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Asthma Exacerbations in Individuals on Glucagon-like Peptide-1 Receptor Agonists for Type 2 Diabetes

To the Editor:

We welcome the finding by Foer and colleagues (1) of a statistically significant reduction in asthma exacerbations after the initiation of GLP-1 (glucagon-like peptide-1) therapy versus other medications for type 2 diabetes mellitus. Whereas earlier work had hypothesized that GLP-1 therapy might lead to improved exacerbation frequency and Asthma Control Questionnaire (ACQ) scores if weight loss above the median was achieved (2), the current work points to an effect of GLP-1 therapy independent of its weight loss–promoting properties.

The authors acknowledge that established atherosclerotic cardiovascular disease (ASCVD) could be a confounder where the secondary outcome, asthma symptoms, is concerned but omitted to state whether this may also be true in the case of the primary outcome (asthma exacerbations). Could the authors clarify whether the inclusion of ASCVD in the propensity score affects the primary outcome?

An analysis limited to the human-analog GLP-1R (GLP-1 receptor) agonists (liraglutide, semaglutide, dulaglutide, and albiglutide) may also be useful in excluding any confounding effect by ASCVD, as the authoritative guidelines cited by the authors favor these agents over the exendin-based GLP-1 receptor agonists (exenatide and lixisenatide) when treatment considerations such as ASCVD or weight management (promoting loss or limiting gain) exist.

Pooling GLP-1 analogs and exendin-based GLP-1 agents in the analysis may limit the study, as it is possible that these two subclasses have slightly different actions, particularly where nonincretin effects (which are less well understood) are concerned. For example, some actions of GLP-1 may be receptor independent; this has been proposed to occur in the liver by transmembrane transport of GLP-1 degradation products GLP-1_{9-36}, GLP-1_{28-36}, or GLP-1_{32-36} where adenylyl cyclase and Wnt signaling is consequently activated (3).

The authors selectively note that Asthma Control Test (ACT) and ACQ use symptoms of "shortness of breath" and "wheeze" to measure symptom control and that patients on GLP-1R agonists had fewer associated encounters coded with these symptoms compared with basal insulin and sulfonylurea users. One could equally note that both ACQ and ACT contain an item measuring rescue bronchodilator use, and the exploratory analyses identified no differences across groups compared with GLP-1R agonist users for short-acting β_2-agonist prescriptions during the study period, thus underlining the need for a prospective trial to assess whether GLP-1 therapy results in improvements exceeding the minimal clinically important difference in composite scores, such as the ACT and ACQ, as well as in objective asthma outcomes preferred for regulatory approval, such as FEV_1.

We also observe that this study does not allow for patients to be phenotyped as type 2 high or low. Most of the preclinical studies have focused on the effect of GLP-1 on T-helper type 2 (Th2)-type inflammation—for example in BALB/c mice (4)—and none have modeled obesity. Yet those with the unmet need cited by the authors (i.e., those with asthma unresponsive to inhaled corticosteroids) tend to have a Th2 gene expression signature similar to that of healthy control subjects (Th2-low) (5), the proposed "late-onset nonallergic" phenotype, affecting primarily middle-aged women with obesity. Prospective studies are needed to investigate whether the benefits demonstrated in this study are evenly distributed among those with evidence of type 2 high inflammation and those without. A benefit in this latter group is plausible, as GLP-1 is known to ameliorate both dysregulated arginine metabolism and advanced glycation end-product–mediated inflammation—pathways common to both obesity and asthma pathophysiology (6)—and would begin to address their currently unmet need. ■

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Reply to Watchorn *et al.*

From the Authors:

We appreciate the insightful comments by Watchorn and colleagues in response to our report on the association between asthma exacerbations and GLP-1RA (glucagon-like peptide-1 receptor agonist) use in patients with comorbid asthma and type 2 (T2) diabetes mellitus (T2DM) (1). The intersection of metabolic disease and asthma is a complex and compelling area of study with direct implications for treatment strategies (2) and clinical outcomes (3). Increasingly, work is being done to try to disentangle the confounding effects of body mass index, insulin resistance, and other features of the metabolic syndrome (which also increase the likelihood of cardiovascular disease) in asthma (4). Inclusion of atherosclerotic cardiovascular disease (defined as ⩾1 International Classification of Diseases, ninth edition, or International Classification of Diseases, tenth edition, codes) as a variable in our model did not change the primary outcome, as follows: counts of asthma exacerbations in all comparator groups remained significantly ($P \leqslant 0.05$) higher than in the GLP-1RA user group. Atherosclerotic cardiovascular disease was also not a significant predictor ($P = 0.97$) in the primary outcome model. This is consistent with the clinical context, as asthma symptoms (secondary outcome) may be nonspecific, but asthma exacerbations (defined as corticosteroid prescriptions) may be far less so.

Importantly, the authors also raise the question of mechanism as it relates to the heterogeneity of asthma phenotypes on the inflammatory spectrum. Our study cohort was comprised of adults with asthma and T2DM, with a mean body mass index ranging from 34 to 39, clinical characteristics associated with non-T2 asthma (5). In a lean murine model of allergic airway inflammation, the GLP-1RA liraglutide inhibited T2-inflammation pathways (6). Additional preclinical and clinical investigations are underway in our research groups to determine the actions of GLP-1R agonists in T2 and non-T2 airway inflammation. Obese asthma models and patient-oriented biomarker studies would be helpful in providing additional insight to the question of mechanism and would inform the design of prospective studies. Our retrospective observational study was conducted within the context of routine care and was not designed to compare the effects of GLP-1 analogs with exendin-based GLP-1 agents, which would require much larger sample sizes (particularly for detection of a rare outcome) or a prospective study.

In conclusion, Watchorn and colleagues' letter highlights the need for prospective studies of GLP-1RA therapy using single agents within the class (e.g., GLP-1 analogs or exendin-based therapies) in well-phenotyped asthma populations with outcomes aligned with regulatory approval metrics—we absolutely agree, and we look forward to this unfolding area of investigation. ■

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