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Mechanisms of Obesity-related Asthma: Is Insulin Getting on Your Nerves?

To the Editor:

Obesity increases both the incidence and the severity of asthma. Obese asthmatics experience more frequent exacerbations and often respond poorly to currently available asthma medications, which increases healthcare costs and leads to decreased quality of life. Prevention and management of this difficult disease are complicated by the lack of complete understanding of its underlying molecular mechanisms. Although systemic inflammatory mediators, including IL-1β, IL-4, IL-5, and TNF-α (tumor necrosis factor-α), are increased in obesity and metabolic syndrome, their causal role in obesity-related asthma in humans has not been demonstrated (1). Furthermore, increased bronchoconstriction is independent of airway inflammation in obese animals. Clearly, our existing inflammatory paradigms, which have produced significant therapeutic advances for other phenotypes and/or endotypes of asthma, require reexamination in the context of an obesity-related phenotype.

A recent study by Peters and colleagues (2) shows that insulin resistance is independently associated with airflow limitation, blunted treatment responses, and accelerated lung function decline over time in a SARP-3 (Severe Asthma Research Program–3) cohort. Their analysis demonstrates that effects of excess body mass on chest wall mechanics are unlikely to fully explain this association after correcting for body mass index in regression models. Their findings are consistent with those of previous studies, showing that insulin resistance is associated with increased asthma risk. The causal role of insulin resistance in asthma development is suggested by studies showing that insulin resistance frequently precedes the development of asthma symptoms and is associated with worse lung function in humans.

The authors, and an accompanying editorial (3), proposed several potential mechanisms to explain this relationship among insulin resistance, obesity, and asthma. Overlooked in this discussion, however, is the critical role of hyperinsulinemia in development of airway hyperresponsiveness due to nerve dysfunction. Airway parasympathetic nerves, which provide the dominant control of bronchoconstriction through the release of acetylcholine, become hyperresponsive to airway stimulation in the setting of hyperinsulinemia (4), which is usually a compensatory consequence of insulin resistance. Specifically, high concentrations of circulating insulin increase neuronal acetylcholine release by disrupting presynaptic, inhibitory M_2 muscarinic receptor function on parasympathetic nerves. Loss of M_2 receptor function and subsequent increased acetylcholine release increase bronchoconstriction (5). Experimentally, hyperinsulinemia's effects are attenuated by insulin-lowering agents such as metformin and pioglitazone (4, 6, 7).

Interestingly, in Peters and colleagues' study (2), the magnitude of insulin's effect on lung function decline over time in their longitudinal analyses may have been underrepresented because of their use of HOMA-IR (homeostatic model assessment for insulin resistance) only, which is calculated by multiplying fasting plasma glucose (mg/dl) by serum insulin (mIU/ml) and dividing by 405. On the basis of this formula, the main driver of increased HOMA-IR scores may be elevated insulin concentrations during insulin resistance, such as in the prediabetic or early stages of type 2 diabetes, or markedly elevated blood glucose concentrations due to decreased insulin secretion caused by pancreatic decline, as in the late stage of type 2 diabetes. Thus, using HOMA-IR alone in an analysis of the relationship between metabolic disorders and lung function may miss the opportunity to uncover the association between insulin and reduced lung function, which has been shown before in cross-sectional studies and clinical trials. Further exploration and corroboration of insulin concentration and decline of lung function in clinical trials should therefore be of great interest.

Overall, this study has important clinical implications regarding the independent role of insulin resistance in the decline of lung function in obese asthmatics. Results from Peters and colleagues (2) and other relevant investigations (4, 6, 7) provide a strong rationale for designing clinical trials to test whether inhibiting hyperinsulinemia, both alone and in combination with antagonists of nerve-mediated bronchoconstriction (e.g., tiotropium), is an effective treatment for obesity-related asthma. ■

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Zhenying Nie, M.D., Ph.D.*
Allison D. Fryer, Ph.D.
David B. Jacoby, M.D.
Matthew G. Drake, M.D.
Oregon Health and Science University
Portland, Oregon

*Corresponding author (e-mail: niez@ohsu.edu).

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Impact of Insulin Resistance on Asthma: Is There Truly No Role of "Obesity"?

To the Editor:

Obesity reduces FRC and expiratory reserve volume, with implications for airway closure and $\dot{V}/\dot{Q}$ inequalities, especially during times of stress, such as exercise, when many asthmatics report distressing symptoms (1, 2). Obesity-related reduced FRC may offer a mechanism for increased airway hyperresponsiveness, because airway-parenchymal tethering is reduced at lower lung volumes, making it easier for the airways to constrict in response to stimuli (3). Experimentally, when the chest wall is strapped for nonobese individuals, artificially reducing the FRC, an increase in methacholine-induced airway hyperresponsiveness has been noted; conversely, increasing the FRC has been shown to reduce airway hyperresponsiveness (4). Obesity-related compression of the chest wall is also implicated in increased lung derecruitment, either by small airway closure or alveolar atelectasis, manifesting as a reduced FVC (5). Although similar degrees of lung derecruitment have been found between obese adults without asthma and obese adults with late-onset nonallergic (LONA) asthma, there is lower FVC and increased difficulty in recruiting closed alveolar units with a deep breath as well as higher airway hyperresponsiveness among obese individuals with LONA asthma (5). Mechanisms for differences in airway hyperresponsiveness between obese and nonobese individuals with LONA asthma are not fully defined but include increased airway compliance that predisposes to greater airway collapse under a higher chest wall load (3). Thus, through the mechanism of excess adipose tissue around the chest wall, breathing at lower lung volumes and lung derecruitment could be factors in physiological changes, such as airway hyperresponsiveness or collapse, and could contribute to asthma symptoms and severity.

A recent paper by Peters and colleagues (6) tested the hypothesis that insulin resistance worsens lung function among patients with asthma, independent of body mass index (BMI), using two statistical approaches. First, linear regression controlled for BMI revealed an "independent" significant effect of insulin resistance on lung function. Second, a closer look at the morbidly obese patients revealed lower FEV_1 and FVC among those with severe insulin resistance. The authors concluded that "insulin resistance independently associates with low lung function in asthma, and body mass effects on chest wall mechanics are unlikely to explain this association" (6). A strong correlation was found between BMI and insulin resistance, which warrants caution in result interpretation because of risk of multicollinearity. The authors did not share the results of the correlation matrix of BMI, insulin resistance, lung function outcomes, etc., preventing readers from gaining a preliminary understanding of the bivariate associations among the potential predictors and outcomes. Authors also did not report the standardized β coefficient and R^2 for BMI, insulin resistance, and other relevant predictors in the multiple regression model results, making it difficult to judge the relative importance of each predictor. Even if homeostatic model assessment for insulin resistance (HOMA-IR) were found to have the highest regression coefficient and R^2 value, BMI could remain significant in the final model, a finding that would support a role for chest wall mechanics in reducing lung function. Considering the wide range of BMIs in the >40 category (40–70 kg/m^2) and the heterogeneity of lung function outcomes within each HOMA-IR category, BMI could be exerting a substantial effect that was masked by the HOMA-IR categorizations. One could look at narrower ranges of BMIs (30–35, 35–40, etc.) to see if HOMA-IR continues to influence lung function. To summarize, we contend that although insulin resistance may be a plausible mechanism for worsening lung function, and randomized trials targeting insulin resistance in obese patients with asthma may very well follow to clarify causation, the role of obesity on chest wall mechanics and lung function that has been previously established through robust observational and experimental studies cannot be completely discounted as proposed by Peters and colleagues (6). ■

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Dharini M. Bhammar, Ph.D., M.B. B.S.*
The Ohio State University
Columbus, Ohio

Tony G. Babb, Ph.D.
Texas Health Presbyterian Hospital Dallas and University of Texas Southwestern Medical Center
Dallas, Texas

Menglin Xu, Ph.D.
The Ohio State University
Columbus, Ohio

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