

Preface

Urban, Obese, Allergic, and Breathless: The Shape of Things to Come?



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Editor

There has been a paradigm shift in lifestyle and availability of food over the last century that has inverted the health challenges to society. Once the rich were fat, the poor were thin, putting food on the table was a challenge, and communicable infectious diseases were the biggest threats. While this continues in the less-developed world, elsewhere the rich are thin, the poor are fat, and obesity is a major health challenge along with associated noncommunicable diseases. Increasing availability of inexpensive food, reduced necessity of manual work, growth of sedentary recreational activities, and limited access to active lifestyles has driven this change. Beyond the expected increase in well-known obesity-associated diseases like diabetes and cardiovascular disease, this global epidemic of obesity has also been mirrored by equally large increases in asthma.^{1,2} These twin epidemics of asthma and obesity are strongly correlated epidemiologically, and the mechanistic links are also becoming increasingly clear.^{3–5} This special issue is devoted to providing the reader with an understanding of why asthma and obesity are on the rise, the magnitude and mechanism of increased asthma risk in obese subjects, the different clinical profile of asthmatic patients with concomitant obesity, and finally, the proven and expected benefits of adjunct therapies targeting weight loss and/or metabolic function in such patients.

The concept of “obese-asthma” as a new subphenotype of asthma is important for practicing clinicians. Many practices have already seen a shift from the typical asthma patient of the past who started experiencing symptoms early in life and had a strong allergic component to those starting much later in life and without obvious allergic triggers. Such patients are often female and obese and represent a form of obese-asthma.^{5–7} This is an important clinical subphenotype because such patients tend to have high symptoms but little allergic inflammation, as measured by exhaled nitric oxide (exhNO) or sputum eosinophils, and tend to respond poorly to standard

anti-inflammatory therapy, including corticosteroids. It should be noted that exhNO could be an unreliable marker in obese subjects, as discussed subsequently. There are also a substantial number of obese-asthmatics with early-onset asthma and strong allergic component, who require more intensive anti-inflammatory therapy. In this issue, Sherry Farzan and Jennifer Diaz review the clinical implications of the adult obese-asthma phenotypes and highlight the challenges that they pose.

In children, obesity has been strongly associated with asthma but not with other allergic diseases. Rakesh Lodha and colleagues review the available data from childhood studies and find consistent strong associations between obesity and nonatopic asthma but not between obesity and atopic-asthma or other allergic diseases. This challenges experimental models of obese-asthma, where adipose-hormone-mediated inflammation augments Th2 inflammation and the allergic response. It remains possible, however, that adipose hormones have lung-specific effects rather than a general potentiation of allergy. Other important possibilities include induction of asthma-like features by metabolic changes of obesity. Nitric oxide (NO) is important in the regulation of airway tone and airway responsiveness, and NO metabolism has been reported to be abnormal in obese subjects with metabolic syndrome.^{4,8,9} Reduced availability of the substrate L-arginine and the presence of asymmetric dimethylarginine (ADMA), an uncoupler of NO synthases, contributes to reduced NO formation, increased superoxide generation, and increased smooth muscle tone in obesity, metabolic syndrome, and asthma.^{10–14} This also sheds light on why exhaled NO, used clinically as a marker for eosinophilic inflammation, is diminished in obese asthmatics. In this issue, Hartmut Grasemann and Jeremy Scott review the current understanding of the role of ADMA in asthma pathogenesis and conclude that ADMA may represent a novel therapeutic target in correcting the enhanced airways responsiveness in asthma. Others and we have previously proposed a role for hyperinsulinemia in promoting airway hyperresponsiveness (AHR) and remodeling.^{15,16} Insulin promotes airway smooth muscle proliferation and contractility and can also lead to extracellular matrix deposition by fibroblasts. These changes can remodel the airways and lead to AHR independent of inflammation. Insulin resistance (IR) was indeed found to be a stronger predictor of aeroallergen sensitization and asthma than obesity in a Danish cohort, but this has not been consistently seen.^{17,18} This has been reviewed in more detail elsewhere.¹⁶ Interestingly, not only are IR and consequent hyperinsulinemia well known in obesity, but also markers of IR, such as acanthosis nigricans and dyslipidemia, have been noted in asthmatic children.¹⁹ Giovanni Piedimonte and Miriam Perez review the current data on metabolic consequences of asthma to bring out the connections between asthma, obesity, and diabetes.

While IR appears to be one of the important functional threads running through obesity and asthma, there appear to be deeper mechanistic links. At a subcellular level, development of IR has been related to mitochondrial dysfunction and increased mitochondrial reactive oxygen species generation.²⁰ This, together with endoplasmic reticulum stress, represents an emerging interface between obesity, metabolic syndrome, and airway disease, which can be triggered by nutrient overload, inflammation, or cigarette smoke, among others.^{21–26} Unpublished data from our lab suggest that high-fat-diet-induced obesity or high-sugar-diet-induced IR and hyperinsulinemia are both related to ER stress and mitochondrial dysfunction. Spontaneous AHR and remodeling are seen in such mice without any allergic inflammation and also the allergic response is augmented. In this issue, YS Prakash and I review the concept of obesity and asthma as diseases of bioenergetic failure and mitochondrial dysfunction. In support, mitochondrial transfer from mesenchymal stem cells (MSC) strongly attenuates allergic asthma in mice.²³ The effect is clearly related to mitochondrial

transfer because MSC lacking mitochondrial transfer capacity are ineffective, while those that are bioengineered for greater mitochondrial donor potential are much more effective.²⁷ We believe that bioenergetic failure is a common theme between multiple metabolic and cardiopulmonary disorders and merits further examination as a therapeutic target.^{24,28} Possible interventions to improve mitochondrial health are discussed in the review with the expectation that these may have benefit in asthma. Of these, Coenzyme Q10 supplementation has been reported to be potentially beneficial in steroid-resistant asthmatics.^{29,30} Benefit in obese-asthma remains to be tested.

Current guidelines for the management of asthma do not recognize obesity as a guiding factor in determining optimal therapy. Since obese asthmatics do not respond as well to the recommended standard controller therapies as normal-weight persons, this is a critical gap in the recognition and management of an important subgroup. This issue has two important reviews that address this gap and provide information to the reader regarding additional options for poorly controlled severe asthma patients, who are also obese. First, since many of the mechanisms of pathogenesis of asthma relate to metabolic consequences of caloric excess, adiposity, and adipose hormones, it is intuitive that caloric restriction and weight loss should be recommended. However, this does not work for all patients, and evidence of substantial benefit is required for initiation of therapeutic programs beyond counseling. Njira Lugogo and Timothy Heacock review the evidence for medical or surgical weight loss strategies in the management of obese-asthma and conclude that weight loss should be encouraged as a means of improving asthma symptoms and control, but there are insufficient data to recommend surgical interventions for weight loss solely for the purpose of improving asthma.

Second, other than nutritional and lifestyle modification, there may be an additional role for drugs and/or supplements that target the principal pathological abnormalities. Statins and metformin have been found to be effective agents for the treatment of asthma in animal models and are also suitable for the treatment of obesity-associated metabolic dysfunction.^{4,31–33} Metformin, in particular, has been associated with attenuation of the augmented allergic inflammation in obese mice on a high-fat diet. One of the mechanisms by which statins work seems to be induction of dimethylarginine dimethylamino hydrolase1 and inhibition of arginase, thereby resulting in an increased ratio of L-arginine/ADMA, thereby increasing L-arginine bioavailability to NOS.^{34,35} In an alternate approach, L-arginine supplementation at high doses is similarly effective, probably by restoring a normal L-arginine/ADMA ratio, overcoming the uncoupling effects of high ADMA and promoting NO synthesis.^{36–38} There are some concerns, however, on whether increased arginase-mediated degradation of L-arginine may worsen asthma and simultaneous arginase inhibition may be required.³⁸ Nicholas Kenyon and colleagues review the current data on such novel therapies targeting asthma and the comorbidities that accompany obesity. In their severe asthma clinics, they have found that female-predominant severe asthmatics with a mean body mass index of 30 or more, benefited from statin treatment. They are also currently testing the benefit of L-arginine supplementation in severe asthmatics, who are predominantly overweight/obese and female. Nutritional supplements like L-arginine and omega-3 fatty acids are other exciting considerations for future treatment of asthma that may additionally attenuate the metabolic syndrome. Overall, there is a pressing need for greater recognition of the obese-asthma subtypes and a move toward more targeted therapies.

Notwithstanding any of the mechanisms by which obesity leads to asthma and the many possible therapeutic strategies for obese-asthma, it seems certain that the twin

epidemics of asthma relate mostly to external modifiable factors. Given that an ounce of prevention is better than a pound of cure, we must also focus on the underlying risks that are driving both obesity and asthma. Since rapid increases in obesity and asthma have been seen in childhood, this requires consideration of prenatal and postnatal factors. In particular, calorie-rich but nutrition-poor food products and environmental pollution are modifiable social risks that retard the development of our lungs even before we are born and accelerate the decline thereafter. In this issue, Debra Palmer and colleagues along with Sundeep Salvi and Sneha Limaye shed light on this poorly understood facet in both of their articles. It emerges that protection of the nutrition of young women and provision of a clean environment are time-critical interventions that cannot be delayed further. However, more is not always better, whether calories or supplements! For example, maternal folate supplementation in late pregnancy, when the risk for neural tube defects has already passed, has been associated with increased risk of allergy and asthma.³⁹ Could this prevalent practice be altering the epigenome and driving the ever higher peaks in the prevalence of these diseases?

It is time to heed the eloquent call by Giovanni Piedimonte and Miriam Perez in this issue, "If we want to prevail in the war against chronic airway diseases that so far have eluded any therapeutic strategy, it is essential to recognize that the months spent in our mother's womb may be the most consequential of our lives, and identify the intrauterine and early life events shaping the development of the respiratory system to prevent or redirect dysfunctional phenotypes before they result in actual disease." This emphasized, I encourage you to enjoy the expert reviews in this special issue that explore each of these aspects in greater detail.

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