, adherence, phagocytosis, ability to kill phagocytosed microorganisms with free radicals and respiratory burst are impaired in DM [81, 82]. A reduced complement system C4 and humoral immunity associated with a reduced number and response of T cells increase the susceptibility of diabetic patients to infection [83, 84]. Furthermore, hyperglycemia and insulin resistance impair collective surfactant D-mediated host defenses of the lung in T2DM [85]. Loose junctions between airway epithelial cells, which increase the transepithelial glucose gradient along with an increase in the glucose concentration of the airway surface liquid due to hyperglycemia, may dampen the airway defense against infection, resulting in lung bacterial overgrowth in DM [86] (Fig. 2). *Staphylococcus aureus* and *Streptococcus pneumoniae; influenza virus; opportunistic pathogens such as Klebsiella pneumoniae, Pseudomonas aeruginosa; and fungal infections with Mucorales and Aspergillus species, are frequent causes of lung infection in DM [83, 87, 88]. Hospitalization during the influenza epidemic was found to be six times higher in diabetic patients than in nondiabetic individuals [89]. It has been reported that pneumonia has the greatest prevalence, incidence and severity among diabetic patients with elevated HbA1c levels [90]. Furthermore, poor glycemic control in DM may increase the risk of pneumonia-related hospitalization in these patients [90]. DM is associated with a poor prognosis, increasing the rate of pleural effusion and mortality in community-acquired pneumonia [91]. Initial administration of the first antibiotic given not later than 8 h of triage is associated with fewer complications and lower mortality in diabetic patients with pneumonia [92]. Some pharmacological studies have shown that treatment with angiotensin-converting-enzyme inhibitors or statins is associated with a significant reduction in the risk of pneumonia in both type 1 and type 2 diabetic patients [93, 94]. However, the mechanisms behind this protective effect are unclear. The risk of pneumococcal infection remains higher even after vaccination in diabetic patients, presumably due to low vaccine uptake or low effectiveness of the available vaccines [95]. The higher rate of lung infections in diabetic patients is mainly due to hyperglycemia which adversely affecting immune system function, increasing diabetic patients morbimortality. Further studies are necessary to mechanistically evaluate the role of airway glucose hemostasis treatments and of antihypertensive, lipid lowering and immune system-modifying medications on improving immune system function and reducing the respiratory infection frequency in DM patients.

5 DM and pulmonary tuberculosis

It has been shown that a reduction in the immune response associated with DM may increase the risk of developing active tuberculosis by approximately three-fold [96–98]. Several studies have shown that 10%–30% of patients with tuberculosis may also suffer from DM [97–100]. Diabetic patients are also prone to develop drug-resistant tuberculosis resulting in antituberculosis treatment failure, disease relapse after the completion of treatment and increased mortality [101–103]. Alveolar residential cells (monocytes and macrophages) play an important role in the pathogenesis of tuberculosis [104]. *Mycobacterium tuberculosis* infects alveolar macrophages, and the pathogen accumulates and replicates in macrophages, resulting in cellular death and shedding of bacteria to other pulmonary cells [105]. In diabetic patients, reduced opsonization, and binding and phagocytotic activity of monocytes towards *Mycobacterium tuberculosis* may increase the susceptibility of these patients to tuberculosis [103, 106, 107]. The role of neutrophils, natural killer T cells and dendritic cells in the context of DM and tuberculosis is not clear [108, 109]. Studies on the role of the adaptive immune system in diabetic patients with tuberculosis have led to conflicting results. Some studies have shown a reduction in T cell proliferation and T cell-associated cytokine production, especially interferon γ, in diabetic patients with tuberculosis [110, 111]. However, other studies have found higher numbers of T helper type 1 and 17 cells but lower frequencies of T regulatory cells and a higher
production of related cytokines, including interferon γ, tumor necrosis factor-α, Interleukin (IL)-17A/F, IL-2, IL-1β, granulocyte macrophage colony-stimulating factor and IL-5, IL-10 and transforming growth factor β (TGFβ), in diabetic patients with tuberculosis than in matched nondiabetic tuberculosis patients [112–114]. Type 1 and 17 cytokine production was positively correlated with HbA1c levels in diabetic patients with tuberculosis [114]. T2DM does not show any effect on the numbers or subset distribution of CD8+ T and NK cells, but it alters the CD8+ T and NK cell response to Mycobacterium tuberculosis [115]. T2DM patients with active tuberculosis show higher frequencies of mycobacterial antigen-stimulated CD8+ T cells and NK cells expressing type 1 and type 17 cytokines [115]. However, cytotoxic markers of CD8+ T cells and NK cells are decreased in these patients [115]. It is assumed that the higher frequencies of T cell response and altered phenotype and function in CD8+ T cells and NK cells in diabetic patients with tuberculosis yields a less functional but excessive immune-mediated pathology than that in nondiabetic tuberculosis patients. Tuberculosis susceptibility in DM needs to be explored from immunological and biochemical aspects. The molecular mechanism of hyperglycemia and insulinaemia on macrophage and lymphocyte phagocytic, chemotactic and antigen presentation responses to Mycobacterium tuberculosis needs to be investigated in more detail. Epidemiological studies on the association of DM and tuberculosis should distinguish between T1DM and T2DM to determine the effect modification by age and type of diabetes.

6 DM and cystic fibrosis

DM is the most common and life-threatening complication of cystic fibrosis due to pancreatic insufficiency and the abnormal timing and delayed and blunted secretion of insulin [116]. Cystic fibrosis-related diabetes (CFRD) reduces survival and increases the mortality in cystic fibrosis patients with diabetes compared with that in nondiabetic cystic fibrosis patients [117]. There is a difference in the pattern of diabetes in CFRD compared to that of T1DM and T2DM, but the micro- and macrovascular complications of CFRD, except cardiovascular disease, appear to be similar to those seen in other types of diabetes [118]. CFRD adversely affects lung function (average forced expiratory volume in one second of 52% in cystic fibrosis patients with diabetes compared with 72% in nondiabetic patients) [119–121]. A decline in the lung function of CFRD patients is seen for several years prior to the diagnosis of CFRD [122, 123]. The severity of pulmonary dysfunction is positively correlated with the degree of insulin deficiency (causing glucose intolerance and protein catabolism) in patients with CFRD [121]. Some studies have found that insulin treatment improves lung function and increases forced expiratory volume in one second in patients with CFRD [124–127]. Staphylococcus aureus and Pseudomonas aeruginosa coinfections are associated with CFRD, which accelerates the pulmonary deterioration and lung function decline in CFRD patients [128]. It still needs to be clarified whether the dampened immune function due to hyperglycemia (as discussed above in DM and lung infection) is also partly responsible for the Staphylococcus aureus and Pseudomonas aeruginosa coinfections in CFRD patients. Further basic and clinical studies are required to investigate the relationships of hyperglycemia, insulin deficiency and long-term insulin therapy with pulmonary function in CFRD.

7 DM and asthma

Asthma is a chronic inflammatory disease mediated by T helper type 2 (Th2) cells [129]. On the other hand, T1DM is mediated by Th1 cells. Considering the Th1/Th2 paradigm (cytokines from either the Th1 or Th2 phenotype exerting suppressive activities on the development and activity of the other phenotype), previous findings have shown a negative association between T1DM and asthma [130–133]. A recent case-cohort study among Finnish children showed that participants with previously diagnosed asthma were at an increased risk of subsequent development of T1DM but that children with previously diagnosed T1DM presented a decreased risk of subsequent development of asthma, suggesting a distinct interrelation of the sequential appearance of these two diseases [134]. Overall, there is increasing evidence for a positive correlation between the occurrence of T1DM and symptoms of asthma at the population level [135–137]. It is assumed that factors influencing the susceptibility to the coincident occurrence of asthma and T1DM may cluster in countries, attributed to genetic and/or early environmental exposures [135–137]. It has been suggested that autoimmune diseases such as T1DM and allergic diseases such as asthma may have some common immunopathogenetic mechanisms, influenced by environmental factors such as lifestyle and living conditions [138]. A positive correlation between HbA1c levels and asthma occurrence has been reported among young individuals with T1DM [139]. Rachmiel et al. (2006 and 2011) showed that patients suffering from T1DM and asthma present a unique intermediate Th1/Th2 cytokine profile, combining features of both diseases [140, 141]. Animal studies have revealed that the coinduction of T1DM and asthma significantly reduces airway inflammation and airway hyperresponsiveness [142–146]. Decreased release of sensory neuropeptides; reduced influx of eosinophils, number of degranulated mast cells and histamine release; and increased inhibitory neuronal muscarinic receptor 2 function in the lung were the main suggested mechanisms for the ameliorative effect of DM in asthma models [142–146]. Findings on the
role of T2DM and asthma prevalence are inconsistent, most likely due to different study designs and populations [147–150]. However, T2DM and obesity may increase the risk of asthma to two and three times greater than that in normal subjects, respectively [151, 152]. Obesity decreases the effectiveness of asthma therapy and increases the rate of hospitalizations due to asthma exacerbations to levels nearly five times greater than those of asthmatic subjects without obesity [153]. It has been shown that gestational DM and obesity are associated with an increased risk for childhood asthma [154, 155]. It is now clear that insulin can inhibit surfactant A and D production via a phosphoinositide-3-kinase pathway, shift T cells towards a Th2-type response, promote mast cell survival and degranulation via a phosphoinositide-3-kinase pathway, activate pulmonary inflammatory macrophages, and proliferate and contract airway smooth muscle cells via the mitogen-activated protein kinase, Ras homologue kinase and phosphoinositide-3-kinase pathways [22, 23, 156–160] (Fig. 3). Increasingly, evidence suggests that DM and asthma are multiply linked through various pathophysiological mechanisms. It is concluded that not only type 1 and type 2 diabetic patients but also offsprings of diabetic mothers are at increased risk of developing asthma. Indeed, there is an increasing demand to investigate the underlying molecular mechanisms by which different types of DM and obesity, hyperglycemia and hypo/hyperinsulinemia affect asthma induction, progression and severity. However, the role of COPD as a risk factor for DM remains controversial [167]. Some studies have shown a higher risk of DM in patients with COPD compared with that in control subjects [168, 169], whereas other studies have not found any association between COPD and DM [170, 171]. Anti-inflammatory treatment with corticosteroids (locally and systemically) is used in patients with COPD to improve their quality of life and reduce the frequency of exacerbations. It has been shown that inhaled corticosteroids in patients with COPD are not associated with an increased risk of new onset DM, hyperglycemia or a significant change in HbA1c levels [172, 173]. On the other hand, metformin treatment over a 2-year follow-up period in patients with coexisting DM and COPD reduced emergency room visits and hospitalization, especially in low-complexity COPD [174]. A recent cohort study showed that metformin treatment reduces the risk of all-cause mortality in patients with coexisting T2DM and either stable or exacerbated COPD [175]. It is realized that DM may increase the risk of COPD, worsening the quality of life and increasing the rate of exacerbation and mortality in COPD patients. However, the complex interaction between DM and COPD requires more detailed prospective population-based investigations, considering which disease (DM or COPD) appears first, as well as the type and duration of DM and severity of COPD, glycemic condition of the patients, smoking status and treatment strategies in these diseases.

8 DM and chronic obstructive pulmonary disease (COPD)

Chronic inflammation and systemic oxidative stress—associated with increased levels of CRP, TNF-α, IL-1, IL-6, and fibrinogen—are shared features in COPD and DM [13, 161]. However, the association and interplay between DM and COPD are not clearly understood. Ehrlich et al. (2010) demonstrated a higher incidence of COPD in diabetic patients with higher body mass index (29.80 ± 6.48) and HbA1c (>6.7%) [65]. It has been recently shown that the pulmonary function in diabetic patients with ≥10 pack-years of smoking is reduced compared to that in nondiabetic smokers [162]. This pulmonary malfunction is associated with significant reductions in activity-related quality of life and exercise capacity [83]. DM may increase the risk of COPD exacerbation and mortality [163, 164]. Hyperglycemia, i.e., random blood glucose ≥7 mmol/l is associated with poor outcomes and increased COPD-related morbidity and mortality in hospitalized patients in the intensive care unit [165]. Hyperglycemia (i.e., random blood glucose ≥7 mmol/l) upon presentation to the intensive care unit was found to be a useful predictor of poor outcomes and to confer the greatest risk of treatment failure with noninvasive ventilation in patients with severe COPD [166]. The reports on the association of DM and ALI or ARDS reveal inconsistent findings [176–182]. It has been shown that T2DM does not affect the lung physiopathology in patients with ARDS [177]. Recently, a large, global observational study found no association between DM and ARDS progression or hospital mortality from ARDS [178]. However, many studies have shown that both T1DM and T2DM may prevent the development of ARDS in patients with predisposing ARDS risk factors [166, 182–186]. However, the beneficial effect of DM on ARDS development does not reduce the mortality among patients in whom ARDS develops [176, 182, 187]. The preventive mechanism of DM against ARDS development is not completely understood. Studies on experimentally induced DM show that the preventive effect may be attributed to decreased neutrophil numbers and function, impaired nuclear factor κ-light-chain-enhancer’ of activated B-cells activation, reduced superoxide generation, insulin growth factor and its receptor deficiency, leptin resistance and lower concentrations of inflammatory cytokines such as tumor necrosis factor-α, IL-1β, IL-6, and prostaglandin E2 [188–194]. It has been assumed that insulin may modulate the development of ALI/ARDS in DM. In clinical studies,
DM causes systemic macro- and microvascular dysfunction, but considering the large pulmonary vascular network, the impact of DM on the pulmonary vasculature is still not clear [205, 206]. Epidemiological studies have revealed that diabetic patients are at higher risk for developing pulmonary hypertension associated with markedly worse survival [207–210]. Animal experiments have shown that experimental streptozotocin (STZ)-induced T1DM causes pulmonary vascular endothelial dysfunction through oxidative stress [211, 212]. Insulin resistance and undiagnosed DM are common in patients with pulmonary hypertension [213, 214]. In non-diabetic patients with pulmonary hypertension, a significant positive correlation was observed between HbA\textsubscript{1c} levels and worse long-term prognosis [215]. Gestational diabetes may be a risk factor for pulmonary hypertension in newborns [216]. Recently, Grinnan et al. 2016 reviewed the possible mechanisms of DM-induced pulmonary hypertension based on the existing research information [217]. The suggested mechanisms include right ventricular failure [218], increasing endothelin levels, platelet-derived growth factor and TGF-\beta production [219, 220], higher insulin-like growth factor expression and lower peroxisome proliferator-activated receptor gamma expression [221, 222], reduced endothelial nitric oxide synthase activity and nitric oxide production [223] and reduced prostacyclin production [224]. More detailed human and animal studies are recommended to elucidate the exact underlying mechanism that may spare the pulmonary vasculature from (or make it prone to) toxic effects of DM, such as hyperglycemia, hyperinsulinemia, oxidative stress and chronic inflammation. The incidence of pulmonary hypertension in different types of DM should be defined in more robust epidemiological studies.

### 11 DM and pulmonary fibrosis

Aging is an important contributing factor in both DM and pulmonary fibrosis, increasing the possibility that lifestyle-related diseases such as DM and/or obesity may affect the initiation and/or progression of pulmonary fibrosis [225, 226]. Increased thickness of alveolar capillary walls, alveolar walls and pulmonary arteriolar walls, representing lung fibrotic histopathological changes, have been reported in autopsied lungs from diabetic patients [227]. However, in contrast to this study, no differences in the alveolar walls or intimal fibrosis and medial thickening of small vessels in the autopsied lungs were seen between DM and control groups [228]. Specific types of nodular fibrosis, a combination of inflammatory cells and excessive deposition of collagen and extracellular matrix, were the only typical changes observed in the lungs of these patients [228]. It has been shown that alveolar epithelial cells and the endothelial capillary basal lamina are significantly thicker in diabetic patients than in control subjects [229, 230]. A first Japanese case-control study showed that DM increases the risk for developing pulmonary fibrosis [231]. A case-control study from the United Kingdom found an association between IPF and DM, the strongest association being with insulin use [225]. Another Mexican case-control study showed that T2DM is the most important independent risk factor associated with pulmonary fibrosis [232]. Furthermore, it has been shown that T1DM is also an independent risk factor for pulmonary fibrosis [233]. Two Korean case-control studies demonstrated the association of DM with IPF [234, 235]. A higher prevalence of hypertension, cardiovascular disease, and other malignancies, excluding lung cancer, has been shown in IPF patients with DM than in IPF patients without DM [235]. A Danish cohort study showed that DM is the third most frequently observed comorbidity of pulmonary fibrosis after cardiovascular disease and arterial hypertension [236]. This study suggested for the first time that DM significantly increases mortality in IPF patients [236]. Advanced glycation end product-modified protein accumulation has been shown in lung macrophages in remodeling lesions of pulmonary fibrosis, suggesting that chemical modification by AGE might be involved in DM-induced pulmonary fibrosis [237]. Taking all these findings together, it may be concluded that DM is one of the main comorbidities in patients with IPF (Fig. 4). The recognition and management of comorbidities in IPF may limit disease progression and increase survival in these patients. The pathogenic mechanisms implicated in the association of DM and IPF are currently not understood and remain to be elucidated in further clinical and
experimental research. The following chapter focuses on the current in vitro and in vivo experimental studies that have been conducted to investigate the possible mechanisms of DM-induced pulmonary fibrosis.

12 Mechanisms involved in DM-induced pulmonary fibrosis in vitro and in vivo

Experimental investigations have shown an increase in the lung volume and weight in a STZ-induced rat model of T1DM [238]. Increases in the amount of collagen, elastin and hydroxyproline along with reduced breakdown of glycated connective tissue proteins are involved in the promotion of lung fibrosis by diabetes [238–240]. In a STZ-induced diabetic mouse model, hyperglycemia-induced lung fibrosis was more severe than that in mice treated with bleomycin (a standard drug for experimental lung fibrosis induction in animal models) [239]. Furthermore, enlargement of air spaces, increased alveolar surface area and a greater number of alveoli have been reported in the rat model of DM [240]. AGE accumulation in the lung due to hyperglycemia may increase lung oxidative stress, resulting in lung fibrotic changes [241]. Hyperglycemia induces oxidative stress, ROS and reactive nitrogen species generation, and impairment of the capacity of the antioxidative defense system are the major causes of T1DM-induced lung fibrosis [242, 243]. Nitric oxide and peroxynitrite are considered to play a critical role in lung fibrotic pathogenesis in STZ-induced T1DM [244].

Inflammatory cell infiltration into the lungs of both experimental type 1 and type 2 diabetic animals may also play important roles in the development of DM-induced lung fibrosis [245, 246]. Enlargement of the interstitium and increased thickness of the alveolar walls and basement membrane have been reported in OVE26 transgenic mice, which develop diabetes spontaneously 2 to 3 weeks after birth [247]. Plasminogen activator inhibitor-1 is increased in STZ-induced diabetic mice that develop lung fibrosis through impairment of the coagulation and fibrinolytic systems [233, 248, 249]. TGF-β/Smads signaling, the most important signaling pathway in the initiation and progression of pulmonary fibrosis, is increased in the lungs of STZ-induced diabetic rats [245]. An increase in signal transducer and activator of transcription 3 and connective tissue growth factor in the STZ-induced rat model of diabetes may result in lung damage associated with fibrosis [250]. Treatment with insulin normalizes hyperglycemia and ameliorates signal transducer and activator of transcription 3 or connective tissue growth factor expression in diabetic rats, suggesting a role for hyperglycemia in the pathogenesis of lung fibrosis [250] (Fig. 2). It has been shown that angiotensin II plays a critical role in diabetic lung fibrosis, at least in part through NADPH oxidase-mediated nitrosamine damage in two models of STZ-induced T1DM and OVE26 diabetic mice [251]. However, angiotensin (I–VII), by opposing the actions of angiotensin II, reduces systemic inflammation, decreases the total amount of collagen in the lung and ameliorates lung pathological remodeling and fibrosis, which are associated with T2DM.
Platelets are the main source of cytokines, such as TGF-β and platelet-derived growth factor, which are implicated in the development of pulmonary fibrosis [253]. Platelet dysfunction and platelet granule abnormalities may contribute to DM-induced lung fibrosis through the initiation of inflammation, oxidative stress and the secretion of profibrotic cytokines such as TGF-β and platelet-derived growth factor [254]. Hyperinsulinemia, a major feature of T2DM, increases collagen deposition in the lungs and stimulates airway hyperresponsiveness through increasing contractile effects on airway smooth muscle cells [255]. Furthermore, hyperinsulinemia promotes epithelial-mesenchymal transition and fibrosis through activation of the phosphoinositid-3-kinases/protein kinase B β-catenin pathway and produces deleterious structural and functional changes in the lung [255] (Fig. 3). Necropsy analysis of diabetic cats confirmed a significant increase in pulmonary fibrosis in these animals compared with that in control nondiabetic cats [256]. Taken together, these clinical and nonclinical studies suggest that diabetes may be an important risk factor for the initiation and progression of pulmonary fibrosis, albeit through unclear mechanisms.

13 Conclusion and outlook

Diabetes mellitus-related complications in multiple organs, such as those of the cardiovascular system, central nervous system, kidneys, nerves and retina, have been extensively studied in both human and animal models. Despite emerging clinical reports on the diabetic lung, the mechanism involved in diabetes-induced pulmonary disorders has been poorly studied. Therefore, intense efforts are required to better identify and quantify pulmonary risks in patients with DM, not only by focusing on the description of the statistical relation between DM and lung diseases but also through investigating the mechanisms for these comorbidities. Targeting multiple risk factors associated with DM is essential to curbing the growing prevalence and progression of pulmonary complications in diabetic patients. Although the optimization of glycemic control plays an important role in improving pulmonary complications, the direct role of insulin and other antidiabetic drugs in the respiratory tract needs to be clarified in future research. Clinical and experimental studies are needed to better understand the lung disease process in diabetic patients in order to improve medical management and the prevention of pulmonary complications in these patients. Multifaceted investigations utilizing suitable translational animal models and large prospective human population-based studies will help scientists and clinicians translate the acquired knowledge into effective and meaningful clinical interventions. There is an increased population with undiagnosed DM, which can cause serious health problems, particularly lung comorbidities. From a public health perspective, the early treatment of lung comorbidities in patients with diagnosed and undiagnosed DM may have a strong potential to improve the quality of life and survival in these patients.

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