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A review article on the impact of diabetes mellitus on COPD patients.

Nomathemba Ndebele, Akriti Singh, Tapiwa Chapupu

School of Pharmaceutical Sciences , Lingayas Vidyapeeth University Faridabad -121101 Haryana.

*Corresponding authors :
1.Akriti Sign:School of pharmaceutical sciences, Lingayas vidyapeeth University faridabad ,121101, Haryana
Email id: akriti.rai154400003@gmail.com
Mobile number:+91 83549 60084
2 .Tapiwa Chapupu (University of Zimbabwe) Harare Zimbabwe
Email id:drtapiwa98@gmail.com
Phone number:+263 77 113 1301

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Background
Chronic obstructive pulmonary disease (COPD) is the leading cause of morbidity and mortality worldwide. There is evidence to support a connection between COPD and diabetes mellitus (DM), another common medical disorder. However, additional research is required to improve our knowledge of these relationships and their possible implications. In this study, we investigated the impact of DM on patient outcomes through the clinical course of COPD.

Abstract
This article is a systematic review of the relationship between chronic obstructive pulmonary disease (COPD) and type-2 diabetes mellitus (T2DM). The review found that recent evidence suggests that diabetes can worsen the progression and prognosis of COPD, and that COPD increases the risk of developing T2DM. However, additional research is needed to better understand these relationships and their possible implications. COPD , according to articles in 2007 and 2012 , it was believed to be the third leading cause of death ,which therefor is strongly supported by the death of 2.3 million people in 2019 and it has continued to be one of the most risk factors of mortality till date.
Another condition that is said to be more common in COPD patients is cerebral vascular disease. This is likely due to the fact that these two conditions share risk factors such as ageing, smoking, and genetic predisposition, as well as additional risk factors such as physical inactivity, vasculopathy, and disturbed oxygenation that are made worse by COPD. Despite the clinical importance of cerebrovascular illness in COPD patients, there is little to no literature about how it affects the condition. The prognosis of COPD patients was negatively impacted by concomitant cerebrovascular illness, according to the current study. Although the exact causes of the impairment of lung function in patients with cerebrovascular disease are unknown, it has been reported that these patients also have a higher risk of dysphagia and aspiration pneumonia. The underlying mechanisms are also unknown.

Methods
To successfully conduct the research of this review , I used different articles from the year 2007 till date and other information from MedPub and feedback of research questionnaire from different researchers.

I. Introduction

What is COPD ?

COPD is a group of progressive lung diseases that block the airflow and make it difficult to breathe .These diseases include chronic bronchitis, emphysema, and as well asthma is considered to be part of these diseases. Chronic bronchitis irritates the bronchial tubes which carry air in and out of the lungs .In response they swell up (get inflamed) and mucus which is referred to as phlegm builds up along its lining which late cause narrowing of the air passage hence less air circulation and difficulty in breathing. On the other hand ,emphysema is the breakdown of the alveoli, called as air sacks which transfer oxygen into the blood and takes out the carbon dioxide, therefor the damage of these cause restricted air exchange and transportation.

The common risk factors of COPD are air pollution, aging, respiratory infections,bronchial asthma ,low socio-economic status etc .

DM and MetS are top leading causes of morbidity and mortality world wide. The disturbances in glucose metabolism are more common in COPD group than COPD free individuals.

What are the impacts of COPD?
Symptoms include breathing difficulty, cough, mucus (sputum) production and wheezing. It's typically caused by long-term exposure to irritating gases or particulate matter, most often from cigarette smoke, that is why most people who smoke or are exposed to smoke are in risk of these diseases. People with COPD are at increased risk of developing heart disease, lung cancer and a variety of other conditions associated with COPD.

In patients with chronic obstructive pulmonary disease (COPD), cardiovascular comorbidities are highly prevalent and associated with considerable morbidity and mortality. This coincidence is increasingly seen in context of a “cardiopulmonary continuum” other than being simply attributed to shared risk factors such as cigarette smoking. Overlapping symptoms such as dyspnea or chest pain lead to a worse prognosis due to missed concomitant diagnoses. In most cases medication is often withheld because of unfounded concerns about side effects or adverse effects of the medicines. Despite the frequent coincidence, the current guidelines are still mostly restricted to the management of the individual disease. The future diagnostic and therapeutic strategies have to be therefore guided by an integrative perspective as well as a refined phenotyping of disease entities.

Keywords: COPD, comorbidities, cardiovascular, diagnostics, therapy

When You Have COPD and Type 2 Diabetes
Some people have more than one serious chronic health problem and this pose as a very high risk in managing your treatments more complex. And it may have many life changes to be adjusted to.

If you have chronic obstructive pulmonary disease (COPD), you may also have metabolic syndrome or type 2 diabetes. All of these are chronic health conditions. They have similar risk factors, such as smoking and aging. COPD increases the risk of metabolic syndrome or type 2 diabetes but it doesn't cause them like how other people might think or believe. But many people have both at the same time henceforth COPD can make it harder to control type 2 diabetes .

With COPD, your airways are blocked or collapsed and because of this, air doesn't flow normally in your lungs, it is difficult due to constriction of air passage caused by inflammation. It's harder to breathe this causes shortness of breath and in some serious cases death may occur.

When you have diabetes, your body has trouble using a sugar called glucose or not producing enough as required. The hormone insulin is needed to help your body utilise glucose. With type 2 diabetes and metabolic syndrome, your body doesn't make enough insulin or can't use the insulin it makes. This results in the level of sugar in your blood to become too high. Over time, high blood sugar can damage blood vessels. This can lead to health problems in many parts of the body.

Complications of COPD and type 2 diabetes
Both COPD and type 2 diabetes are treated with medicines(drugs). People with both type 2 diabetes and COPD may find it hard to manage all of the medicines they need at the same time,and also some of the medicines are incompatiblethat is ,they may affect each other in a way that can be very harmful ,which you need to report any kind of adverse effects or abnormal observations. Your healthcare providers may need to change the medicines you take and how much you take as well as to advise on which kind of medicines to take which may not cause these adverse effects.

Also, type 2 diabetes can worsen the condition of COPD. High blood sugar can affect the blood vessels in your lungs and over time the damage caused to the blood vessels can make COPD symptoms worse.

COPD can make it harder to control type 2 diabetes. COPD can make you feel less able to do physical activity because of shortness of breathe which makes the body lack oxygen. This can make your blood sugar hard to control. Getting physically activite helps to make your blood sugar go down or lowers blood sugar . And some COPD medicines, such as steroids you take by mouth or high doses of inhaled steroids, may complicate the control of one's level of blood sugar.

Managing both COPD and type 2 diabetes
Metabolic syndrome, type 2 diabetes, and COPD are ongoing health problems and one has to work with their healthcare providers and follow a proper plan to manage these conditions. Here are some steps one may take to improve their symptoms of COPD and type 2 diabetes:

Quitting of smoking. Smoking is the absolute main cause of COPD and it increases your risk of diabetes and other associated disease. Both smoking and diabetes harm blood vessels which is a very high risk of death .Quitting can help make your symptoms better and reduce your risk of other problems that may come along. Do ask your provider about things that can help you quit they will provide with adequate and useful information.

Watching your blood sugar. If you have COPD and diabetes, managing your blood sugar is very important. Alway check and record your blood sugar levels as often as advised by your medical advisor. This will help show changes in your blood sugar that may need attention and change in treatment or improvement.Health care provider can assist you to know what your ideal blood sugar range is. They can also teach you what to do if your blood sugar is too high or too low.

Take your medicines. Medicines help treat both diabetes and COPD and are advisable and should be properly taken as prescribed by the physician. They can also reduce the chances that you will have serious complications that may be requiring medical attention from time to time. Take your medicines every day as directed by your pharmacist,doctor , physician or any qualified personnel that has prescribed. Always talk with your provider first and ask where you do not understand , report every unnusual symptoms. They can help you change types or doses of medicines if needed.

Check in with your healthcare team. COPD and diabetes need to be closely managed with your medical advisor so one has to be very attentive and keeping all appointments. Contact your healthcare provider when you have any queries or concerning symptoms or questions. Make sure you know how to contact your healthcare team after office hours and on weekends and holidays.

Making lifestyle changes
An important part of managing diabetes, as well as your overall health, is to keep a healthy weight. Here are ways to do that:

Eat healthy foods. Center your diet on more fruits, vegetables, lean proteins (meat, fish, nuts), and whole grains. These foods are high in nutrition and low in fat and calories. Your healthcare provider or a dietician can help you make nutrition changes.

Exercise. Physical activity lowers your blood sugar. It helps your body need less insulin. Ask your healthcare provider to OK your exercise plan before you start.

Lose weight if needed. If you are overweight, losing even a few pounds can improve your blood sugar. Your healthcare team can help you lose weight in a healthy way.

Keywords that have been used: chronic obstructive pulmonary disease, diabetes, hyperglycemia, inflammation, oxidative stress, insulin, metabolism

COPD and hormonal dysregulation
From theoretical point of view ,the alterations in insulin opposing homornes can explain the relation between the development of COPD and dysglycemia .It also has to be noted that the evidence is scant and very controversial . We will discuss the data on COPD and hormones which are associated with MetS and type 2 diabetes .Some reports have been found which link the abnormalties in androgen metabolism with the development of type 2 diabetes mellitus , the exact mechanism of this association is unclear but they maybe related to beneficial effects of testosterone on weight ,insulin sensitivity and modulation of inflammation .
Svartberg et al showed that men with lower testosterone had lower numbers of FEV1 and FVC independently from potential confounders .Laghi et al enrolled 101 patients with COPD and measured both free and total testosterone which they later found out through their research that approximately 40% of patients with COPD were not producing enough testosterone ,they were hypogonadal ,however they could not find any association between testosterone levels and pulmonary function. The prevalence of hypogonadism in patients with COPD has shown to be greater than the COPD free individuals .However the studies of Laghi et al and Van Vliet et al showed that hypogonadism was associated with decreased physical endurance muscle weakness and proinflammatory state among the patients with pulmonary diseases(COPD).
COPD, systemic inflammation and oxidative stress, As in many other chronic medical conditions, COPD is associated with low grade systemic inflammation. Various factors can contribute to this finding such as the spill of inflammatory mediators from the pulmonary system into the circulation, hypoxia, effects of obesity and hormonaldisturbances.
Current evidence suggests that excessive oxidative stress can be a risk factor for new onset type 2 DM and conversely, oxidative stress may be a consequence of new onset type 2 DM . COPD as well as other pathologies, in which hypoxia is a feature is associated with an excessive oxidative state . The reader is referred to a comprehensive review of hypoxia and metabolism for a more detailed discussion of this topic .It is believed that inflammation increases the risk of future type 2 DM. Pradhan et al. studied 27,628 females to assess the impact of inflammatory biomarkers on the new onset type 2 DM . They group found that the highest quartile of IL-6 and CRP gave a RR of 2.3 (95% CI 0.9-5.6) and 4.4 (95% CI 1.5-12.0) respectively. Spranger et al., studied 27,548 individuals to assess the relationship between inflammation and new onset type 2DM .
These researchers found that interleukin-1beta (IL-1β) and IL-6 may be useful predictors of the development of new onset type 2 DM.

What is the link between COPD and Type 1 and 2 Diabetes Mellitus: could there be a relationship between Diabetes and COPD?, and how do these comorbidities have an impact on each other .

Chronic obstructive pulmonary disease (COPD) patients frequently suffer from multiple comorbidities, resulting in poor outcomes for these patients. Diabetes is observed at a higher frequency in COPD patients than in the general population. Both type 1 and 2 diabetes mellitus are associated with pulmonary complications, and similar therapeutic strategies are proposed to treat these conditions. Epidemiological studies and disease models have increased our knowledge of these clinical associations. Several recent genome-wide association studies have identified positive genetic

correlations between lung function and obesity, possibly due to alterations in genes linked to cell proliferation; embryo, skeletal, and tissue development; and regulation of gene expression. These studies suggest that genetic predisposition, in addition to weight gain, can influence lung function.

Cigarette smoke exposure can also influence the differential methylation of CpG sites in genes linked to diabetes and COPD, and smoke-related single nucleotide polymorphisms are associated with resting heart rate and coronary artery disease. Despite the vast literature on clinical disease association, little direct mechanistic evidence is currently available demonstrating that either disease influences the progression of the other, but common pharmacological approaches could slow the progression of these diseases. Here, we review the clinical and scientific literature to discuss whether mechanisms beyond preexisting conditions, lifestyle, and weight gain contribute to the development of COPD.

Lifestyle risk factors are considered central to the development of type 1 and 2 diabetes mellitus and chronic obstructive pulmonary disease .Hence daily physical activity of COPD patients is reduced in the early phases of the disease, as compared with healthy age-matched controls, and worsens over time . Poor medication adherence is described in patients with these diseases, resulting in increased hospitalization rates. However, a series of clinical studies described herein link COPD and T1D and T2D. Equally, studies in disease models provide mechanistic evidence to suggest that comorbid diabetes and COPD feedback influence the progression of the other disease. This review will focus on the epidemiology, physiology, molecular data, and disease models linking diabetes and COPD.

Epidemiological Evidence Linking COPD to T1D

The prevalence of T1D was previously reported to be increasing over the past decade . Reduced total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLCO), pulmonary elastic recoil, and end-expiratory lung volume are detected in patients with T1D. This impaired lung physiology is inversely correlated with glycated hemoglobin levels . Changes in collagen glycation of lung parenchyma and alveolar microangiopathy may contribute to this altered pulmonary dysfunction. In a small comparative study, T1D patients exhibited normal spirometry and pleural pressure, but a higher dynamic elastance during hypoxia, possibly indicating peripheral airway involvement .

Epidemiological Evidence Linking COPD to T2D

T2D is a leading comorbidity in COPD . A population-based retrospective study from Italy demonstrated a higher prevalence of T2D in COPD patients (18.7%) compared to the general population (10.5%) . In this study, women with COPD were significantly more likely to develop T2D compared to women without COPD . Another population-based study in Taiwan showed that T2D was present in 16% of patients with COPD, and within a 10-year follow-up period, T2D was newly diagnosed in 19% of COPD patients, showing increased prevalence and incidence of the disease. Additionally, the association between diabetes and pulmonary disease did not extend to asthma, according to one prospective cohort study , suggesting a specific interplay between COPD and diabetes.

Hyperglycemia is an independent predictor of poor outcomes in patients admitted to the hospital and intensive care unit (ICU). In a study looking at patients admitted with acute decompensated respiratory failure complicating COPD, baseline hyperglycemia upon presentation was identified as a good predictor of clinical outcomes, determined by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score .Mortality rates are high in patients with COPD, as demonstrated by death in almost 80% of patients within nine years of hospital admission due to acute exacerbation of COPD, and diabetes was associated with decreased long-term survival in these patients . Diabetes and cardiovascular diseases were associated with increased mortality in a cohort of COPD patients, when adjusted for age, gender, and smoking pack-year history .

T1D Affects Specific Lung Function Parameters

T1D is associated with decreased TLC, lung elastic recoil, diffusion capacity to transport carbon monoxide (DLCO), and pulmonary capillary volume . These changes in pulmonary function were present, even in the absence of established pulmonary disease. Non-smokers with T1D who were not previously diagnosed with the pulmonary disease had decreased distance in the 6-minute walk test, forced expiratory volume in one second (FEV1), TLC, and DLCO . Poor glycemic control, duration, and severity of diabetes were associated with worsening lung function, observed by changes in forced vital capacity (FVC) and FEV1 . Patients with higher hemoglobin A1c (HbA1c) have lower FVC, FEV1, vital capacity, and peak expiratory flow (PEF) . These abnormalities can be mitigated

in just three months after correction of hyperglycemia .

Systemic inflammation plays a significant role in the pathogenesis and progression of COPD and diabetes. C-Reactive Protein (CRP) levels are inversely associated with FEV1 and FVC at baseline . These changes are present in both sexes and are independent of smoking, obesity, and the presence of other respiratory pathologies, such as asthma . Lung responses appear to be altered by complications of diabetes, with impaired autonomic nerve function in the lungs of T1D patients . In a study testing the responses of diabetic subjects and non-diabetic controls to hypoxia, hypercapnia, and exercise, approximately 25% of diabetic subjects had evidence of impaired sensitivity to hypoxia or decreased ventilatory response to hypercapnia. More recently, the approach to evaluating autonomic dysfunction using assessing cardiorespiratory function has created a body of evidence that proposes that these abnormalities could potentially be corrected with new interventions .

T2D Affects Specific Lung Function Parameters

The alveolar microvascular function is impaired in T2D non-smokers compared to controlled subjects, as demonstrated by decreased DLCO . When using the German COPD and Systemic Consequences–Comorbidities Network (COSYCONET) cohort, hyperlipidemia (prevalence of 42.9%) is associated with lower intrathoracic gas volume and higher FEV1, when adjusting for risk factors and other comorbidities.

Metabolic Syndrome in COPD

Metabolic syndrome (MetS) represents a major public health challenge and confers a five-fold increase in the risk of T2D and a two-fold increase in the risk of developing cardiovascular disease (CVD) within five to ten years .MetS is defined by a constellation of closely related cardiovascular risk factors, including obesity, altered lipids, increased blood pressure, and impaired fasting glucose . A recent cohort of 7358 adults described the association between MetS and pulmonary function. The risk of MetS was higher in patients with airway obstruction than in those without (odds ratio (OR) 1.47; confidence interval (CI) 1.12–1.92), and after adjusting for body mass index (BMI), central obesity was significantly associated with airflow obstruction (OR 1.43; 95% CI 1.09–1.88) .

According to the International Diabetes Confederation, neither COPD nor cigarette smoking was included as fundamental risk factors of MetS. However, an increased prevalence of MetS is observed in COPD patients compared to the general population (21–62%) . In particular, patients with earlier stages of COPD exhibit the highest prevalence of MetS. COPD patients with MetS often display worsened courses of the disease, as observed by greater percent-predicted FEV1 reduction, increased dyspnea, and greater use of inhaled steroids . Two COPDGene studies found that diabetes is more frequent in subjects with airway disease than emphysema on CT . Therefore, it is warranted to monitor COPD patients without emphysema for diabetes, hypertension, and hyperlipidemia.

II. Discussion

Lifestyle are risk factors considered as central to the development of type 1 and 2 diabetes mellitus (T1D and T2D) and chronic obstructive pulmonary disease (COPD) as discussed on the introduction above. All daily physical activities of COPD patients are reduced in the early phases of the disease, as compared with healthy age-matched controls, and worsens as time passes by. Poor medication adherence is described in patients with these diseases, resulting in increased hospitalization rates. However, a series of clinical studies described herein link COPD and T1D and T2D. Equally, studies in disease models provide mechanistic evidence to suggest that comorbid diabetes and COPD feedback influence the progression of the other disease. This review will focus on the epidemiology, physiology, molecular data, and disease models linking diabetes and COPD and their impact on each other.

Evidence linking COPD to Diabetes

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as fundamental risk factors of MetS. However, an increased prevalence of MetS is observed in COPD patients compared to the general population (21–62%) . In particular, patients with earlier stages of COPD exhibit the highest prevalence of MetS . In the general population, MetS becomes more prevalent with increasing age .COPD patients with MetS often display worsened causes of the disease, as observed by greater percent-predicted FEV1 reduction, increased dyspnea, and greater use of inhaled steroids . Two COPDGene studies found that diabetes is more frequent in subjects with airway disease than emphysema on CT . Therefore, it is warranted to monitor COPD patients without emphysema for diabetes, hypertension, and hyperlipidemia.

Cigarette Smoking in Diabetics

In a cohort study detailed by George et al., after calculating the attributable risk of COPD, cigarette smoke (CS) accounted for 19% of cases in T1D and 30% of cases in T2D, compared to 26% of cases in non-diabetics . While it is important to note that MetS and hyperglycemia are also described as risk factors for reduced lung function in healthy non-smoking subjects , CS may nonetheless play a role in the pathophysiology of COPD in diabetics. A recent large-scale cross-trait GWAS paper investigating genetic overlap between COPD and several cardiac traits (resting heart rate, high blood pressure, coronary artery disease, and stroke) from the UK Biobank, the CARDIoGRAMplusC4D Consortium, and the International Stroke Genetics Consortium demonstrated smoke-related single nucleotide polymorphisms (SNPs) located in the 15q25.1 region that were associated with cigarette smoke usage, resting heart rate, and coronary artery disease . This region was also linked to COPD in a separate study . It is suggested that this smoke-related 15q25.1 region may play a role in the severity of nicotine, alcohol, and opioid dependence , partially due to it containing three nicotinic cholinergic receptor genes (CHRNA5-B4). A non-synonymous single-nucleotide polymorphism of CHRNA5, rs16969968, can result in impaired ciliogenesis and the altered production of inflammatory mediators in airway epithelial cells [43]. Cigarette smoke exposure can also influence differential methylation of CpG sites on genes linked to T2D, such as ANPEP, KCNQ1, and ZMIZ1 .

Alpha-1 Antitrypsin and Diabetes

Several clinical trials were undertaken to investigate the potential for alpha-1 antitrypsin (AAT) infusions as a treatment for diabetes , specifically type 1 diabetes mellitus. Raising blood levels of AAT with augmentation therapy has been reported to prevent T1D development and it prolong islet allograft survival , increase insulin release capacity , and inhibit pancreatic β-cell apoptosis . AAT treatment also significantly reduces HbA1c levels. There is an association between AAT deficiency with an increased risk of developing T2D . High levels of degraded AAT are observed in the urine of T2D patients with diabetic kidney disease . We recently published a review focusing on AAT and diabetes, which can be accessed for further reading on this topic .

Animal Models of T1D and T2D in COPD

There are many studies investigating obesity and pulmonary diseases, but here, we will only discuss T1D and T2D models with noted pulmonary involvement. Alloxan-induced T1D rats are more susceptible to emphysematous lesions in response to porcine pancreatic elastase (PPE) instillation compared to nondiabetic control mice . The diabetic rats had a reduced number of neutrophils in the bronchoalveolar lavage fluid (BALF) and diminished repair of the alveolar walls in response to emphysema. Insulin treatment restored these changes in neutrophil numbers and the magnitude of emphysematous lesi. Mice with cystic fibrosis-related diabetes (CFRD) have increased blood glucose concentration, which is associated with impairment in bacterial clearance from the lung in diabetic mice .Streptozotocin (STZ)-induced hyperglycemia in rats results in lung oxidative stress, as well as changes in lung structure and gas exchange . The same pathomorphological modifications of the lungs, including thickening of the alveolar–capillary barrier, collapsed alveolar epithelium, and destruction of the matrix, are observed in STZ-induced hyperglycemia in hamsters . The structural modifications were more pronounced and developed at a faster rate in hamster models of diabetes associated with hyperlipidemia. Other research groups demonstrated that STZ-induced T1D in rats results in a pulmonary fibrosis phenotype . Therefore, hyperglycemia associated with diabetes likely contributes to the pathophysiology of lung diseases.

The Link between COPD and T1D

Diabetic patients exhibit thickening of the pulmonary basal lamina . Furthermore, T1D patients who have never smoked exhibited thickening of the alveolar-capillary membrane . These morphological features are commonly found in diabetic microangiopathy and hence, may explain the decrease in DLCO in T1D. Similar histopathological

pulmonary changes are also observed in experimental models of T1D . Aside from morphological changes, fibrotic changes in the small airways due to chronic inflammation can progressively result in COPD. TGF-β can trigger fibrotic changes in the lungs in human patients and experimental T1D models . While T1Ds are more susceptible to impaired lung function and structural changes leading to COPD , the exact mechanisms underlying the association between the two diseases are not yet known. Here, i will outline possible mechanism links between these diseases .

Inflammation

Similar to T1D, chronic inflammation is observed in T2D. Individuals with obstructive lung diseases have significantly elevated abdominal adipose tissue , and obesity is common in the early stages of COPD Adipose tissue inflammation is also present in individuals with mild-to-moderate COPD . Furthermore, individuals with COPD have higher levels of plasma CRP compared to control subjects, and CRP levels positively correlate with macrophage infiltration of adipose tissue upon biopsy . Various adipokines, including adiponectin, are associated with worse outcomes in COPD. However, this study had significant confounding factors, with differences in sex, age, pack-years, BMI, methacholine responsiveness, and ethnicity among its group. Obesity increases levels of adipokines and alters cellular immunity. A recent cross-trait genome-wide association study (GWAS), using 457,822 subjects of European ancestry from the UK Biobank, found a positive genetic correlation between BMI and later-onset asthma, with onset at or after 16 years of age . They identified 34 shared loci among 3 obesity-related traits and 2 asthma subtypes and, utilizing an obesity mouse model, identified 2 genes (acyl-coenzyme A oxidase-like (ACOXL) and myosin light chain 6 (MYL6)) playing a significant role in both diseases. Equally, a recent GWAS study utilizing data on 100,285 subjects from the China KadoorieBiobank (and the UK Biobank) identified 9 novel loci for FEV1, 6 for FVC, and 3 for FEV1/FVC linking lung function to obesity.

The biological pathways linking lung function to obesity were cell proliferation; embryo, skeletal, and tissue development; and regulation of gene expression. This study also suggested that BMI had a negative effect on lung function over an eight-year follow-up . These studies suggest that genetic predisposition, in addition to weight gain, can influence lung function. In addition, individuals with T2D are more susceptible to infection, possibly due to the increased risk of skin barrier disruption from diabetic neuropathy and diminished cellular immunity, including suppressed cytokine production and defective phagocytosis .

Insulin resistance could contribute to this diminished cellular immunity in T2D, as insulin administration decreases infection and complication rates in T2D populations . Insulin has anti-inflammatory effects and suppresses ROS production . Insulin also acts through PI3 kinase and ERK pathways to increase the secretion of IL-6 and TNF-α from activated LPS-treated macrophages . Insulin therapy also has direct effects on the lung, inducing prostaglandin-mediated airway smooth muscle contraction . Furthermore, the incretin glucagon-like peptide 1 (GLP-1), responsible for raising insulin during meals, may play a role in ROS and influence the responses for the receptor for advanced glycation end-products (RAGE). GLP-1 receptor agonists have anti-inflammatory benefits in the treatment of bronchial hyperresponsivenessand obesity-related asthma . Additionally, the nod-like receptor, containing a pyrin domain 3 (NLRP3) inflammasome, is linked to the development of COPD and other pulmonary condition. NLRP3 is significantly upregulated in an in vitro model of COPD exacerbation . NLRP3 also participates in obesity-induced inflammation and induces insulin resistance .

Inflammation in the lung affects peripheral energy utilization. For instance, NF-kB-activation in the lung attenuates the suppression of hepatic glucose production by insulin and induces insulin resistance in peripheral tissues . Inflammation in the lung may negatively affect systemic glucose homeostasis by decreasing the recruitment of skeletal muscle capillaries that deliver glucose and insulin to myocytes, thereby increasing blood glucose levels .

Hyperglycemia and Hyperinsulinemia

High sucrose intake negatively affects lung mechanics and alveolar septal composition in mice, causing pulmonary extracellular matrix remodeling and reduced elasticity . Hyperglycemic individuals exhibit elevated glucose concentrations in nasal secretions compared tonormoglycemicindividuals . High airway glucose may foster a favorable environment for microbial colonization, with

glucose in bronchial aspirates increasing the risk of respiratory methicillin-resistant Staphylococcus aureus in intubated patients . Hyperglycemia can enhance the contractility of airway smooth muscle via the Rho-associated-coil-containing protein kinase pathway, intracellular calcium releases, and phosphorylation of myosin-targeting subunit-1 .

AGEs are formed as a consequence of chronic hyperglycemia via non-specific glycation and deposited throughout the body, leading to serious complications, such as endothelial cell disruption with subsequent micro-and microvasculature damage and, ultimately, organ failure . In the lung, microvascular and parenchymal changes induce systemic hypoxia and dysregulate energy metabolism. AGEs also exert potent signaling activity when bound to RAGEs. AGE-RAGE complexing induces the expression of inflammatory genes in target cells via the NF-kB pathway . Similar to T1D, sustained activation of the NF-kBpathway is observed in T2D . In addition, AGEs also increase plasma CRP and TNFα secretion from mononuclear cells in individuals with T2D . RAGE is overexpressed in the airway epithelium and smooth muscle of patients with COPD . The role of AGE and RAGE in T2D and COPD require further exploration, but represents mechanistic areas of interaction for both diseases. Recently, a meta-analysis suggested that lower soluble RAGE is a biomarker for the presence of emphysema and airflow obstruction.

Treatment of diabetes mellitus and COPD

Metformin

Metformin, is undoubtedly the most common antidiabetic drug, recommended as the first-line therapy for T2D due to its efficacy, safety, and beneficial effects of reducing HbA1C levels and weight.It is generally tolerable and has favorable cost . Moreover, it reduces cardiovascular (CV) mortality, all-cause mortality, and CV events in T2D patients with coronary artery disease (CAD), but not in non-diabetic patients with CAD or with a history of myocardial infarction (MI) . Interestingly, a recent retrospective study demonstrated that metformin treatment for 2 years improved survival rates in COPD patients with T2D. Equally, Mendy et al. found a reduction in mortality of patients with chronic lower respiratory diseases treated with metformin . Metformin was piloted as therapy for many conditions outside of diabetes, including treatment of severe COPD exacerbations . Metformin inhibits proinflammatory NF-kB signaling in human vascular wall cells , potentially dampening lung microvascular complications of T2D. Metformin improves glycemic control in T2D patients and therefore, reduces the formation of AGEs, but additionally, it is an effective scavenger of AGEs . Another recent animal study suggested that activation of 5′-adenosine monophosphate-activated protein kinase (AMPK) by metformin could reduce abnormal inflammatory responses in mice with elastase-induced emphysema, as well as cellular senescence .

In COPD, changes to the aero-digestive microbiome are apparent and are associated with disease progression and exacerbations . Metformin is known to change the composition of gut microbiota, induce improved insulin resistance, and decreased tissue inflammation . Additionally, metformin reduces the frequency of lung infections, as demonstrated by the reduction in the glucose-induced growth of Staphylococcus aureus. A study by Wishwanath et al. highlighted the potential use of metformin to reduce the hyperglycemia-induced growth of Pseudomonas aeruginosa. Metformin was also found to enhance the macrophage bactericidal activity and improve survival in Legionella pneumonia . Osteoporosis is more prevalent in patients with advanced COPD due to the direct effect of inhaled or oral corticosteroids. Metformin has anti-inflammatory properties and can decrease the prevalence of osteoporosis in patients with GOLD group D COPD .

Metformin may improve health status, symptoms, hospitalizations, and mortality in patients with COPD and T2D . In an unmatched cohort study in Taiwan, T2D patients who had used metformin as an anti-diabetic agent were less likely to develop COPD, with a hazard ratio (HR) of 0.56 (95% CI 0.537–0.584) . In a prospective open-label trial of patients with moderate and severe COPD who also had T2D, the use of metformin showed improvement in symptoms and transitional dyspnea index scores compared to the baseline . However, physiological outcomes, including PFTs and exhaled nitric oxide, were unchanged in this study . Metformin was also studied regarding COPD exacerbations in patients without T2D, but failed to demonstrate any improvement in blood glucose control, nor effects on CRP or clinical outcomes in the non-diabetic population . A recent study in Taiwan suggested that metformin use in patients with T2D and COPD was associated with higher risks of pneumonia, hospitalization for COPD, and invasive mechanical ventilation. However, a recent observational study demonstrated that metformin

use was associated with lesser emphysema progression over time in humans , possibly due to metformin protecting against smoke-induced lung, renal, and muscle injury, mitochondrial dysfunction, and ER stress in mice.

There appears to be mounting evidence of common signaling and genetic signature links between COPD, T1D, and T2D. Promisingly, treatments for these isolated conditions seem to have broad-acting effects that ameliorate COPD and diabetes symptoms and slow disease progression. Given the alarmingly increasing burden of COPD and diabetes worldwide, identification of modifiable risk factors, intervention options, and novel therapeutic options are of interest.DM therapies other than insulin and pulmonary function.

As discussed above insulin therapy may improve DLCO ,which acts as a surrogate marker of alveolar capillary function. However, inhaled insulin is not generally recommended for widespread use, because of concerns about poor absorption and theoretically plausible side effects.Kim et al. retrospectively analyzed the data from 61patients with type 2 DM with a concomitant diagnosis of COPD . These investigators showed that treatment with an oral insulin sensitizer, such as metformin or thiazolidinedione improved FVC in the recruited individuals; this observation was thought to be due to improved respiratory muscle function. However, this study was critically reviewed and potential limitations were highlighted . From a theoretical point of view, anti-diabetic medications may improve endothelial function , and may also via this mechanism improve thefunctionality of pulmonary vasculature and gas diffusion.

Moreover, anti-diabetic agents have been shown to be associated with a decreased risk of lung cancer in Taiwanese adults . This is particularly relevant, since COPD is considered to be a risk factor for lung cancer independently from smoking . Indeed, metformin can prevent tobacco induced lung carcinogenesis and can activate apoptosis of lung cancer cells. As was shown by Tan et al., metformin may improve the efficacy of chemotherapy targeted against non-small lung cancer in patients with type 2 DM .Metformin may be beneficial in the prevention of cancer general, in patients with type 2 DM and may in fact decrease mortality in patients with cancer and concomitant type 2 DM. However, Bodmer et al. failed to find any effect of metformin administration on the risk of lung cancer .Furthermore, metformin has been shown to ameliorate ventilator induced lung injury, recently demonstrated in a rabbit model.

DM were associated with reduced values of FEV1.Researchers from Australia studied the data from the Fremantle Diabetes Study and showed that DM was associated with lower values of FEV1, VC, FVC and peak expiratory flow (PEF) . More importantly, they found that patients with DM had a greater rate of annual decline in pulmonary function and, in addition, that, DM related airflow limitation was associated withincreased mortality.
McKeever et al. analyzed data from the Third National Health and Nutrition Examination Survey to study the association between glucose control and lung function. They showed that patients with DM had lower values of FEV1 and FVC, but not a decrease in the ratio of FEV1 to FVC. It is very importantto note that the poor control of DM was associated with worse pulmonary function. Litonjua et al. analyzed data from the Normative Aging Study. They demonstrated that patients with DM had lower FEV1and FVC values, even after adjustment for age, gender,smoking, height and weight. However, the presence of DM was not associated with an accelerated decline ofpulmonary function in comparison with patients without DM.

Based on the above data, two major possibilities exist: either that, DM independently contributesto the pathophysiology of accelerated decline in pulmonary function or that DM is just a marker for decreased performance of respiratory muscles and physical endurance.

III. Conclusion

Impact of DM on the COPD outcome

As I have mentioned above, the presence of COPD is associated with an increased risk of comorbid diseases and DM in particular . Comorbid diseases including DM increase the risk of COPD exacerbation and mortality and as shown by Gan et al. and others, the risk of DM development is associated with elevated fibrinogen and other markers of inflammation. In fact, this prion-flammatory state may act as an independent risk factor and predictor for COPD exacerbations .Interestingly, a lower DLCO is associated with an increased risk of COPD exacerbation, and as discussed above, diabetes mellitus can be considered as a risk factor for the development of alveolar problems of inflammation. Dahl et al. showed that elevated CRP levels increased the risk of COPD flares . Thus, DM may aggravate the disease course via its proinflammatory profile.

It should be emphasized that patients with frequent COPD exacerbation have a much more rapid disease progression and related mortality, which gives a particular attention to this clinical group .On the other hand, all types of DM are associated with a significantly increased risk of infections, such as pneumonia and bronchitis and other diseases. DM that is associated with hyperglycemia may increase the risk of pulmonary infections by making glucose present in the respiratory tree, which in turn predisposes to an infectious complication . On the other hand, airway inflammation can increase local glucose availability, thus causing a vicious cycle. As shown by Phillips et al., glucose in the bronchial tree significantly increased the risk of methicillin resistant staphylococcus aureus (MRSA) infections in mechanically ventilated patients . MRSA infections are well known for difficulties in management and high rates of related morbidity and mortality .McAlister et al. studied the data from 2,471 patients admitted to hospital with community acquired pneumonia (CAP) and analyzed the impact of hyperglycemia on admission to CAP outcomes [206]. These investigators showed that admission glucose levels >11.0 mmol/l were associated with a greater level of in hospital mortality and morbidity. As mentioned previously, researchersfrom China demonstrated a positive association betweenIR, hyperglycemia and worsened outcomes during COPD exacerbation .Baker et al. analyzed the data from 284 patients admitted to hospital with COPD exacerbation .Enrolled patients were subdivided into four groups according to their glucose levels:<6.0 mmol/l, 6.0-6.9 mmol/l, 7.0-8.9 mmol/l and >9.0 mmol/l. This group demonstrated that all levels of increase in glucose were associated with increased COPD related morbidity and mortality.

Chakrabarti et al. studied 88 patients with COPD exacerbation, which required the initiation of noninvasive lung ventilation to assess the impact of glucose control on disease outcomes . These researchers showed that hyperglycemia may be a clinically useful predictor of poor outcomes among patients with severe COPD flare up requiring non-invasive ventilation. Interesting findings were found by Küpeli et al., who studied 106 patients with COPD, including 29 with MetS to test the impact of MetS on COPD exacerbation . It was shown that patients with MetS had a higher rate of COPD flares, and this was related to an increase in fasting glucose, triglyceride level and CRP. COPD, MetS and DM are common and underdiagnosed medical conditions which fairly raises awareness of these patients.

It was predicted that COPD will be the third leading cause of death worldwide by 2020 which thereof became true and this must raise awareness for better attention treatment.Theburden of this disease is even greater if we consider the significant impact of COPD on cardiovascular mortality. COPD may be considered as a novel risk factor for new onset type 2 DM. The pathophysiology of this is likely to be very complex with several factors being involved which may include, inflammation and oxidative stress, administration of glucocorticosteroids, COPD related skeletal muscle dysfunction and abnormalities in adipokine metabolism etc. However, COPD should not be considered as a risk factor for type 1 DM, because of the unique pathophysiology of type 1 DM and different ages at disease presentation.

On the other hand, diabetes may act as an independent factor negatively affecting lung structure and function. Diabetes can cause muscle and neuronal damagewhich is relevant to deficient function of respiratory muscles. Moreover, diabetes is independently associated with lower physical performance, which can be disabling for patients with COPD, who already have some limitation in physical performance. DM is able to detrimentally affect alveolar capillary membrane and decrease DLCO, similarly to other microangiopathic complications, such as diabetic nephropathy. Furthermore, DM is associated with the presence of glucose in airway secretions, and this may contribute to the increased risk of pulmonary infections seen in diabetics. MetS can increase the risk of COPD exacerbation, and diabetes is associated with worsened outcomes of COPD flares. On the top of that, coexistent OSA may increase the risk for type 2 DM in some individuals.

Antihyperglycemic medications may in fact improve DLCO, as has been shown with insulin in patients with DM. However, concerns about safety and pharmacokinetics preclude the recommendation for inhaled insulin to be used at this time. On the other hand, oral antihyperglycemic medications such as metformin and thiazolidinedione may improve FVC in patients with DM. Moreover, metformin has been shown to have antitumor effects and may increase survival in patients with lung cancer. Thus, it is essential to look at COPD as a potential independent risk factor for the incidence of MetS and type 2 DM and for a complicated course of DM. Conversely, both types of DM and MetS are associated with a worsened clinical course of COPD and a greater degree of morbidity and mortality.

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