

Is Impaired Glucose Metabolism the Missing Piece in the Obesity-Asthma Puzzle?

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Summary. Obesity is a major risk factor for several conditions including atherosclerotic disease, metabolic syndrome, and upper airway dysfunction. However, the purported link between obesity and asthma has remained more difficult to define, in part due to limitations in past epidemiologic studies and the inherent challenge in accurately defining asthma in children. It is possible that obesity leads to asthma only in the presence of a mediating variable such as an obesity-related conditions such as esophageal reflux or insulin resistance. The article by Karampatakis and colleagues in this week's edition of the journal is important because it addresses the hypothesis that altered glucose metabolism/insulin resistance associates with bronchial hyperresponsiveness (BHR), a central and objectively measured marker of asthma. They studied pre-pubertal children with and without asthma with a range of body mass indices and found for the first time in pre-pubertal asthmatic children that both insulin resistance and impaired glucose tolerance were more closely related to BHR than was obesity. Their work opens the way for directed mechanistic study of the effects of impaired glucose metabolism on airway development during childhood and airway responsiveness, and for the study of insulin sensitizing therapies in children to prevent lower airway disease. *Pediatr Pulmonol.* 2017;52:147–150. © 2016 Wiley Periodicals, Inc.

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Readers of the journal are well aware of obesity's effect on the health of populations across the globe. It is a major risk factor for several conditions including atherosclerotic disease, metabolic syndrome, and upper airway dysfunction among others.¹ Additional attention has been paid in recent years to a possible link between obesity and risk of lower airway disease, though the link has proven more difficult to define, particularly in children. An association between obesity and risk for new asthma would hold considerable public health significance. In many regions around the world, chronic childhood asthma remains one of the leading causes for missed school, Emergency Department visits, hospitalizations and intensive care admissions.^{2,3} High-quality longitudinal studies have reported that obesity increases the risk for new asthma,^{4,5} though the replication of this link has not been consistent. Among the 18 English-language longitudinal studies listed in PubMed that report on the risk of obesity and later asthma,^{6–23} many were able to show an increased asthma risk in only subsets of patients.^{13–15,17,18,21,22} More than half of all

longitudinal studies were fully negative,^{6–12,19,20,23} showing no increased risk of asthma related to obesity. Among the studies showing only partial association, the effects of race, gender, atopic status, and timing of obesity were remarkably inconsistent which undermines the likelihood that it is obesity in particular that directly

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causes asthma.¹⁴ These inconsistencies across studies could reflect various types of reporting bias (white hat bias²⁴ or p-value “hacking”²⁵) or the presence of a mediating or confounding unmeasured third factor that correlates with obesity. Establishing an accurate link between obesity and asthma risk is also challenged by the difficulty in accurately diagnosing asthma. Asthma is known to be over-diagnosed in the clinical setting which makes using patient report of physician-diagnosis very problematic as a hard outcome for clinical research^{26,27}; and misclassification of asthma is a particular concern in patients with obesity, since obesity by itself can cause shortness of breath, chest tightness, “wheezing”, and exercise-induced dyspnea.^{28,29} To reach a more accurate understanding of the obesity-asthma link, studies should employ objective measures of airway function.^{30–32}

The article by Karampatakis and colleagues in this week’s edition of the journal is important because it addresses some of these missing pieces. They demonstrate for the first time in pre-pubertal asthmatic children that insulin resistance (IR) and glucose intolerance, known sequelae of obesity, are closely associated with objectively defined bronchial hyperresponsiveness (BHR). Hyperinsulinemia, which is variably present in obesity, may be the mediating or third factor linking the two conditions and provides a new direction for intensive investigation. Insulin receptors are present in the developing lung, and past animal models support insulin as an asthmogenic factor. In animal models^{33–37} and models of human airway smooth muscle (ASM),³⁸ researchers have shown that insulin enhances ASM contractility and proliferation. In clinical studies, metabolic syndrome and IR have also been associated with asthma diagnosis,^{39,40} and lung function impairment.^{41,42} However, to date, no studies have demonstrated a link between IR and objective markers of BHR in children with asthma.

Karampatakis and colleagues sought to assess the relationship between IR and BHR among young children with a range of body mass index (BMI) levels with and without asthma. They recruited 71 pre-pubertal children from the outpatient clinics at the Aristotle University Medical School in Thessaloniki, Greece between 2011 and 2014. On all children, the researchers conducted a detailed history and physical examination and tested fasting insulin and plasma glucose, spirometry, and mannitol bronchoprovocation challenge. Obese children also underwent a standardized oral glucose tolerance test (OGTT). Participants formed four groups and were compared based on their presence or absence of study-defined obesity and confirmed asthma. Obesity was defined as a sex- and age-adjusted BMI ≥ 95 th percentile, while asthma-status was determined by past physician-diagnosis and evidence of bronchial hyperresponsiveness

(BHR). Unfortunately, markers of atopy such as total or specific IgE or exhaled nitric oxide were not measured. BHR was quantified by PD15 (provocating dose of mannitol to achieve 15% drop in forced expiratory volume in 1 second (FEV1)), which increases with decreasing airway responsiveness. Among non-asthmatics in the study, obesity status did not influence PD15, while among asthmatics, PD15 was significantly lower (signifying enhanced responsiveness) in children with obesity. IR was measured in all participants using the homeostatic model assessment of insulin resistance (HOMA-IR),^{43,44} with a higher value suggesting greater insulin resistance. Among obese participants, a HOMA-IR ≥ 2.5 was associated with significantly lower PD15 (greater BHR); while among all asthmatic participants, a similarly close association between IR and BHR was demonstrated. Among obese asthmatics, importantly, BMI_z was not associated with changes in PD15, suggesting that obesity by itself was not a causal factor in BHR. Similarly, children with impaired glucose tolerance also displayed greater BHR irrespective of BMI. The measurement of BHR used by Karampatakis and colleagues was notable. BHR can be measured using a number of direct and indirect bronchoprovocation methods. Though the direct methacholine challenge is commonly used, it has limited diagnostic specificity, and is a poor indicator of airway inflammation or response to asthma therapy which are important phenotypic traits in childhood asthma. The indirect mannitol challenge used here is more specific to asthma and has superior correlation (compared to methacholine challenge) to airway inflammation.⁴⁵ Overall, these data assembled by Karampatakis are consistent with IR and altered glucose metabolism being the key factor in obesity-related BHR, rather than stemming from obesity alone. The current study did not test possible mechanisms by which IR leads to BHR, however we speculate that hyperinsulinemia is enhancing ASM contractility and contractile protein expression via variable combinations of mast cell activation,^{33,34} rho-kinase and phosphatidylinositol (PI) 3-kinase related signaling, and altered small airway parasympathetic innervation.⁴⁶

These important results bring several new questions. What are the relative effects of hyperglycemia versus hyperinsulinemia on airway function? Since BHR is known to be affected by both baseline airflow limitation and the degree of acute responsiveness, further work is needed to delineate the relative contributions to insulin-related BHR. How quickly does lung function impairment and BHR occur with the onset of IR? These questions would need longitudinal assessments of glucose metabolism, insulin resistance, and bronchial responsiveness. Lastly, intervention studies with mast cell stabilizer and anticholinergic medications and insulin sensitizers (exercise, dietary modification or

metformin) would further elucidate mechanisms present in insulin-related BHR.

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