Chair's Summary: Obesity and Associated Changes in Metabolism, Implications for Lung Diseases

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The world is in the midst of an unprecedented obesity epidemic. This is having a major impact, not only on *patterns* of diseases within populations, but also on the *pathogenesis* of diseases. Diseases we have come to understand in the context of lean populations (and animal models) may be profoundly altered by the obese state. The purpose of the 2017 Transatlantic Airway Conference was to discuss the effects of obesity and metabolism on lung pathophysiology.

The effect of obesity on pulmonary disease is perhaps best understood in the context of asthma. Asthma, once commonly a childhood-onset allergic disease, is now often an adult-onset disease in obese subjects, with little in the way of type 2 inflammation. Some have argued that many symptomatic obese patients do not have asthma. Certainly many do not have early-onset allergic disease, but they often suffer with severe, later-onset disease complicated by obesity. To dismiss patients because they do not fall into disease paradigms established decades earlier in leaner populations is to ignore the evolution of human disease. Those seeking to understand the nature of current human lung disease have much to learn about how the respiratory system is altered by the physiologic and metabolic perturbations that characterize obesity.

The very terms “obesity” and “body mass index” are conceptually limiting progress in understanding these diseases. These terms simply imply increased mass. Certainly mass loading can lead to profound changes in the physiology of the respiratory system, changes that need more

sophisticated approaches to measurements and modeling of disease (1). But increased mass is only one isolated facet of this complex condition. The purpose of this conference was to discuss some of the myriad changes that can variably characterize the obese state, alterations that, together, profoundly alter physiology, and engender pathophysiology. These changes impact normal respiratory physiology and every disease encountered in pulmonary medicine.

The obese state is accompanied by altered environmental exposures, including diet, the built environment, and environmental pollution. A high-fat meal can have direct effects on airway inflammation (increasing airway neutrophilia) and airway muscle function (decreasing bronchodilator responsiveness), and diets high in fruit and vegetables (the opposite of typical obesogenic diets) may decrease asthma exacerbations (2) (S332–S338). Many of the effects of a high-fat meal on lung inflammation and function are very rapid and so likely related to immediate changes in circulating mediators. The effects of fruit and vegetables on the airway might not be immediately obvious, but recent insights regarding how the microbiome might alter circulating short-chain fatty acids provide clues into how this might happen (3).

Airway microbiome is known to affect the risk of developing asthma in children (4); gut microbiome is likely at least as important as that in the airway, and might be particularly important in the setting of obesity. Gut microbiome affects weight gain and glucose metabolism (5), immune development (3), and susceptibility to

disease (6). Altered gut microbiome in infants is a risk factor for the development of early-onset allergic airway disease (7). How this might relate to asthma in the context of obesity needs further investigation, but some insights come from the work of Trompette and colleagues (3). Obesogenic Western diets are low in soluble fiber; this deficit changes the gut microbiome, which alters circulating short-chain fatty acids, affecting immune function and allergic airway disease (3). However, these studies do not explain how changes in the microbiome could affect the nonallergic airway disease in obesity. Shore's work (8) (S357–S362) shows that the gut microbiome is involved in airway reactivity observed in obese mice in response to ozone, and so provides insight into the interaction between the gut microbiome and nonallergic obese asthma. Over the last few decades, changes in diets, antibiotic use, and exposure to pathogens have occurred. These factors affect the gut microbiome, contribute to obesity, and have major effects on the immune system and the pathogenesis of lung disease.

The obese state is often accompanied by changes in cellular metabolism related to altered glycolytic and mitochondrial function, which are recognized to be key factors in the development of obesity-associated cardiac and liver disease. Mitochondria are not only involved in energy production, but affect critical cell processes, such as reactive oxygen signaling and calcium signaling. Changes in cellular metabolism are a normal component of immune cell activation, and so changes in cellular metabolic function can alter immune function. For example,

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leptin-mediated increases in mammalian target of rapamycin activation and glycolysis appear to reduce the ability of lymphocytes to respond to acute challenges (9), and Green and Beck (10) (S406–S409) reported how changes in glycolytic activity of CD8 cells reduce responsiveness to influenza vaccine in obesity. Understanding how changes in cellular metabolism might affect not only immune cells, but also structural cells in the lung (11), will lead to insights into changes in obesity and also into normal homeostatic functioning of the lung.

The obese state is accompanied by increased adipose tissue, but the quantity and functioning of adipose tissue may vary widely between individuals having the same body mass index. Adipose tissue, particularly visceral adipose tissue, can produce a number of proinflammatory cytokines and hormones that circulate and may have direct effects on the lung, and asthma in obese individuals appears more closely associated with visceral than subcutaneous adipose inflammation (12). Metabolic abnormalities appear to be particularly prominent in patients with chronic obstructive pulmonary disease (COPD), as discussed by Wouters (13) (S389–S394), and likely contribute to comorbidities in this population. Whether

COPD itself might contribute to adipose tissue-related inflammation is not known, but, given that intermittent hypoxia worsens insulin resistance in sleep-disordered breathing, it is possible that hypoxia in patients with severe COPD (and other lung diseases) could worsen metabolic disease in these patients (14). There may be a bidirectional relationship between adipose tissue dysfunction and the respiratory system.

Another factor that might contribute to abnormal cellular function in obesity is lipid mediator signaling. Perhaps this is best understood in the context of macrophage function. Macrophages process and secrete a variety of lipids, which regulate circulating lipids and normal homeostasis of adipose tissue (15). How these processes might become dysregulated in lung macrophages in the setting of obesity and lipid excess is not known. However, as discussed by Fessler (16) and Fessler and Summer (17), oxysterols appear to have an important role in lung inflammation, so abnormalities of cholesterol signaling could lead to profound changes in lung immunity.

As we seek to better understand the effects of obesity on lung disease, it is important to be aware of the limitations of our experimental models. In fact, many

different experimental animal models are used to model obesity and lung disease. These sometimes produce conflicting results, which likely reflect important differences between metabolic derangements in the various models. Each model (and patient) is a confluence of elements of the obese state, with varying expressions of each discrete element (18). Animal models allow us to isolate and examine individual pieces of the obese milieu. Relying on any one of these animal models would be a mistake, but a thorough understanding of how these models concord and differ will inform us on similar variations in human disease (19). Thus, insights gained from different models will be valuable for understanding lung disease in obesity.

There is an ever-increasing number of patients suffering pulmonary complications related to the obese state. The accompanying articles summarize important work that is helping us to understand the effects of systemic and cellular metabolic disarray in obesity. A better understanding of disease in these patients will also provide insights into the central role of metabolic factors in regulating normal pulmonary function. ■

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