Novel Therapeutic Strategies for Adult Obese Asthmatics

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KEYWORDS

• Severe asthma • L-Arginine • Nitric oxide • Metformin • Statins • Obesity

KEY POINTS

- In the future, treatment regimens for obese, adult asthmatics may include several interventions that interfere with pathways common to several metabolic and nutritional disorders.
- The diabetic drug, metformin, could decrease inflammatory mediators of asthma by improving insulin sensitivity and altering adenosine monophosphate–activated protein kinase (AMPK).
- The cholesterol-lowering class of medications, statins, could have beneficial effects on both airway inflammation and structural remodeling in asthma.
- L-Arginine supplementation may benefit a subset of severe asthmatic patients with impaired nitric oxide (NO) synthase function in the lung.

INTRODUCTION

Adult obese patients with worsening asthma despite appropriate controller drug therapy are extraordinarily complicated to manage and treat. For example, consider a 40-year-old woman with a medical history notable for adult-onset nonallergic

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asthma, obesity, diabetes mellitus, and sleep apnea whose course has been punctuated by several emergency department admissions in the past year. She already requires continuous oral prednisone and 4-drug therapy for her asthma. How should such a patient be evaluated and treated for the foreseeable future? Although asthma is a complex syndrome that affects an estimated 26 million people in the United States, there are gaps in the recognition and management of asthmatic subgroups. Extrapolating results from short-term, randomized clinical trials to a broad, heterogeneous population of asthmatics treated in community settings is fraught with difficulty and can result in repeated trial-and-error therapeutic interventions. The ability to recognize different asthma phenotypes, to adapt and integrate care when comorbidities exist, and adopt new treatments is still lacking. Although published guidelines, including the National Asthma Education and Prevention Program Expert Panel Report 3 and the World Health Organization Global Initiative for Asthma, present stepwise evaluation and therapeutic recommendations for chronic persistent asthma management, they do not outline coherent plans for the care of adult-onset obese asthmatics.

This article proposes alternative approaches that may prove to be future treatments for adult obese asthmatics who do not respond to the standard controller asthma therapies of inhaled corticosteroids, bronchodilators, and antileukotriene (LT) drugs. Parallels are drawn between seemingly disparate therapeutics through their common signaling pathways (**Fig. 1**). Specifically, how metformin and statins potentially improve airway inflammation through activation of AMPK, a key regulator of cellular metabolism and energy production, and through their effects on NO is described. In addition, nutritional supplements, such as L-arginine, omega-3 (n-3) fatty acids, and other minerals and vitamins that are currently studied and may potentially be used in combination with conventional therapies are described.

METFORMIN, INSULIN RESISTANCE, AND ASTHMA

The metabolic syndrome with insulin resistance may characterize subsets of asthmatics more than is recognized. The relationship between obesity, insulin resistance, and asthma has been clearly established; however, the mechanisms by which they influence the pathogenesis of asthma is unclear.[1] Metformin is a biguanide class oral antidiabetic drug used to treat type 2 diabetes mellitus and insulin resistance. Although metformin reduces glucose production in the liver through inhibition of gluconeogenesis, the precise mechanisms are unknown and it may have differing modalities in different cell types. Metformin may indirectly activate AMPK by increasing AMP:ATP ratios through mild but specific inhibition of the mitochondrial respiratory chain complex I in hepatocytes, skeletal muscle, endothelial cells, pancreatic B cells, and neurons.[2] Peroxynitrite, generated by inhibition of complex I, activates AMPK through a c-Src and PI3K–dependent pathway in bovine aortic endothelial cells.[3] Metformin also directly activates AMPK through the inhibition of AMP deaminase in isolated skeletal muscle.[4] In the lung, metformin up-regulates AMPK expression and activity and diminishes proinflammatory cytokine secretion in human bronchial epithelial cells, down-regulating IκB kinase activity and inhibiting nuclear factor (NF)-κB.[5]

Obese asthmatics are less responsive to typical asthma controller therapy possibly because of contributing factors, such as an increased proinflammatory environment, that blunt the efficacy of treatment,[6] yet there have been studies that have shown no difference in induced sputum eosinophils, a biomarker of airway inflammation, between obese and lean asthmatics.[7,8] In a study of obese and lean asthmatics by Desai and colleagues,[9] however, there were similarities in sputum eosinophil counts between the 2 groups but an increase in interleukin-5 (IL-5), a mediator of eosinophil