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Review Article

**IMPACT OF DIABETIES MELLITUS ON PULMONARY  
FUNCTION TEST IN COPD PATIENTS****Raksha<sup>1</sup>, Pranjul Jain<sup>2</sup>, Ravindra<sup>2</sup>, Gomti Patel<sup>3</sup>, Mrs. Sunayana Kesharwani<sup>1\*</sup>**Adina Institute of Pharmaceutical Sciences, Sagar (M.P.)<sup>1</sup>Daksh Institute of Pharmaceutical Sciences, Chhatarpur, (M.P.)<sup>3</sup>**Article Received:** March 2022**Accepted:** April 2022**Published:** May 2022**Abstract:**

*COPD is a multisystemic inflammatory illness that affects more than only the lungs. The link between reduced lung function and diabetes has been investigated for many years, suggesting that the lung could be a target organ in diabetes. Diabetes mellitus (DM) pulmonary effects are poorly understood. Some publications have observed normal pulmonary functions in diabetes individuals and even concluded that spirometry is not required. In other investigations, people with DM had altered respiratory parameters. Furthermore, the duration of diabetes and glycemic control have different effects on pulmonary function. The present review focus on impact of diabetes mellitus on pulmonary function test in COPD patients.*

**Key Words:** Diabetes Mellitus, Pulmonary function, COPD Patients**Corresponding author:****Mrs. Sunayana Kesharwani***sunayanakesharwani@gmail.com*

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**INTRODUCTION:**

Sixty-five million people are estimated to suffer from moderate to severe chronic obstructive pulmonary disease (COPD), which is predicted to become the third leading cause of death worldwide by 2030 [1]. COPD is characterized by persistent and usually progressive airflow limitation, which occurs in response to long-term exposure to noxious particles or gases (e.g. air pollution or smoking). These irritants cause an inflammatory response in the lungs, leading to shortness of breath, coughing and sputum production. In addition, in the majority of cases, acute exacerbation of COPD (AECOPD) is triggered by respiratory tract infections. Diagnosis of COPD severity is based on symptoms, exacerbation frequency and the degree of airflow limitation as assessed by pulmonary function testing. Treatment of COPD involves lifestyle modifications as well as the use of pharmacotherapies including bronchodilators and corticosteroids for AECOPD. Notably, COPD is known to be associated with several important chronic comorbid diseases, including hypertension, cardiovascular disease, obstructive sleep apnea and type-2 diabetes mellitus (T2DM) which are already partially interrelated [2].

Diabetes mellitus is also a chronic condition with severe global consequences. Indeed, in 2013, there were an estimated 382 million people (8.3% of the adult population) suffering from diabetes worldwide. However, approximately half of those with diabetes remain undiagnosed. Moreover, the rate of diabetes has steadily increased, and it is predicted that there will be around 600 million people with this condition by 2035 [3].

T2DM, which represents about 90% of diabetes cases, results mainly from a sedentary lifestyle and adiposity, together with genetic predisposition. T2DM is characterized by the failure of blood glucose control due to a combination of insulin resistance and pancreatic beta cells not functioning. As a consequence of its pathogenesis, T2DM is commonly associated with diabetic dyslipidemia (i.e. an increase in plasma triglycerides, remnant lipoprotein and small dense low-density lipoprotein and a decrease in high-density lipoprotein), fatty-liver disease and a chronic inflammatory state. Over time, diabetes can lead to serious complications, including macrovascular (cardiovascular) and microvascular disease (e.g. diabetic nephropathy, retinopathy and neuropathy).

Approximately 10% of patients with diabetes also suffer from COPD; this is a grey zone, however, and there is a need to distinguish COPD from obesity-

related pulmonary dysfunction. Recent studies have shown that T2DM can worsen the progression and prognosis of COPD, increasing the odds of COPD-related mortality. On the other hand, diabetes-associated adiposity has been shown to have a protective effect in patients with COPD, even reducing mortality [4].

Nevertheless, controversy remains as to whether there is a causal relationship between T2DM and COPD, and it is also possible that this interaction only occurs in a subset of patients (i.e. diabetics with neuropathy). Conversely, it has also been suggested that COPD constitutes an important risk factor for the development and/or progression of T2DM [5], a phenomenon that does not apply to type-1 diabetes. Thus, although COPD and T2DM represent distinct disease entities, there might indeed be a pathophysiological connection that links these important chronic conditions.

It is of scientific and clinical importance to obtain an understanding of the risk factors that drive the development of T2DM and/or COPD and the potential consequences of therapeutic intervention for these diseases. Here, we have compiled and reviewed the available data on the interaction between COPD and T2DM. We also discuss the implications of this research. Taken together, this information not only highlights the complex relationship that might exist between COPD and T2DM, but also contributes to our knowledge regarding preventative care for patients.

**Systematic Search Strategy:**

The terms 'diabetes' and 'hyperglycemia' were searched in combination with 'chronic obstructive pulmonary disease' and 'COPD'. This search was then extended by manual screening of the references of the included papers to identify additional supporting information.

**Study Selection:**

Included studies fulfilled the following criteria:

- (1) they were published as a primary research article in a peer-reviewed journal,
- (2) they reported results that either indirectly or directly yielded insight into the relationship between COPD and diabetes and
- (3) they were written in English.

**The Adverse Effects of Hyperglycemia on Lung Function:**

Although recent evidence seems to indicate that diabetes and elevated blood glucose constitute important comorbidities that have an impact on lung function, the mechanistic explanation for this

relationship remains illdefined. Nevertheless, it is possible that hyperglycemia leads directly to adverse effects on the lungs (i.e. glycosylation of the connective tissues, reduced pulmonary elastic recoil, increased muscle weakness and/or inflammation), which can result in restrictive alterations. In this regard, studies have demonstrated that pulmonary function tests are significantly decreased in subjects with T2DM in comparison to healthy controls ; this might be the result of direct exposure to elevated blood sugar [6].

In line with this, it was reported that metabolic syndrome, insulin resistance and systemic inflammation constitute important risk factors for reduced lung function in healthy, nonsmoking subjects , which suggest that even in the absence of smoking, diabetes can lead to similar effects on pulmonary function. It has also been proposed that reduced lung volume and airflow limitation might be considered as chronic complications of T2DM . In fact, diabetic subjects have been found to display reduced pulmonary function even after controlling for known risk factors, along with significant reductions in exercise capacity and quality of life across functional stages of airflow limitation [7] .

Notably, even though forced expiratory volume in 1 s (FEV<sub>1</sub>) and forced vital capacity (FVC) were found to be consistently lower in diabetic subjects, these deficits did not seem to be progressive in the long term . With regard to decreased lung function in diabetic patients, a study in rats confirmed that hyperglycemia has the potential to impact the respiratory system by inducing oxidative stress, structural changes in the lung tissue and altered gas exchange. Moreover, postmortem studies in humans have indicated that the epithelial and capillary basal membranes of the alveoli are significantly thicker in diabetic subjects when compared to age-matched controls ; this is consistent with the notion that hyperglycemia can lead to structural modifications in the lung. In addition, an experimental model of hyperglycemia led to increased levels of inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor alpha (TNF $\alpha$ ) and IL18 [8].

C-reactive protein levels were also found to be elevated in individuals showing impaired glucose tolerance, and the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study observed increased systemic inflammation based on these levels when diabetes was a comorbidity of COPD . This emerging model suggests that hyperglycemia can drive inflammatory responses, which can ultimately lead to restrictive

changes in the lung tissue and reduced pulmonary function. Notably, such alterations would have the potential to exacerbate ongoing immune-related processes, thereby driving the pathophysiology of COPD. [9]

#### **The Impact of Diabetes on Patients with COPD: Effects of Preexisting Diabetes on the Course of COPD/ AECOPD:**

Several key pieces of evidence have recently suggested that preexisting T2DM leads to adverse effects in patients suffering from COPD . More recently, the negative effects of diabetes on COPD were confirmed by the ECLIPSE study, a multicenter investigation that evaluated 2,164 clinically stable COPD subjects and 582 individuals with normal lung function (both smokers and nonsmokers) in order to identify predictors of disease progression. ECLIPSE identified that diabetes increased the odds of mortality when coexistent with COPD and that it was associated with higher Medical Research Council dyspnea scores as well as a reduced 6-min walk distance . In addition to affecting the prognosis of COPD patients, it has been suggested that diabetes increases the risk of developing severe pulmonary conditions, such as asthma and COPD. Furthermore, pulmonary hypertension has been found to be more severe in patients with COPD and T2DM . The impact on the actual daily quality of life in COPD patients, however, is a matter of controversy [10].

Diabetic patients with AECOPD, on the other hand, were found to frequently (in 50–80% of patients) display hyperglycemia during their hospital stay and exhibit an increased length of hospitalization and mortality when compared to patients without diabetes [11]. A blood glucose level of  $\geq 7$  m M has been found to be significantly associated with these adverse consequences, with the risk for combined outcome (i.e. longer hospital stay and death) increasing by 15% for each 1-m M increment in blood glucose . Moreover, it was also reported that the length of hospital stay after AECOPD increased by 10% for each 1-m M increase in mean glucose. These findings suggest a potentially negative impact of the diabetic condition on AECOPD. This is not surprising, as other acute conditions having been shown to induce hyperglycemia as a result of stress (e.g. myocardial infarction and stroke), irrespective of baseline glucose tolerance [12] .

Thus, a large proportion of patients experiencing AECOPD have the potential to experience the negative effects of hyperglycemia. Nevertheless, these results have not been observed in all studies that have examined hospitalized AECOPD patients,

and it has been suggested that hypoglycemia (rather than hyperglycemia) may actually be more detrimental for outcome (i.e. longer hospitalization). In addition, with regard to the treatment of AECOPD, it has been reported that hyperglycemia (i.e. blood glucose  $>11$  m M) is independently associated with a late failure (i.e. after 48 h) of noninvasive ventilation following initial success [13].

Accordingly, it was demonstrated that hyperglycemia (blood glucose  $\geq 7$  m M) within 24 h of admission could be used to predict clinical outcome in COPD patients presenting with acute hypercapnic respiratory failure and requiring noninvasive ventilation. Nevertheless, it is still not known whether acute hyperglycemia occurring during AECOPD-related hospitalization is a direct cause of poor outcomes or is simply a marker of other adverse factors (e.g. treatment modification). [14]

In spite of the overwhelming findings demonstrating the potential deleterious role of diabetes in the treatment, prognosis and progression of COPD, there are also some data that suggest positive effects related to diabetes in COPD. Although a recent systematic review described that diabetes was associated with increased long-term mortality in patients admitted for AECOPD, the analysis also revealed a reduction in short-term COPD-related mortality in those with diabetes. This protective effect of diabetes was also observed in a study by McGhan *et al.* [15], who reported that diabetes was associated with a reduction in readmissions for patients who had survived an episode of AECOPD. So far, it remains unclear how diabetes could lead to these types of protective effects, although preferential care of diabetic patients could represent a contributing factor.

#### **Diabetes, COPD and Infection:**

There is some evidence to support the fact that diabetes and hyperglycemia can augment the ability of bacteria to infect the lungs of COPD patients. Indeed, elevated glucose concentrations may directly stimulate bacterial growth or promote bacterial interaction with the airway epithelium. It is also possible that certain facets of the immune system become impaired during hypoglycemia-induced immunomodulation, leading to increased susceptibility to bacterial pathogens. Indeed, there is a precedence for diminished immunity in diabetic patients, including impaired polymorphonuclear leukocyte phagocytic functions. In this regard, a recent study using a mouse model of cystic fibrosis-related diabetes suggested that hyperglycemia leads

to reduced bacterial clearance from the lungs, despite the formation of a robust inflammatory response [16].

Taking these data into consideration, it is interesting that Moretti *et al.* [13] reported that all of the patients admitted for AECOPD, who presented with elevated blood glucose levels and failed noninvasive ventilation, developed pulmonary infections that may have contributed to poor outcome. Therefore, susceptibility to bacterial infection could represent a life-threatening complication associated with hyperglycemia in COPD patients with diabetes.

#### **The Impact of COPD on Patients with Diabetes:**

**The Effect of Preexisting COPD on Diabetes Manifestation** Even though diabetes has been suggested as a comorbidity that can worsen COPD progression and prognosis, recent evidence also supports that COPD may represent a valuable predictor for the development of diabetes. Indeed, when considering baseline lung function, according to the modified Global Initiative for Obstructive Lung Disease (GOLD) criteria, subjects with GOLD stage 3 or 4 COPD had a higher prevalence of diabetes, a result later confirmed by another study [17].

Thus, COPD appears to constitute an important risk factor for developing T2DM, and several studies have identified that the prevalence of diabetes is higher in COPD patients [18]. Over a follow-up period of 20.9 years, the Normative Aging Study found that FVC, FEV<sub>1</sub> and maximal midexpiratory flow rate (MMEF) were associated with insulin resistance. Likewise, 6 other studies, which included follow-ups of 4–13.9 years, observed that impaired lung function is a predictor of diabetes [19]. Nevertheless, although an association between reduced pulmonary function and the incidence of diabetes was observed by analysis of data from the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, a link between COPD and diabetes could not be confirmed [20].

A later report by Wannamethee *et al.* [21] concluded that while restrictive impairment of lung function was associated with the incidence of T2DM, obstructive impairment was not. Notably, 1 study did not observe any increase in the incidence of diabetes in COPD patients; this could have resulted from the large population of underweight individuals in the cohort.

#### **Systemic Inflammation in Metabolic Syndrome and the Link to COPD:**

A plausible explanation for the association of COPD and T2DM incidence may be that COPD leads to

diminished physical activity and the progressive development of metabolic syndrome. In fact, Park and Larson [22] recently reported that over half of the COPD patients in their study presented with metabolic syndrome, with greater physical activity and less sedentary time being associated with lower rates of this comorbidity. Nevertheless, it was also proposed that the increased rates of metabolic syndrome in COPD patients could be linked to systemic inflammation, supporting a more primary and direct role for COPD pathogenesis in the induction of T2DM [23].

Indeed, insulin resistance has been linked to inflammatory mediators (e.g. IL-6 and TNF $\alpha$  soluble receptor-I) in patients with COPD. Moreover, low grade systemic inflammation has been shown to predict the incidence of T2DM. Takenaka *et al.* [24] recently developed a mouse model in which IL-18 was expressed in the lungs to induce COPD-like symptoms. Interestingly, these mice developed impaired glucose tolerance over time, supporting a direct link between pulmonary inflammation and diabetes. Nevertheless, exposure to in-erefore, future studies on the role of inflammation in the pathogenesis of diabetes should expand our understanding of the potential interaction of inflammatory processes that occur during COPD as well as the development and progression of diabetes.

#### **The Role of Corticosteroid Therapy in Diabetes Onset and Progression:**

Another possible mechanistic explanation for the increased prevalence of diabetes in COPD patients relates to therapeutic interventions for AECOPD. Current international guidelines suggest a course of at least 7 days of systemic glucocorticoid therapy for the management of AECOPD, and high doses of inhaled corticosteroids are frequently used. Although the short-term benefits of these treatments are clear, it is known that prolonged exposure to corticosteroids can lead to substantial side effects in COPD patients and even death. In this respect, there is evidence to support the notion that steroid therapy for COPD can lead to the development or worsening of diabetes. [25]

A recent retrospective study of claims data from the Australian Government Department of Veterans' Affairs revealed that patients with both diabetes and COPD display an increased risk of diabetes-related hospitalizations upon high-dose corticosteroid therapy. Therefore, the use of corticosteroids might not be recommended in diabetic patients due to the potential for a dose-dependent augmentation in blood

glucose levels and an increased risk of diabetes progression [26].

The Department's cooperative study group found that hyperglycemia occurred significantly more often in glucocorticoid-treated AECOPD patients than in controls, with rehospitalization rates due to serious infections being higher in the long-term-steroid treatment group. Burt *et al.* [27] describe that treatment with a corticosteroid (prednisolone) led to a circadian cycle in COPD patients, with hyperglycemia occurring in the afternoon and evening. Moreover, the use of inhaled corticosteroids was associated with a 34% increase in the rate of diabetes. Strikingly, this risk for diabetes onset and progression was shown to increase in response to higher inhaled-corticosteroid doses, which are similar to those currently prescribed for COPD treatment [26].

There is also some conflicting data with regard to corticosteroid use and diabetes. Although it was reported that elderly patients using oral corticosteroids showed an increased risk for diabetes, inhaled-corticosteroid users did not. Another investigation involving elderly patients treated with inhaled-corticosteroids observed no link with diabetes. In addition, in a retrospective analysis of double-blind, controlled trials, no connection between corticosteroid use and diabetes could be confirmed. Therefore, whether high-dose and/or long-term steroid use in COPD patients causes T2DM is a topic that will require further investigation. Considering that inhaled-steroid use is usually linked to disease severity and exacerbation frequency, it is possible that medications as well as disease will be found to account for the interaction between inhaled steroids and diabetes in COPD. However, the possible role of steroid therapy in diabetes development and the dangers of corticosteroid use in COPD patients with diabetes as a comorbidity must be considered in the clinical setting. [28]

Although corticosteroids have been well-accepted as one option for the treatment of specific COPD phenotypes, it has been suggested that the optimal dose and the length of the treatment regimen need to be better-defined due to the substantial risk of possible side effects, including diabetes. In this regard, a recent randomized clinical trial, REDUCE (Reduction in the Use of Corticosteroids in Exacerbated COPD), compared short-term (5-day) systemic glucocorticoid treatment with the conventional 14-day treatment in patients presenting to the emergency department with AECOPD [29].

It was found that the 5-day regimen was not inferior to the 14-day treatment with regard to a reexacerbation within 6 months of follow-up. Investigations have now indicated that lowering steroid doses may be appropriate and beneficial in the treatment of COPD. This suggests that the current standard of care could be effectively altered to reduce the duration and dose of treatment, thereby diminishing the potential for therapeutic side effects (e.g. the development of diabetes). However, more investigations will be required to verify the efficacy of these treatment strategies. Increased selectivity with regard to the patients receiving steroid therapy (i.e. the best risk-to-benefit ratio) has been encouraged. Overall, a better understanding of how COPD therapies can influence the development and progression of T2DM as well as the improvement of therapeutic regimens for AECOPD can lead to safer and more effective patient care. [30]

#### **Clinical Implications of the COPD-Diabetes Connection:**

The relationship between T2DM and COPD has significant implications with regard to the clinical management of patients presenting with these morbidities (either alone or in combination). Indeed, both pneumologists and diabetologists must take into account the risks and consequences associated with this potentially important pathophysiological interaction. Considering our current understanding of the link between COPD and T2DM, pneumologists should actively perform screening for T2DM as a frequent comorbidity of COPD. Indeed, COPD patients can be thought of as being at an increased risk for developing diabetes. With regard to treatment, therapeutic options should be carefully and critically contemplated, taking into account the risk-to-benefit ratios associated with the indication for steroid use. It might be beneficial to consider the reduction of diabetes risk as an objective during the selection of therapeutic approaches for COPD. Furthermore, from the point of view of diabetologists, the influence of hyperglycemia on lung function (i.e. lung physiology, inflammatory processes and infection) should be considered in patients with diabetes. Indeed, patients could be routinely screened for lung function as a preliminary measure for determining COPD risk.

In patients with COPD and T2DM, pneumologists and diabetologists should also consider potential treatment interactions associated with the coexistence of these conditions. However, since there is not yet any clear scientific evidence to support general therapeutic recommendations, treatment may be complicated. In this regard, current treatment

strategies may need to be based, first and foremost, on ongoing diabetes care. In particular, special attention should be given to the contraindication to metformin for hypoxic (or imminent) respiratory insufficiency. There is a current need to develop specific guidelines that relate to the effective treatment and therapeutic objectives in patients with COPD and diabetes. For this reason, clinical studies comparing the reciprocal efficacy and safety of existing therapies are warranted. Taken together, considering the interaction of COPD and T2DM, collaboration between pneumologists and diabetologists is fundamental for enhancing patient care.

#### **CONCLUSION:**

According to the World Health Organization, more than 180 million people worldwide have diabetes, with the number expected to double by 2030. The incidence and prevalence of diabetes mellitus (DM) in Asian Indians is increasing at an alarming rate. Diabetes is a micro-macrovascular disease that affects a variety of organs. The pulmonary consequences of diabetes mellitus have been inadequately studied, with mixed outcomes.

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