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Editorial

COPD and Metabolic Syndrome: Unanswered Questions and Opportunities for Innovation

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Abbreviations:

6MWD=6-minute walk distance; **BMI**=body mass index; **COPD**=chronic obstructive pulmonary disease; **ECLIPSE**=Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; **FFMI**=fat-free muscle index; **GLP-1 RA**=glucagon-like peptide-1 receptor agonist; **HRQoL**=health-related quality of life; **SGLT2is**=sodium-glucose cotransporter 2 inhibitors; **T2DM**=type 2 diabetes mellitus

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Introduction

The treatment paradigm for patients with chronic obstructive pulmonary disease (COPD) and multimorbidity is shifting from a COPD-centered approach towards an integrated approach, moving away from considering interactions between COPD and a single comorbidity to integrating management based on clusters of comorbidities with common mechanisms and treatment strategies.[1] Aligned with this shifting paradigm, analyses of large data sets have revealed a unique cluster of patients with COPD that have several comorbid conditions comprising the metabolic syndrome, herein referred to as the metabolic-COPD cluster. Multiple analyses have identified that the metabolic-COPD cluster is characterized by persistent systemic inflammation and has been referred to as the "inflamed comorbid" cluster.[2-4] While individual comorbidities in the metabolic-COPD cluster vary slightly between studies, this cluster generally includes obesity, cardiovascular disease, dyslipidemia, hyperglycemia, and hypertension.[2-4]

The metabolic syndrome is defined as having 3 of the following clinical features: elevated waist circumference, hypertriglyceridemia, low high-density lipoprotein, hypertension, or type 2 diabetes mellitus (T2DM). Metabolic syndrome affects approximately 35% of adults in the United States and up to 47% of patients with COPD.[5,6] Additionally, metabolic syndrome is a risk factor for incident cardiovascular disease, a highly prevalent comorbidity in COPD, and all-cause mortality.[7] This perspective will highlight several research gaps related to the metabolic-COPD cluster. Addressing these research gaps will help advance towards integrated management of patients with COPD and multimorbidity.

Outcomes Research in Metabolic Syndrome and COPD

The association between identified metabolic clusters and the impact on COPD outcomes has yielded mixed results. Several studies have used cross-sectional analyses to examine the association between metabolic COPD and health-related quality of life (HRQoL).[2-4] Agusti et al[2] showed that the

Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort participants with persistent inflammation and mild to severe COPD exhibited a metabolic phenotype, with higher body mass index (BMI) and higher prevalence of cardiovascular disease. This group had lower HRQoL. In contrast, Vanfleteren et al[3] found no difference in HRQoL for the metabolic cluster in their cross-sectional single-center study including patients with moderate to severe COPD compared to other clusters (cardiovascular, psychologic, cachectic, and less comorbidity clusters). Rennard et al[4] also analyzed the ECLIPSE cohort, using cluster analysis—a different methodology—to identify a metabolic cluster. Other clusters identified included a moderate-quasi stable cluster (mild COPD without significant progression of emphysema), emphysematous exacerbators, functional emphysema (progression of emphysema with preserved 6-minute walk distance [6WMD]), and a mixed cluster. The metabolic (or inflamed comorbid) cluster had the second lowest quality of life compared to the other clusters.[4] Both the Agusti analysis and the Rennard analysis examined the association between their identified metabolic-COPD group and longitudinal exacerbation and mortality data. In the Agusti analysis, the persistently inflamed metabolic group had a higher annual rate of moderate to severe COPD exacerbations and mortality compared to individuals who were not in this group.[2] In the Rennard analysis, the metabolic cluster also had the lowest survival, but not the highest risk of COPD exacerbation.[2,4] These 3 studies demonstrate an inconsistent impact of the metabolic-COPD cluster on various COPD-related outcomes,[2-4] potentially due to differences in study populations and the severity of COPD studied, the comorbidities comprising the metabolic-COPD clusters, and differences in comparators between studies. Given the high prevalence of metabolic syndrome in COPD, further research is needed using consistent definitions and consistent comparators to determine the impact of the metabolic-COPD cluster on patient outcomes.

The relationship between individual comorbidities that comprise the metabolic-COPD cluster and outcomes is also mixed. Diabetes, a key component of the metabolic syndrome, has been consistently associated with worse survival.[8,9] On the other hand, obesity has been shown in some studies to have a negative effect on COPD outcomes, and in others to have a paradoxical benefit, termed the "obesity paradox."[10-13] In an analysis of the COPD Genetic Epidemiology study that included participants with spirometry-confirmed COPD, progressively higher classes of BMI-defined obesity were associated with reduced 6WMD, worse dyspnea, poorer HRQoL, and increased hospitalized exacerbation.[10] These findings are intuitive from a physiological standpoint, as obesity results in the increased work of breathing and impaired respiratory mechanics.[14,15] In contrast, a cross-sectional retrospective analysis of the Taiwanese Obstructive Lung Disease study found that obesity was associated with decreased exacerbation frequency.[13] In another retrospective analysis of hospitalized older adults (age>65) with COPD identified in administrative claims data, those who were overweight and obese had lower mortality compared to normal weight individuals.[12] Aside from study population differences, one potential reason for these conflicting signals is that BMI may be a poor surrogate for obesity in certain individuals, and other indices, such as fat-free mass index (FFMI), may more accurately reflect body composition.[16] Decline in FFMI, representing true skeletal muscle loss, does in fact consistently correlate with worse COPD-specific outcomes.[17] However, defining obesity by BMI may result in inconsistently measured adiposity in patients, particularly in those with high muscle mass. Furthermore, the type and distribution of adipose tissue impacts subsequent outcomes. In a single-center cohort of former and current smokers, visceral adipose tissue was associated with lower walk distance while subcutaneous adipose tissue was protective and associated with less emphysema progression.[18] To further our understanding of obesity's impact in COPD, more research is needed using precise measures of muscle mass and adiposity and assessing how changes in these measures impact COPD outcomes. This information will provide greater insight into the complex interaction of lean and fat mass and COPD outcomes and help guide safe weight loss in patients who are in the metabolic-COPD cluster.

Intervention Trials in Metabolic Syndrome and COPD

Pharmacological and nonpharmacological interventions to treat metabolic syndrome in the context of COPD are needed. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized the treatment of metabolic syndrome and are increasingly being used to treat T2DM. However, questions remain regarding whether GLP-1 RAs are the ideal medication to treat T2DM in patients with COPD. Foer et al[19] compared treatment with GLP-1 RAs, dipeptidyl peptidase 4 inhibitors, sulfonylureas, and sodium-glucose cotransporter 2 inhibitors (SGLT2is) and the risk for moderate or severe exacerbations in patients with comorbid COPD and T2DM. Based on findings that GLP-1 RAs decrease airway hyperreactivity and mucous hypersecretion in preclinical models, investigators hypothesized that initiation of GLP-1 RAs would lead to fewer exacerbations in COPD patients with diabetes compared to other antihyperglycemic drugs.[20,21] The authors found that compared to sulfonylureas, GLP-1 RAs were consistently associated with a decreased risk of moderate and severe exacerbation, even when accounting for baseline BMI. Unlike in the asthma population, SGLT2is had a protective effective compared to GLP-1RAs in mild COPD, though the mechanism underlying this benefit is unknown. This important study illustrates the ways in which

treatment for T2DM can be customized based on having a COPD comorbidity. These findings need to be confirmed in larger populations, and with clinical trials testing GLP-1 RAs in patients with COPD and metabolic syndrome.

When testing interventions in COPD patients with multimorbidity, it is important that non-COPD–specific outcomes are also closely examined. The Intervention Study in Overweight Patients with COPD tested a low-intensity behavioral weight loss intervention versus usual care among patients with COPD who were overweight or obese.[22] While this pragmatic intervention did not result in clinically meaningful differences in the primary outcome, 6MWD, a statistically significant decrease in the Framingham risk score was identified in the intervention arm.[22] Given the elevated risk of cardiovascular disease in patients with metabolic syndrome and COPD, this reduction in risk is likely to be clinically impactful. Future intervention studies should consider composite primary outcomes, such as cardiopulmonary events, which recognize COPD in the context of multimorbidity to provide a more relevant and holistic measure of effectiveness.

Finally, there is a significant need for interventions to reduce inequities in the prevalence and receipt of treatment for comorbidities included in the metabolic cluster, particularly for Black women. Comparing Black versus Non-Hispanic White women with COPD, Black women have a higher BMI and are more likely to have hypertension, elevated low-density lipoprotein, and diabetes.[23] Among patients with COPD who have an indication for statin therapy, the receipt of statins was 26% lower among Black women compared to White men.[24] While culturally-tailored interventions exist to improve receipt of treatments for metabolic syndrome in Black communities, these interventions are often not adapted to overcome COPD-specific barriers.[25,26] Prior research has shown that managing an index comorbidity that is highly symptomatic, such as COPD, can compete with the time required to receive guideline concordant care for a less symptomatic comorbidity, such as hypertension.[27] These issues are likely even further magnified in situations where patients experience COPD-related symptoms such as breathlessness, combined with structurally mediated barriers such as lack of transportation or close proximity to nutritious foods.

Health Services Research in Metabolic Syndrome and COPD

Management of patients with the metabolic-COPD cluster provides the perfect opportunity to consider alternative care models to optimize care delivery for our patients with COPD. Many common care models in the United States, consisting of asynchronous and fragmented care provided separately by primary care physicians and specialists, do not foster the holistic management needed by our COPD patients. We have highlighted that individualized care is needed, particularly considering the "obesity paradox." Attention is needed to ensure that treatments for metabolic syndrome that result in weight loss also preserve muscle mass. Standard therapy for COPD, such as prednisone for exacerbations, may worsen glycemic control, and recent literature has shown that taking a COPD diagnosis into account can be beneficial in selecting medications to treat T2DM.[19] An integrated care delivery model is likely to benefit patients with barriers to accessing care. A single multidisciplinary clinic, where both pulmonologists and primary care physicians collaboratively care for patients in the same space, could lead to comprehensive care plans with primary care and specialist input. Such collaborative care models exist to provide oncologic care (i.e., tumor board) and integrated primary care and mental health but remain to be developed to meet the needs of our patients with COPD.[28] Studies testing multidisciplinary care alone, and not as part of a bundled intervention that includes other components such as financial interventions or case management, are lacking.[29] Studies are needed to develop and test a multidisciplinary clinic approach to provide real-world guidance on how to care for patients in the metabolic-COPD cluster in a manner that is holistic and individualized.

Conclusions

As the management of COPD shifts away from examining each comorbidity individually, the recognition of comorbidity clusters can aid in providing integrated, holistic care to our COPD patients. Among these clusters, the metabolic-COPD cluster is associated with persistent inflammation, lower HRQoL, and increased all-cause mortality. We have identified several research questions that should be prioritized for this patient population, ranging from developing a consistent definition of the metabolic-COPD cluster, providing a greater understanding of the "obesity paradox," mitigating health inequities in the COPD population, and implementing and testing the effectiveness of multidisciplinary clinics. Tackling these unanswered questions related to the metabolic-COPD cluster will help us advance toward innovative patient-centered approaches to managing the aging, multimorbid COPD population.

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