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Asthma in adults with diabetes: treat their diabetes with metformin, improve their asthma?

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Keywords

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After decades of increasing prevalence in numerous countries, asthma affects over 300 million people worldwide. Similarly, the prevalence of obesity has doubled since the 1980s, and according to the World Health Organization it now affects over 600 million people around the world (with an additional 1.3 billion being overweight)[1]. Obesity is a major risk factor for diabetes, and it is also associated with higher risk of asthma. Obese people with asthma tend to have more symptoms, more frequent exacerbations, lower quality of life, and decreased response to asthma medications[2–4]. The pathways linking obesity to asthma have not yet been fully elucidated, but are likely multifactorial and include a mechanical effect on the lungs and the airways, genetic predisposition, epigenetic modification, dietary changes, a pro-inflammatory state, and others.

The metabolic complications of obesity –insulin resistance, the metabolic syndrome, and diabetes– likely play an important role in the pathophysiology of "obese asthma"[5,6]. The association between obesity and asthma is greater in the presence of insulin resistance[7]. Independent of obesity, subjects with diabetes may be at higher risk of asthma[8]. Similarly, insulin resistance and the metabolic syndrome have been associated to lower lung function among obese adolescents, with a more pronounced decreased among obese adolescents with asthma[9]. In light of these and other similar studies, it is crucial to determine whether preventing or adequately treating and controlling these complications of obesity may reduce asthma morbidity.

In this issue of *Respirology*, Li *et al.* use data from the Taiwan National Health Insurance Research Database (NHIRD) to evaluate whether the use of metformin among subjects with asthma and diabetes is associated with the risk of asthma exacerbations, emergency room visits, or hospitalizations[10]. Using a retrospective cohort approach, the authors analyzed insurance claims and medication data from 1,332 patients with concomitant asthma and diabetes: 444 taking metformin for their diabetes, and 888 age- and sex-matched subjects who were not using metformin. For each subject, they looked at data over a period of three years after the first prescription of metformin. After adjusting for several clinical covariates, they found that metformin use was associated with significantly reduced risk of asthma exacerbations (OR=0.39, 95% confidence interval [CI]=0.19–0.79%) or hospitalizations (OR=0.21, 95% CI=0.07–0.63%).

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Metformin is one of the most commonly prescribed oral anti-diabetic drugs; its mechanism of action is not completely understood, but proposed pathways include the activation of AMP-activated protein kinase (AMPK), an enzyme that plays an important role in the regulation of insulin signaling and glucose metabolism[11]. It also increases insulin sensitivity and may antagonize glucagon, thereby reducing blood glucose levels[12]. Metformin has been shown to attenuate allergic eosinophilic airway inflammation in obese mice, normalizing levels of eotaxin and tumor necrosis factor alpha (TNF-α) in bronchoalveolar lavage, and restoring levels of AMPK in lung tissue[13]. It may also inhibit airway smooth muscle cell proliferation through AMPK-dependent pathways[14]. Interestingly, AMPK induction by metformin ameliorates sodium and water transport in cystic fibrosis airway epithelial cell cultures[15]. Thus, there is evidence that metformin may have a potential role in the treatment of asthma. The study by Li and colleagues expands our current knowledge in two key aspects: First, it adds another important step to establish causality in the association between insulin resistance (or hyperglycemia) and asthma morbidity in humans. Second, and more importantly, it demonstrates an important clinical benefit among adults with asthma and diabetes taking metformin.

The present study has several strengths, including the use of matched data from a large, population-based cohort; the longitudinal nature of the analysis; the use of both diagnostic code and medication records to ensure accuracy; and the adjustment for multiple covariates and potential confounders such as short- and long-acting beta-agonists (SABA and LABA), inhaled corticosteroids (ICS), and oral steroids. At the same time, the study has limitations that are inherent to claims and coding database analysis. For instance, several covariates were not available in the NHIRD database that could be important confounders, including information on body mass index, tobacco smoking, race and ethnicity, socioeconomic status, allergen or pollution exposures, etc. Importantly, the database provides no information on medication compliance (for either asthma or diabetes), asthma severity, or blood glucose levels. Thus, we cannot ascertain whether the results are directly related to the use of metformin, to better diabetes control with improved glycaemia, or to other potential confounders.

In a world with 1.9 billion overweight/obese people, 400 million people with diabetes, and over 300 million people with asthma, the results reported in this issue of *Respirology* are novel and important, and certainly merit further investigation. Future studies should build on these findings, and improve on the current limitations by conducting prospective studies in cohorts specifically designed to address the effect of metformin on asthma outcomes. It is premature to recommend clinicians to modify their management of these patients, but if the results were replicated in independent cohorts, they would likely constitute sufficient grounds to consider randomized clinical trials. Future research will also have to address whether the effects of metformin on asthma are limited to patients with diabetes, or whether it may also be beneficial in subjects with obesity, insulin resistance, or the metabolic syndrome.

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