What About Neutrophils in Obese Asthma?

To the Editor:

In their excellent review of the mechanisms linking obesity with asthma, Dixon and Poynter (1) discuss the multifactorial etiology of the obese–asthma association with a particular focus on three proposed phenotypes: asthma that is caused by obesity and is driven by changes in airway structure and function, rather than airway inflammation; preexisting asthma that is complicated by obesity and coexists with allergic airway inflammation; and obese–asthma that is worsened by increased susceptibility to environmental irritants and pollutants. We believe a fourth phenotype of obese–asthma exists and is characterized by increased airway neutrophilia. Our research has demonstrated an association between obesity and sputum neutrophilia; interestingly, this association is only evident in females, as we found obese males to have similar sputum neutrophil concentrations to their nonobese counterparts (2). We have also shown that neutrophilic asthma is present in almost three times as many obese compared with nonobese females with asthma (43% versus 16%; $P = 0.017$) (2). The occurrence of this phenotype has been confirmed by Telenga and colleagues (3), who found increased sputum and blood neutrophils in obese compared with nonobese participants; again, this observation was limited to females with asthma. Similarly, Marijse and colleagues (4) found sputum neutrophils were highly elevated in obese (median [interquartile range (IQR)], 66 [31, 79]%) compared with healthy-weight (median [IQR], 25 [12, 52]%) adults with asthma ($P = 0.020$), whereas sputum eosinophils were similar between groups. The existence of a neutrophilic obese–asthma phenotype is supported by a recent cluster analysis, which identified two clusters that were characterized by obesity coupled with high levels of either neutrophilic or mixed granulocytic airway inflammation (5). Although not all studies of obesity have observed an association between obesity and neutrophilic airway inflammation, we agree with Dixon and Poynter that there are a number of manifestations of obese–asthma, and therefore studies that have combined participants that are dissimilar in etiology may have confused and/or diluted potential associations. However, neutrophilic asthma does appear to exist in a subset of the population of patients with obese–asthma, and we believe that it too should be considered as a discrete phenotype of obese–asthma, with further research required to better define its etiology. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Hayley A. Scott, Ph.D.
Hunter Medical Research Institute
Newcastle, NSW, Australia
The University of Newcastle
Callaghan, NSW, Australia
and
The University of Queensland
Brisbane, QLD, Australia

Lisa G. Wood, Ph.D.
Peter G. Gibson, M.B.B.S.
Hunter Medical Research Institute
Newcastle, NSW, Australia

and

The University of Newcastle
Callaghan, NSW, Australia

References

1. Dixon AE, Poynter ME. Mechanisms of asthma in obesity: pleiotropic aspects of obesity produce distinct asthma phenotypes. *Am J Respir Cell Mol Biol* 2016;54:601–608.
2. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. *Eur Respir J* 2011; 38:594–602.
3. Telenga ED, Tideman SW, Kerstjens HAM, Hacken NH, Timens W, Postma DS, van den Berge M. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012;67:1060–1068.
4. Marijse GS, Seys SF, Schelpe A-S, Dilissen E, Goeminne P, Dupont LJ, Ceuppens JL, Bullens DM. Obese individuals with asthma preferentially have a high IL-5/IL-17A/IL-25 sputum inflammatory pattern. *Am J Respir Crit Care Med* 2014;189:1284–1285.
5. Moore WC, Hastie AT, Li X, Li H, Busse WW, Jarjour NN, Wenzel SE, Peters SP, Meyers DA, Bleecker ER; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol* 2014;133:1557–1563.e5.

Copyright © 2016 by the American Thoracic Society

Reply

From the Authors:

We thank Dr. Scott, Dr. Wood, and Dr. Gibson for their letter, which raises several important points. We readily acknowledge that the phenotyping of asthma in obesity is in its very early stages, and judicious stratification of obese patients with asthma could afford insight into subtype-specific pathology to ultimately intervene in these patients.

One of the limitations with the current approach to understanding obesity and asthma is the frequent assumption that obesity is a single uniform disease process in which body mass index has consistent effects on the airway. Another limitation is that many studies have compared asthmatics of different body mass indexes in an attempt to understand the differences between lean and obese patients with asthma; this methodology has been invaluable in providing direction for our early research in this field but makes it impossible to discern which differences are simply manifestations of obesity unrelated to asthma (e.g., obese patients are known to have increased circulating leukocytes and derangements in adipokines [1]) and which are indeed related to the development of airway disease in obesity. We need studies that carefully phenotype both the obesity and the asthma. Work such as that conducted by Scott and colleagues, with careful phenotyping of both airway disease and obesity, is critical to understand the nature of the relationship between asthma and obesity (2); this work does indeed suggest an airway neutrophilic phenotype, particularly in females, that responds to weight loss (3). How this phenotype might relate to stimuli such as pollutants, diet, and microbes acting in an obese host who is likely more susceptible to these insults (4) is surely deserving of further investigation. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Anne E. Dixon, M.A., B.M.B.Ch.
Matthew E. Poynter, Ph.D.
Department of Medicine
University of Vermont

References

1. Herishanu Y, Rogowski O, Polliack A, Marilus R. Leukocytosis in obese individuals: possible link in patients with unexplained persistent neutrophilia. *Eur J Haematol* 2006;76:516–520.
2. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, Wood LG. Relationship between body composition, inflammation and lung function in overweight and obese asthma. *Respir Res* 2012;13:10.
3. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, Wood LG. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. *Clin Exp Allergy* 2013; 43:36–49.
4. Dixon AE, Poynter ME. Mechanisms of asthma in obesity: pleiotropic aspects of obesity produce distinct asthma phenotypes. *Am J Respir Cell Mol Biol* 2016;54:601–608.

Copyright © 2016 by the American Thoracic Society