

Diabetes and Glycemic Dysfunction in Asthma



Tianshi David Wu, MD, MHS *Baltimore, Md*

Because of its heterogeneity, investigators have long sought to characterize asthma into distinct phenotypes and endotypes, seeking to gain insight into pathobiology toward development of targeted treatment options. Although studies have differed in their conclusions and classifications, asthma among individuals without allergy and evidence of atopic sensitization, referred to by the variably overlapping terms T2-low asthma, nonallergic asthma, or noneosinophilic asthma, has been consistently identified.¹ Efforts to understand risk factors for severe and poorly controlled asthma, apart from traditional allergic triggers, may be especially relevant to these individuals.

Prediabetes and diabetes have been recently identified as risk factors for asthma exacerbations in adults.²⁻⁴ These conditions clinically manifest as fasting hyperglycemia and, in the case of type 2 diabetes, are characterized by stereotyped elevations in insulin resistance and systemic inflammation. Mechanistic studies have shown that insulin exposure, which is initially increased in those with insulin resistance, causes animal and human airway smooth muscles to adopt a procontractile phenotype and heightens their sensitivity to neurally mediated bronchoconstriction.⁵⁻⁷ Diabetes has also been speculated to precipitate mucus metaplasia through increased availability of beta-catenin.⁸ Hyperglycemia, separate from insulin resistance, favors growth of bacterial organisms and has observational associations with greater risk of respiratory infection.⁹ Such reports provide some evidence that the spectrum of disorders in glucose homeostasis, ranging from clinically silent insulin resistance to diabetes and frank hyperglycemia, may directly impact asthma morbidity.

However, prediabetes and diabetes are often comorbid with obesity and dyslipidemia, other linchpins within the metabolic syndrome. These conditions, with their attendant biochemical, cellular, and physiologic changes, can occur upstream of diabetes and have also been linked with more severe and uncontrolled asthma.¹⁰ In the setting of these complex relationships, carefully designed studies are necessary to distinguish factors that are independent, implying possible benefit from their intervention, and that are dependent, useful for identifying patients at a higher risk for poor outcomes.

In this issue, Yang et al¹¹ shed further light on this question by examining the relationship of glycated hemoglobin (HbA_{1c}) with pulmonary function and asthma exacerbations in the UK

Biobank, a large population study of adult participants recruited from the United Kingdom. HbA_{1c} relates to an individual's average concentration of blood glucose in the previous 3 months, and it is used to both diagnose prediabetes and diabetes and monitor their response to treatment. Readers should note that the HbA_{1c} is reported in this study as mmol/mol, and that a 11 mmol/mol difference corresponds to a 1% difference in HbA_{1c}.¹²

The authors constructed a cross-sectional cohort of 47,606 individuals with asthma but without physician-diagnosed diabetes. Within this cohort, they report a positive association between HbA_{1c} and lifetime odds of an asthma hospitalization and an inverse association between HbA_{1c} and FEV₁ and forced vital capacity, 2 measures of pulmonary function. In categorical analysis, compared with those with HbA_{1c} in the nondiabetic range, individuals with HbA_{1c} in the prediabetic and diabetic range had 68% higher odds of reporting a lifetime asthma hospitalization and a *Z*-score difference of 0.015 in FEV₁ and forced vital capacity. These results were maintained in a sensitivity analysis removing those who smoked greater than 10 pack-years, and with respect to hospitalizations, removing those who reported their asthma hospitalization before their HbA_{1c} measurement.

This study comes with key strengths. The sample size is the largest to date to have examined this question. The population is well characterized, owing to the rigorous study procedures of the UK Biobank, which allowed for better adjustment of relevant confounders including smoking, inflammation, and body mass index. The hospitalization outcome was determined through examination of health record data, which overcomes limitations of participant recall, and it is a particularly relevant measure of asthma morbidity. Finally, the sensitivity analysis excluding those who had asthma hospitalizations in the past, before their HbA_{1c} measurement, did not cause qualitative differences in point estimates despite some loss of statistical significance, which enhances confidence in the directionality of the association.

The exclusion of participants with physician-diagnosed diabetes is a notable design choice. By doing so, the authors better safeguard the validity of the measured HbA_{1c} as a marker of metabolic health. Individuals with diabetes will likely use medications that decrease HbA_{1c} and may also alter health behavior upon diagnosis, introducing pathways that would distort the association under study. However, as a consequence of this decision, the study does not apply to individuals with established diabetes, which has implications for potential populations who may benefit.

There are some important limitations that were appropriately acknowledged by the authors. This includes the restricted age (adults aged 40–69 years) and the cross-sectional study design, especially as it pertains to lung function, which did not incorporate available temporal data within the analytic methods. Perhaps more critically, there was no adjustment for

Division of Pulmonary and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, Md

Conflicts of interest: The author declares no relevant conflicts of interest.

Received for publication July 15, 2020; accepted for publication July 16, 2020.

Corresponding author: Tianshi David Wu, MD, MHS, 1830 East Monument St, 5th Floor, Baltimore, MD 21205. E-mail: twu38@jhmi.edu.

J Allergy Clin Immunol Pract 2020;8:3416-7.
2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2020.07.011>

medication use characteristics and for other forms of metabolic dysregulation, including dyslipidemia and hypertension.

In addition, the lung function differences in this study are suggestive of a restrictive pattern, characterized by a diminished FEV₁ and forced vital capacity without differences in their ratio, rather than an obstructive pattern, which would be more reflective of asthma. This association, which has been consistently reported in diabetes, is hypothesized to reflect pulmonary parenchymal glycation and early fibrosis rather than asthma-related airways disease.¹³ As also acknowledged by the authors, the magnitude of these differences is minor and of uncertain clinical significance.

Taken together with previous work, this study builds upon evidence that disorders of glucose metabolism may increase asthma morbidity. More questions naturally arise: which factors within the regulatory pathway are most important; do these associations apply in patients with clinically silent insulin resistance; what occurs in the presence of other metabolic diseases; and in what time scale can changes be attributed? Such questions are ideally answered in longitudinal studies with specific attention to biological intermediaries relevant to glucose homeostasis. Although certainly compelling, it is premature to consider intervention in these conditions as an option to improve patients with asthma, and more studies are needed.

More broadly, it remains unclear whether “metabolic asthma” exists as a distinct endotype or an epidemiologic phenomenon. Metabolic dysfunction is a complex network of conditions that are often comorbid, many of which have their individual claims on asthma. Disentangling these important concepts is necessary to understand whether intervention in glycemic and metabolic dysfunction can meaningfully improve asthma outcomes.

REFERENCES

1. Fitzpatrick AM, Chipps BE, Holguin F, Woodruff PG. T2-“low” asthma: overview and management strategies. *J Allergy Clin Immunol Pract* 2020;8:452-63.
2. Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, et al. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. *Am J Respir Crit Care Med* 2020;202:973-82.
3. Wu TD, Brigham EP, Keet CA, Brown TT, Hansel NN, McCormack MC. Association between pre-diabetes/diabetes and asthma exacerbations in a claims-based obese asthma cohort. *J Allergy Clin Immunol Pract* 2019;7:1868-1873.e5.
4. Price D, Wilson AM, Chisholm A, Rigazio A, Burden A, Thomas M, et al. Predicting frequent asthma exacerbations using blood eosinophil count and other patient data routinely available in clinical practice. *J Asthma Allergy* 2016;9:1-12.
5. Singh S, Bodas M, Bhatraju NK, Pattniak B, Gheware A, Parameswaran PK, et al. Hyperinsulinemia adversely affects lung structure and function. *Am J Physiol Lung Cell Mol Physiol* 2016;310:L837-45.
6. Nie Z, Jacoby DB, Fryer AD. Hyperinsulinemia potentiates airway responsiveness to parasympathetic nerve stimulation in obese rats. *Am J Respir Cell Mol Biol* 2014;51:251-61.
7. Schaafsma D, McNeill KD, Stelmack GL, Gosens R, Baarsma HA, Dekkers BGJ, et al. Insulin increases the expression of contractile phenotypic markers in airway smooth muscle. *Am J Physiol Cell Physiol* 2007;293:C429-39.
8. Agrawal A, Mabalirajan U, Ahmad T, Ghosh B. Emerging interface between metabolic syndrome and asthma. *Am J Respir Cell Mol Biol* 2011;44:270-5.
9. Baker EH, Baines DL. Airway glucose homeostasis: a new target in the prevention and treatment of pulmonary infection. *Chest* 2018;153:507-14.
10. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;141:1169-79.
11. Yang G, Han Y-Y, Forno E, Yan Q, Rosser F, Chen W, et al. Glycated hemoglobin A1c, lung function, and hospitalizations among adults with asthma. *J Allergy Clin Immunol Pract* 2020;8:3409-15.
12. Sacks DB. Measurement of hemoglobin A(1c): a new twist on the path to harmony. *Diabetes Care* 2012;35:2674-80.
13. Pitocco D, Fuso L, Conte EG, Zaccardi F, Condoluci C, Scavone G, et al. The diabetic lung—a new target organ? *Rev Diabet Stud RDS* 2012;9:23-35.