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A Potential New Treatment Option for Asthma in the Setting of Obesity or Insulin Resistance?

The epidemic of obesity now affects ∼42% of U.S. adults, whereas metabolic syndrome affects approximately 37% of adults in the country, including over 60% of obese individuals (1–3). Both disorders can contribute to increased asthma risk and morbidity (4, 5). "Obesity-related asthma," a heterogeneous asthma phenotype, results from various contributing factors and mechanisms, such as insulin resistance and metabolic dysregulation (6). Although there is ongoing research and debate on whether obesity leads to asthma or vice versa (or whether both result from a shared, earlier causal process), the pressing reality is that many obese patients with asthma have a more severe disease that does not fully respond to the usual treatments. Weight loss—whether medically or surgically induced—can lead to improved asthma outcomes, especially if metabolic dysregulation resolves (7, 8). However, weight loss is difficult to achieve and even more challenging to sustain, and therefore identifying better therapeutic options for patients with obese asthma constitutes a critical research need.

In this issue of the *Journal*, Foer and colleagues (pp. 831–840) tackle this need by evaluating the association between glucagon-like peptide-1 receptor agonists (GLP1-RAs) and asthma outcomes (9). Using data from 4,373 patients with type 2 diabetes (T2D) and asthma, they compared asthma exacerbation rates between patients starting GLP1-RAs and those initiating other medications as part of T2D treatment escalation. After adjusting for propensity scores and other covariates, they report that patients starting GLP1-RA therapy have lower asthma exacerbation rates than those initiating sulfonylureas, insulin, SGLT2 inhibitors, or DPP4 inhibitors over a 6-month period. The findings were robust to adjustment for changes in body mass index and HbA1c, suggesting the associations are independent of improvements in weight or glycemic control. Even more importantly, the estimated effect sizes were larger when the analysis was restricted to patients with moderate and severe asthma, and the associations remained significant despite the fact that the sample was markedly smaller. They also report that GLP1-RAs are associated with fewer healthcare encounters for asthma symptoms, although those findings were somewhat less robust in the sensitivity analyses. The study has several important strengths, including the use of detailed clinical data extracted from the electronic record database of a large academic healthcare organization, which allowed the authors to adjust for important covariates at different time points. The large database allowed for the exclusion of numerous comorbidities and conditions that may confound or mimic the diagnosis of asthma, and the authors also took care in adjusting for a propensity score calculated based on the probability of initiating GLP1-RA versus other T2D medications.

The report builds on existing preclinical evidence of a potential role of GLP1 signaling in asthma. GLP1 receptors are expressed in airway epithelium and airway smooth muscle. In murine models of asthma, liraglutide reduces IL-33 release and mucus secretion in response to allergen challenges as well IL-4 and IL-13 production by group 2 innate lymphoid cells (10). In *ex vivo* human airways, GLP1 receptor activation modulates airway hyperreactivity (AHR), and treatment with GLP1-RA exendin-4 prevents AHR in response to both histamine and high glucose concentrations (11). GLP1-RAs

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such as liraglutide or exenatide could therefore tackle obese asthma by treating obesity and insulin resistance but also airway inflammation and AHR. GLP1 receptor–mediated inhibition of NF-κB signaling may also have effects in other lung disorders, including chronic obstructive pulmonary disease and acute lung injury.

One of the main limitations of the current study was the very low frequency of exacerbations in the cohort, which can lead to several issues despite the appropriate use of zero-inflated Poisson regression. Low counts could explain why some sensitivity analyses yielded conflicting results. For instance, some results were nonsignificant when including patients with at least two prescriptions. It is also unclear why patients taking GLP1-RAs had lower asthma exacerbation rates than those on other medications, yet they were at higher risk of having "any" exacerbation during follow-up than patients on SGLT2 inhibitors. Incidence rate ratios (IRRs) can appear quite large, but it is difficult to evaluate how clinically meaningful the differences are. For example, DDP4 inhibitors had an IRR = 2.45 for exacerbations compared with GLP1-RAs, but the raw exacerbation rates were 0.24 versus 0.17 per year (one exacerbation every ∼2.1 vs. ∼2.9 yr, respectively). Beyond the IRR, having an adjusted risk difference (or absolute risk reduction) would have helped better estimate required sample sizes for future, prospective studies of these medications in asthma. Finally, given the sample size available from a large clinical data repository, it would have been helpful to compare GLP1R agonists versus metformin or to evaluate whether both medications offer synergistic advantages. Prior studies have shown that metformin may also improve asthma outcomes in diabetes (12, 13), and the drug was also associated with lower exacerbation rates in this cohort.

Despite these limitations, the study by Foer and colleagues represents a novel and important step in identifying potential new therapeutic agents for obese asthma. A small prospective study in patients with T2D but without respiratory disease found improvements in FEV_1 and FVC among subjects receiving metformin and GLP1-RAs compared with those receiving metformin and insulin (14). Future studies should aim to replicate the findings from these reports in independent populations to assess whether improvements are clinically meaningful and to evaluate these agents in patients with obese asthma without diabetes. Prospective cohorts specifically designed to evaluate the effect of GLP1-RAs on asthma outcomes would overcome some of the limitations of the current study and would help inform the design of eventual clinical trials. ■

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