



Is the association between diabetes mellitus and pulmonary fibrosis real?

Varun Kumar^{1,2,3} and Peter P. Nawroth^{1,3,4}✉

An emerging feature of type 1 diabetes mellitus and type 2 diabetes mellitus is their association with pulmonary fibrosis, which negatively affects the prognosis of patients. Here, we provide a brief update of the field and the remaining open questions.

Since the emergence of modern therapeutics that reduce the risk of diabetic coma, the clinical control of patients with diabetes mellitus now focuses on the prevention and treatment of late complications. More importantly, improvements in life expectancy of patients with diabetes mellitus has led to the emergence of a wide range of complications, including in the lungs. In the past few years, the amount of literature on lung disease in patients with diabetes mellitus has expanded enormously, with many papers suggesting there is a direct association between pulmonary fibrosis and type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM)^{1–3}. However, owing to various technical and clinical limitations, a clear link between clinical diabetes mellitus and pulmonary fibrosis is not yet available³.

Several factors might explain the uncertainty about the link between diabetes mellitus and pulmonary fibrosis. Among these, a large number of the most recent studies were primarily observational and, therefore, lacked long-term data validation. Another reason for this uncertainty is that the tools used for diagnosing pulmonary fibrosis vary across diagnostic centres. These tools include assessing clinical symptoms, in combination with a 6-minute walking test, lung function tests (including body plethysmography, diffusion capacity, multidetector CT scan, spirometry and bronchoalveolar lavage) and lung biopsy⁴. These factors make comparative analysis very challenging. Moreover, it is difficult for clinicians to differentiate between lung and cardiac disease, as patients with symptoms such as breathlessness without fever are typically referred to a cardiologist. In addition, a decline in forced vital capacity is not sufficient to diagnose pulmonary fibrosis, because complete lung function testing and a multidetector CT scan are needed. Therefore, well-defined screening protocols with advanced diagnostic tools are needed.

Nevertheless, there seems to be a prevailing notion that diabetes mellitus increases the risk of pulmonary fibrosis, to a similar extent to smoking^{1,4}. Furthermore, studies revealed that restrictive lung disease (a disease that restricts the expansion of lung during breathing) is also associated with prediabetes; in patients with T1DM, restrictive lung disease is also associated with glucose control⁵. In addition, the association between pulmonary

fibrosis and nephropathy has been demonstrated in a cross-sectional study that included patients with T2DM, using a combined approach of assessing clinical symptoms and conducting clinical tests⁶. Some studies indicate that patients with diabetes mellitus and pulmonary fibrosis have multiple comorbidities that are clinically challenging⁷. Breathlessness in combination with restrictive lung disease was found in about 10% of the patients with prediabetes, 20–25% of patients with newly diagnosed T2DM and 25–30% of patients with long-term (≥5 years) T2DM¹. Importantly, the presence of albuminuria increased the risk of restrictive lung disease, and the severity of interstitial lung disease (detected by multidetector CT) correlated with clinical symptoms¹. However, more prospective studies in non-smoking patients with T1DM and T2DM are required, in which clinical symptoms, together with assessment of lung function and a multidetector CT scan, are used to confirm the diagnosis. These prospective studies could also address whether the morphology of pulmonary fibrosis related to diabetes mellitus is similar to or distinct from other forms of pulmonary fibrosis. In addition, a multi-centre study involving patients with T1DM or T2DM would be needed to study the role of control of hyperglycaemia on the course of pulmonary fibrosis. Such a study is important, as many of the drugs used to treat patients with T1DM or T2DM also affect the lung^{1,3,7}.

Given the prevailing inconsistencies and weaknesses of clinical data, data from animal models of diabetes mellitus are currently used to argue for a causal relationship between diabetes mellitus and pulmonary fibrosis. The most obvious factor is the activation of many of the same pathways in T1DM or T2DM^{1,2} and similar risk factors for both pulmonary fibrosis and diabetes mellitus⁴, including ageing⁸. In addition, an association with pulmonary fibrosis has been found in streptozotocin-induced and streptozotocin-independent diabetes mellitus in rodents and other mammals⁹. This finding supports the suggestion that there is a causal relationship between T1DM or T2DM and pulmonary fibrosis.

In various models of pulmonary fibrosis, senescence and the senescence-associated secretory phenotype

¹Department of Internal Medicine-I and Clinical Chemistry, University Hospital Heidelberg, Heidelberg, Germany.

²European Molecular Biology Laboratory, Advanced Light Microscopy Facility, Heidelberg, Germany.

³German Center for Diabetes Research (DZD), Neuherberg, Germany.

⁴Joint Heidelberg-IDC Translational Diabetes Program, Helmholtz-Zentrum, Munich, Germany.

✉e-mail: peter.nawroth@med.uni-heidelberg.de

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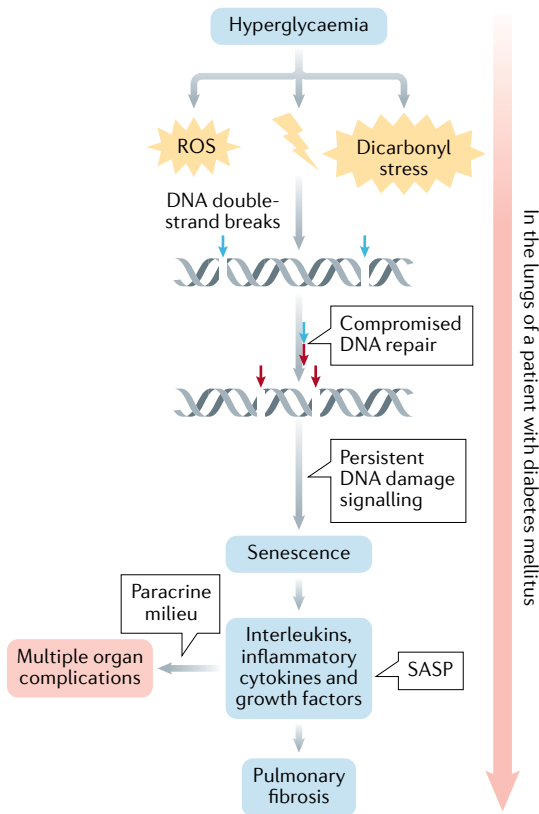


Fig. 1 | The onset and progression of pulmonary fibrosis in diabetes mellitus. A disrupted dialogue between DNA double-strand breaks signalling and the timely DNA repair in diabetes mellitus contributes to the activation of persistent DNA damage signalling, thus permanently blocking the cell cycle by activating the senescence programme. Senescence triggers metabolic and transcriptional changes to activate a senescence-associated secretory phenotype (SASP), marked by the active secretion of interleukins, inflammatory cytokines and growth factors that affect the normal homeostasis of other cells through paracrine signalling, thus modulating the tissue integrity. Senescence and the SASP milieu activate a cascade, resulting in pulmonary fibrosis, marked by reduced lung capacity, breathlessness and inflammation, thus representing a non-healing compromised lung function. ROS, reactive oxygen species.

(SASP) results in the secretion of cytokines, matrix remodelling proteases and profibrotic factors, which cumulatively promote pulmonary fibrosis^{2,10}. Given the central role of senescence in pulmonary fibrosis, the events triggering senescence and the SASP have been widely studied. For instance, diabetes mellitus-linked reactive oxygen species, dicarbonyl stress and the maladaptive metabolic environment perpetuate persistent DNA damage signalling (FIG. 1) to promote the onset of pulmonary fibrosis^{2,10}. A direct association between diabetes mellitus and impaired DNA repair has been shown in animal models of T1DM and T2DM².

In both T1DM and T2DM, timely generation of the active DNA repair complex in the lung is impaired^{2,10}. Upon exposure of alveolar type II cells to reducing sugars (that is, a sugar that serves as a reducing agent owing to its free aldehyde or ketone functional groups in its molecular structure, such as glucose, fructose or ribose), the DNA

repair potential of these cells is severely compromised². This defective DNA repair potential was directly correlated to the reducing capacity of the sugar used. Ribose was the most potent, followed by fructose and glucose². At the metabolic level, these sugars shift the redox equilibrium (NAD^+ to NADH) towards NADH , which affects the integrity of the DNA repair system via mitigated sirtuin or PARP signalling, which are directly involved in DNA repair². The decrease of the NAD^+ pool affects the impairment of DNA repair, as the addition of NAD^+ disrupts the binding of PARP1 to its inhibitor, DBC1, which is needed for efficient PARP-dependent DNA repair².

Together with the clinical data on the association of diabetes mellitus with impaired DNA repair, these data shed new light on diabetes mellitus and pulmonary fibrosis for three main reasons. Firstly, timely localization and post-translational modification of nuclear RAGE is central for DNA repair and prevention of pulmonary fibrosis. Secondly, an impaired DNA repair potential of cells cultured under hyperglycaemic conditions triggers a cascade of senescence, SASP and fibrosis. Thirdly, in experimental diabetes mellitus involving animal models, timely assembly of the DNA repair complex by adeno-associated virus-driven nuclear expression of RAGE not only improves persistent DNA damage signalling but also leads to remission of existing pulmonary fibrosis⁸. Reconstitution of nuclear RAGE reduced renal and pulmonary fibrosis in animal models of diabetes mellitus, but albuminuria was not affected². This study indicates that the mechanisms leading to fibrosis or albuminuria are distinct. These findings clarify the mechanisms leading to pulmonary fibrosis in diabetes mellitus and provide mechanistic insight into how disorders such as T1DM or T2DM reduce the capacity for regeneration of damaged organs. Unsolved issues include the question of risk factors for developing pulmonary fibrosis in patients with diabetes mellitus and the optimal therapy for pulmonary fibrosis in these patients.

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Competing interests

The authors declare no competing interests.