The "Obesity Paradox" in Chronic Obstructive Pulmonary Disease: Can It Be Resolved?

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More than one third of patients with chronic obstructive pulmonary disease (COPD) are obese (1, 2), and obesity is associated with alterations in immune function, dyslipidemia, and insulin resistance (3, 4). Whether these deleterious systemic changes cause poor outcomes in COPD remains unknown; however, data from the COPDGene study suggest that obesity is associated with reduced 6 minute-walk distance, worse dyspnea, poor quality of life, and an increased risk for hospitalization for exacerbations (1). Despite these compelling data, the associations with quality of life and exacerbation risk were not independent of comorbidities, and other studies suggest that obese patients with COPD may in fact have a lower exacerbation frequency than their lean counterparts (5). Although these contradictory findings about exacerbations are difficult to reconcile, and there are few data about exacerbation severity in overweight patients, the true obesity paradox in COPD appears to be the more consistent observation that obese patients have reduced in-hospital mortality (6, 7). Findings reported in this month's issue of the *AnnalsATS* by Goto and colleagues (pp. 184–191) shed light on this conundrum, but leave the paradox unresolved (8).

The authors present results from a retrospective cohort study of the State Inpatient Databases, including 180,000 patients admitted for exacerbations of COPD, making it the largest study to investigate the effect of obesity on COPD-related outcomes. As compared with nonobese patients, those with obesity had increased use of noninvasive and invasive ventilation and longer length of stay. Not surprisingly, obese patients were also more likely to have diabetes and congestive heart failure, and yet, in adjusted analyses, their risk for in-hospital mortality was statistically the same as for those with normal weight (adjusted odds ratio, 0.86; 95% confidence interval, 0.75–1.00; $P = 0.06$). Although some might argue that these results disprove the COPD–obesity paradox, we interpret the data to mean quite the contrary. These data suggest that an association between obesity and reduced in-hospital mortality during exacerbations is plausible, and perhaps even likely. In fact, the authors' sensitivity analysis in older adults confirmed this protective association after adjustment for comorbidities (adjusted odds ratio, 0.81; 95% confidence interval, 0.68–0.96; $P = 0.01$). Even if one accepts that there was no statistical relationship between obesity and the risk for death, the results still confirm the paradox, as we would expect to see higher (and not comparable) mortality in obese compared with nonobese patients, just as the authors hypothesized.

If we are to accept that an obesity paradox exists in COPD, then what explains it? As the authors suggest, obese patients may receive more intense inpatient treatment, including mechanical ventilation, and may stay in the hospital longer, despite comparable or perhaps even less severe airflow limitation. Whether this "extra treatment" reflects the need to manage obesity-related comorbidities including congestive heart failure or sleep-disordered breathing is not clear and not answered by this study. Alternatively, a higher body mass index may reflect a difference in body composition related to a greater muscle mass, a predictor of better outcomes in COPD, rather than simply more adiposity (9, 10). Finally, there is no paradox for underweight COPD, which has been consistently associated with poor outcomes (11), and is again in the current study.

The study has several strengths, including its very large sample size and use of data from the robust Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. However, there are a number of weaknesses that, although acknowledged by the authors, may confound the results. Despite the contention that administrative coding accurately identifies the presence of COPD and obesity, the absence of spirometry, oxygen use, and body mass index data is problematic. As Barbarito has suggested, obesity leads to mixed ventilatory dysfunction and the potential for overgrading of airflow limitation (12), so many patients may have been misdiagnosed as having COPD when in fact they had reduced lung volumes. In addition, the State Inpatient Databases sample used in the study is geographically diverse, but the 17% prevalence of obesity is low when compared with the United States as a whole (13), and less than half the frequency observed in the Southeast (14), thus raising questions about the generalizability of the findings.

We applaud the authors for tackling this complicated topic and agree with their

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call for further study of the biology and effect of obesity in COPD. The recent *AnnalsATS* supplement summarizing the proceedings of an international meeting focused on the implications of obesity in lung disease highlights its growing scientific recognition (4). However, although basic science research can aid in understanding the mechanisms of adiposity, we cannot determine the true effect of obesity on COPD outcomes without prospective clinical trials targeting overweight and obese subjects to determine the effects of weight loss. Fortunately, the COPD community and the National Heart, Lung, and Blood Institute have recognized this knowledge gap, and the Intervention Study in Overweight Patients with COPD (INSIGHT) is underway (NCT02634268). Still, resolution of the obesity paradox related to mortality seems far away. ■

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