Obesity: Changing Asthma in the 21st Century

The world is witnessing a major shift in human disease swept in by an unprecedented pandemic, obesity (1). This is changing the nature and presentation of health and disease. An obvious example is type II diabetes; once a disease of elderly overweight adults, this condition is now increasingly diagnosed in children. Lung health is no exception to this new era in human health. Obesity is a major risk factor for asthma. This has been reported in adults and children, in multiple demographic groups, and from countries around the world (2). Asthma in obesity tends to be characterized by poor control (3) and decreased responsiveness to standard controller therapies (4). The epidemiological evidence linking asthma and obesity is compelling.

While the epidemiological evidence linking asthma and obesity is impressive, the mechanistic link between these diseases is far from clear. Obesity has important effects on airway physiology (5), though the relationship between obesity and asthma is far more complex than might be anticipated from simple mass loading. Important insights into the relationship may be gained from recent work on mouse models of obesity and asthma, and also from understanding the changes in adipose tissue and metabolism that take place with obesity. Insights from these basic studies need to be translated into the context of the human airway, and the publication by Lugogo and colleagues in this issue of the *Journal* (pp. 404–411) represents an important step in this direction (6).

Work in mouse models of obesity and asthma has provided important clues into the potential nature of the relationship in humans (7). Airway reactivity is increased in obese mice, even without airway challenge (7). Adipokines such as leptin and adiponectin and cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) appear to be involved in the pathogenesis of airway disease in obese mice (8). Studies in mice have provided a window into potential pathways that may link obesity and asthma in humans.

The last decade has seen major advances in our understanding of the pathophysiology of obesity. Adipose tissue is far from a passive energy storage depot; it is an important endocrine organ with major effects on immune function (9). In lean individuals, alternatively activated macrophages and eosinophils are found in adipose tissue. With obesity, macrophages in adipose tissue expand and take on a proinflammatory M1 phenotype elaborating cytokines such as IL-6, IL-1 β , and TNF- α (10). Changes in macrophage function have been reported in organs other than adipose tissue: Kupfer cell function is altered in the liver, contributing to the development of steatohepatitis (10). These changes in immune function could have profound effects on the pathogenesis of airway disease if they also occur in the human lung.

Studies suggest that alveolar macrophage function may be altered in obesity. Mancuso and colleagues have shown that alveolar macrophage function is altered in leptin-deficient mice: macrophages from obese mice have impaired phagocytosis and abnormalities in leukotriene production (11, 12). This has important implications for host defense. Sutherland and colleagues, in the only previous study of alveolar macrophages isolated from overweight and obese human individuals with asthma, found impaired responsiveness to dexamethasone, of obvious relevance for the steroid resistance typical of obese asthma (13). In the article published in this issue of the *Journal* by Lugogo and colleagues, obese individuals with asthma were found to have altered response both to lipopolysaccharide and to lipopolysaccharide combined with leptin, when compared with obese control subjects, lean subjects with asthma, and lean

control subjects. The investigators were careful to try and exclude the use of steroids, which could affect macrophage function, and although the levels of leptin used in the *in vitro* experiments were higher than that typically reported in obese individuals with asthma (250 ng/ml compared with 20–30 ng/ml in serum [14]), this study is important because it suggests that altered alveolar macrophage function and altered innate immunity are likely to be important features of asthma in obesity.

In addition to changes in macrophage function, the investigators made some noteworthy observations regarding bronchoalveolar lavage cytokines: TNF- α and leptin were particularly elevated in obese individuals with asthma. TNF- α has also been implicated in mouse studies of obesity and asthma (15). Given the therapeutic relevance of this pathway, this observation likely warrants further investigation. Leptin was also particularly elevated in bronchoalveolar lavage fluid of obese individuals with asthma. Shore and coworkers have previously shown that leptin infusion increases airway reactivity in lean mice; this is not related to increases in allergic airway inflammation, suggesting that leptin may be having effects in pathways quite distinct from those involved in allergic asthma (16). The observation that leptin was inversely related to lung function as measured by FEV₁ is also intriguing, given reports that leptin is involved in lung development (17, 18) and may regulate fibroproliferative responses in the lung (19). Further studies evaluating the mechanistic relevance of elevated TNF α and leptin in airway disease in obese individuals with asthma are needed.

The study by Lugogo and colleagues has important implications for our understanding of obesity and asthma. Obesity perturbs immune function, and many of the circulating factors produced by adipose tissue may have effects on airway disease in obese individuals with asthma. It is likely that this leads to a quite different form of asthma than that typically associated with allergic airway disease. This likely explains the lack of response to standard therapies. Therapies developed based on insights gained from the study of lean allergic mouse models of asthma likely have limited relevance for asthma in obesity. Studies such as that of Lugogo and coworkers are essential if we are to understand airway disease in the 21st century.

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ANNE E. DIXON, M.A., B.M., B.Ch.
Department of Medicine
University of Vermont College of Medicine
Burlington, Vermont

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The 6-Minute Walk Test in Pulmonary Arterial Hypertension

How Far Is Enough?

The 6-minute walk test (6MWT) has served as the primary end-point in all placebo-controlled pivotal trials of treatments for pulmonary artery hypertension (PAH) since the first such trial with intravenous epoprostenol nearly 20 years ago (1), and has been the basis for regulatory approval of all currently available medical therapies (2–8). Although secondary measures such as hemodynamics, biomarkers, quality-of-life parameters, and clinical worsening have, to varying degrees, also been examined in most of these studies, the relationship between improvement in exercise capacity and other clinically useful parameters has been inconsistent. Additionally, the demonstration of a statistically significant placebo-corrected treatment effect in rigorously performed clinical trials does not address the critical question faced by physicians who treat patients with PAH: How much change in 6MWT is clinically meaningful? In this issue of the *Journal*, an analysis by Mathai and colleagues (pp. 428–433) helps address this question (9).

Mathai and coworkers (9) retrospectively analyzed data from the Pulmonary Hypertension Response to Tadalafil trial (8), in which PAH subjects were randomized to tadalafil, a phosphodiesterase type-5 inhibitor, or placebo. Unlike prior pivotal drug trials, this study enrolled both treatment-naïve subjects and those who were already receiving background therapy with an endothelin receptor antagonist. Although the overall treatment effect on the 6MWT was 33 m, the subgroup on background therapy had a more modest effect (10). Similar treatment effects have been observed in several other combination trials in PAH, reinforcing the need to identify the magnitude of change in 6MWT that is not just statistically significant, but clinically meaningful as well. Using distributional and anchor-based methodologies, Mathai and colleagues (9) found that an improvement in 6MWT of approximately 33 m is associated with improvement in quality-of-life measures and is, therefore, a clinically meaningful degree of improvement.

A similar but more extensive analysis has recently been performed by Gabler and colleagues (11), who pooled results from 10 randomized clinical trials of PAH-targeted therapy and used the time to clinical worsening as the clinically meaningful comparator for 6MWT change. They found that the clinically meaningful change was in the range of 42 m, similar to the findings of Mathai and colleagues (9). Although these studies both provide useful information from analyses of prior studies, several questions remain unanswered.

The trials used for analysis largely consisted of treatment-naïve subjects, in whom the initiation of an active therapy is likely to produce a large improvement; in contrast, the placebo-treated group is likely to remain unchanged or even deteriorate, thereby magnifying the placebo-corrected treatment effect. In combination studies, in contrast, the magnitude of improvement with active drug on top of background therapy appears to be attenuated, and the placebo-treated subjects, who continue to receive background therapy, generally remain stable or even further improve slightly; since they are less likely to deteriorate during a short trial, the magnitude of placebo-corrected treatment effect is attenuated. This explains the consistent finding of an average treatment effect of 20–25 m in combination trials (7, 12, 13) as compared with values twice that in most *de novo* treatment trials. Furthermore, there may be a dissociation between harder outcomes such as mortality and the magnitude of improvement in 6MWT with combination therapy (13). This prompts the question as to whether the results by Mathai and colleagues (9) and Gabler and colleagues (11) on minimal important difference in 6MWT applies only to treatment-naïve patients and short duration of observation, with less relevance to long-term outcome, particularly for patients on multiple therapies. In the current era of widespread use of combination therapy for PAH despite a paucity of evidence supporting this approach, long-term combination studies that assess both 6MWT and