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Diabetes Mellitus as a Determinant of Prognosis in Chronic Obstructive Pulmonary Disease: More than a Coincidence

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Chronic Obstructive Pulmonary Disease (COPD) is among the most urgent public health issues of today. It is currently the third leading cause of death worldwide, taking the lives of more than 3 million people each year, and the incidence of COPD is rising, especially in low- and middle-income countries.[1] In addition to its hallmark and characteristic of progressive airflow obstruction, COPD has long been recognized as involving systemic illness, marked by skeletal muscle impairment, weight loss, osteoporosis, cardiovascular disease, and systemic inflammation. Diabetes Mellitus (DM), especially type 2 DM, is yet another global epidemic, and currently affects more than 500 million people globally, with projections indicating an even sharper increase in incidence in the next two decades. The coexistence of COPD and DM is increasingly recognized as not just coincidental, but rather a clinically relevant and pathophysiological overlapping syndrome that enhances the burden of both diseases.[2]

The biological connection between COPD and DM is mainly mediated by systemic inflammation and oxidative stress. COPD has long been accepted as a smoking-related disease, but has now been classified as a systemic inflammatory disease. Circulating markers (e.g., TNF-α, IL-6, and C-reactive protein) are consistently reported to be elevated in COPD and have been implicated in the development of insulin resistance, impaired glucose tolerance, and pancreatic β-cell dysfunction. As a result, the chronic inflammatory environment present in COPD provides a microenvironment for DM. Conversely, chronic hyperglycemia in diabetes creates advanced glycation end products, causes endothelial dysfunction, and promotes oxidative stress, which continues to result in airway damage and impaired repair.[3] This bi-directional amplification provides an explanation for the observation that patients who have both conditions have worse disease and outcomes when compared to patients who have either condition alone.

The structural and functional consequences of DM on the lung are significant. Pulmonary microangiopathy in diabetic subjects results in impaired alveolar-capillary gas exchange and loss of lung elastic recoil. Epidemiological studies show that diabetics, even without overt lung disease, have lower forced expiratory volume (FEV_1) and vital capacity than non-diabetic individuals. In COPD patients, this decline is even greater: longitudinal data indicate diabetic COPD patients lose lung function at nearly twice the rate of non-diabetic COPD patients, even after accounting for smoking, age, and cardiovascular comorbidities.[4,5] This accelerated decline results in greater symptom burden, reduced exercise tolerance, and decreased long-term survival.

Immune dysregulation adds complexity to this interaction. Hyperglycemia affects neutrophils, macrophages, and T cells, impairing chemotaxis, phagocytosis, and microbial killing. In COPD, where airway colonization and recurrent infections are

already drivers of exacerbations, that impairment may add significantly to the frequency and severity of acute episodes. Clinical studies show that COPD patients with DM experience an increased frequency of exacerbations and longer hospital stays and have an increased risk of requiring admission to an intensive care unit compared to those without DM.[6] In addition, there is a direct relation with poor glycemic control to worse outcomes during exacerbations, including higher mortality rates in those with high blood glucose levels at the time of presentation.

Interactions between treatments add another layer of complexity. Systemic corticosteroids, an important treatment in flare-ups of acute COPD, will often negatively impact glucose metabolism by increasing insulin resistance and increasing liver glucose generation. As a consequence, anti-diabetic medications may need to be adjusted, which also increases the risk of hyperglycemia-related adverse events if patients are hospitalized. On the other hand, recent investigations suggest that some anti-diabetic medications may have potential benefits for the lungs. Metformin, the first-line treatment for type 2 diabetes, exhibits both anti-inflammatory and antioxidant effects in experimental models. There is also some evidence from observational studies that metformin users have lower rates of exacerbations in their COPD.[7] Thiazolidinediones, while infrequently utilized, also exhibit anti-inflammatory effects that may be beneficial in COPD management, although their use is not without safety concerns. As a result, the potential dual benefit of this class of anti-diabetic medications may present a significant opportunity for future research and clinical applications.

The epidemiology of COPD-DM overlap highlights the scope of the challenge. Diabetes occurs in 10–20% of COPD patients, though prevalence varies by region, age, and smoking history; in specific groups, such as older adults with several comorbidities, prevalence can reach 30% or more. Diabetes in COPD patients appears as either a pre-existing condition or develops after COPD diagnosis. COPD patients are more likely than the general population to develop diabetes during follow-up, due to systemic inflammation, shared risk factors (such as smoking and inactivity), and the diabetogenic effects of corticosteroids. Key findings from Ho et al. show that COPD patients with pre-existing diabetes face a 24% higher risk of all-cause mortality, and those developing diabetes after COPD diagnosis also have increased mortality risk.[3] Thus, diabetes is a significant determinant of prognosis in COPD, not merely a coincidental comorbidity.

In terms of impact on clinical practice, these findings are significant. First, regular screening for diabetes in individuals with COPD should be a routine part of their care. This is especially important in individuals at high risk for diabetes, such as those who are obese, hypertensive, or have a past history of corticosteroid use for their COPD. Recognizing diabetes early will allow individuals to better control their blood sugar levels and possibly lower the risk of developing complications from their COPD. Second, managing COPD in parallel with metabolic health will require the involvement of multiple healthcare professionals, including the patient's pulmonologist, endocrinologist, dietitian, and rehabilitation specialist. This will help ensure all facets of a patient's health can be addressed in parallel to optimize results. Evidence in the literature suggests that diet modifications, routine physical activity, and smoking cessation are effective interventions to address both metabolic control and respiratory function.

Careful consideration should also be given to medication selection. For patients with COPD and diabetes, focus should remain on anti-diabetic agents that neither worsen respiratory symptoms nor increase infection risk. Metformin is likely the most reasonable first-line agent due to its potential anti-inflammatory effects. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2is) are also viable options though less studied in COPD and may offer cardiovascular and weight loss benefits relevant to a multimorbid population.[8] If systemic corticosteroids are necessary for acute COPD exacerbations, ensure glucose is closely monitored and anti-diabetic medications are adjusted as needed to manage hyperglycemia and minimize complications.

From a policy perspective, the multiple burdens of COPD and DM present a significant challenge to healthcare systems. In terms of healthcare use and expenditures, both COPD and DM are costly diseases, and their coexistence only intensifies the impact on healthcare systems.[9] Patients with COPD exacerbation are admitted to the hospital for longer and more expensive treatment, and in addition, patients with COPD and diabetes experience higher rates of readmissions. Therefore, care pathways that explicitly consider multimorbidity should be prioritized. COPD clinical practice guidelines have begun to acknowledge the presence of comorbidity; however, diabetes should be more overtly recognized. Likewise, diabetes care frameworks should explicitly include the assessment of lung health, particularly among long-time smokers or individuals with chronic respiratory symptoms.

Our understanding is incomplete and requires urgent attention. Observational studies provide strong evidence that diabetes impacts COPD outcomes, and further studies should evaluate the effects of aggressive glycemic control on improving COPD outcomes. Similarly, additional research into the respiratory effects of different antidiabetic drug classes would be valuable. Determining whether new therapies, such as GLP-1 RAs or SGLT2 inhibitors, may affect the progression of COPD or exacerbation risk could alter clinical practice.[9] Lastly, mechanistic studies investigating the molecular crosstalk

among hyperglycemia, systemic inflammation, and airway remodeling would support the development of effective interventions.

To summarize, the coexistence of COPD and diabetes mellitus is a clinically important combination of two leading noncommunicable diseases. They not only interact additively (a little more than expected) but also with a synergistic effect; therefore, they increase systemic inflammation, accelerate lung function decline, increase risk of infection, and worsen prognosis. Recognizing diabetes as a component of the determinants of outcomes in COPD sets the tone for a shift in clinical practice to provide integrated, holistic care that addresses both respiratory and metabolic health simultaneously. Furthermore, it highlights a critical need to conduct research on developing therapies that simultaneously improve diabetes and COPD, targeting their shared pathophysiological mechanisms. Through an integrated approach, we can begin to reduce the compounded global burden resulting from a cohort of conditions that include both COPD and diabetes.

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