Pediatric Obesity-Related Asthma: The Role of Metabolic Dysregulation

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abstract

The burden of obesity-related asthma among children, particularly among ethnic minorities, necessitates an improved understanding of the underlying disease mechanisms. Although obesity is an independent risk factor for asthma, not all obese children develop asthma. Several recent studies have elucidated mechanisms, including the role of diet, sedentary lifestyle, mechanical fat load, and adiposity-mediated inflammation that may underlie the obese asthma pathophysiology. Here, we review these recent studies and emerging scientific evidence that suggest metabolic dysregulation may play a role in pediatric obesity-related asthma. We also review the genetic and epigenetic factors that may underlie susceptibility to metabolic dysregulation and associated pulmonary morbidity among children. Lastly, we identify knowledge gaps that need further exploration to better define pathways that will allow development of primary preventive strategies for obesity-related asthma in children.

Pediatric obesity is a major public health issue that has reached epidemic proportions, affecting ∼18% of school-going children in the United States.[1] Although the overall prevalence of pediatric obesity has increased, prevalence rates differ by age, gender, and ethnicity[1] and are partly determined by sociodemographic factors.[2] Notably, obesity is more prevalent among Hispanic and African American children than their non-Hispanic white counterparts.[1]

Asthma, another chronic pediatric disease with increasing prevalence over the past 3 decades, affects ∼10% of all school-age children in the United States.[3] Racial and ethnic differences evident in the prevalence of obesity overlap with those of asthma; namely, asthma is more common among African Americans and Hispanics, particularly Puerto Ricans, compared with non-Hispanic white children.[3] The increase in asthma prevalence is likely multifactorial, ranging from environmental factors including

early-life exposures to allergens to caregiver issues including low caregiver asthma management self-efficacy and empowerment.[4] Similar environmental factors including increased built area with decreased outdoor play, increased screen time, increased intake of high-calorie foods, and caregiver food choices play a role in high childhood obesity prevalence.[5]

Over the past decade, many cross-sectional and prospective epidemiologic studies have found an association between pediatric obesity and asthma.[6–12] A recent meta-analysis, including 6 prospective cohort studies on the effect of body weight on future risk of asthma, found a twofold increased risk in obese children compared with normal-weight children,[12] suggesting that obesity is an independent risk factor for childhood asthma.[12] Clinical studies also suggest that obesity-related asthma is distinct from normal-weight asthma. Obesity-related asthma is associated

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with decreased medication responsiveness[13] and poor disease control,[14–16] particularly among ethnic minority children,[14,15] contributing to increased health care expenditure. However, the mechanisms that underlie these epidemiologic and clinical associations are poorly understood, and this gap precludes scientific advancement toward development of targeted therapies. Here, we review recent scientific studies that begin to elucidate the potential role of metabolic dysregulation and its associated inflammation in pediatric obesity-related asthma. It is important to note that although the majority of studies included in this review defined obesity as BMI >95th percentile, some combined current definitions of overweight and obese (BMI >85th percentile). Moreover, this review focuses on mechanisms underlying obesity-related asthma, rather than incident obesity among children with asthma.

MECHANISMS LINKING OBESITY AND ASTHMA

Many mechanisms may underlie the obesity-asthma association (Fig 1). They range from obesity-mediated alteration of pulmonary function, due to the mechanical truncal fat load and/or inflammation,[17] alteration in macro- and micronutrient intake,[18] and a sedentary lifestyle and its associated obesogenic behaviors.[19] Furthermore, immunomodulatory effects of obesity, mediated by adipocytokines including leptin, have also been postulated to underlie asthma in obese children.[20,21] However, because not all obese children develop asthma, these factors may play a role, but do not explain the higher predisposition for pulmonary morbidity in some, but not other, obese children. Therefore, there is need for better identification of key molecules and biomarkers that may predict asthma

development among at-risk obese children.

Recently, asthma has been associated with insulin resistance,[22] dyslipidemia,[23,24] and metabolic syndrome,[25] measures of metabolic dysregulation that develop in some but not all obese children.[26,27] Moreover, genetic and epigenetic differences in molecules involved in metabolic dysregulation and its associated inflammation have been found in the context of obesity-related asthma. In this review, we initially summarize the better-investigated mechanisms such as the mechanical effect of truncal adiposity on pulmonary function and the association of sedentary lifestyle and dietary intake with obesity-related asthma. We then discuss more recent literature on the association of obesity-mediated inflammation and metabolic dysregulation with pediatric obesity-related asthma and its genetic and epigenetic footprint (Fig 1), which together begin to identify key molecules that likely underlie the complex pathophysiology of obesity-related asthma.

MECHANICAL EFFECT OF OBESITY ON PULMONARY MECHANICS AND ASTHMA

Obesity, and its related measure, truncal adiposity,[28–30] have been associated with asthma,[29–31] and pulmonary function deficits,[28] including among ethnic minority children[30,32] (Table 1). Excess truncal adiposity renders a mechanical disadvantage to the diaphragm due to mechanical fat load and is associated with decreased functional residual capacity (FRC),[33–35] with reduced residual volume (RV) and expiratory reserve volume (ERV).[33–37] Lower FRC influences bronchial smooth muscle stretch, especially at the end of tidal volume exhalation, which leads to perception of increased respiratory effort with normal inspiration.[38] Although obese children have higher forced

expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)[39,40] than normal-weight children, the combination of mechanical restriction and low lung volumes predispose obese children to present with lower FEV_1/FVC ratio,[33] reduced even compared with their normal-weight counterparts[32,39,41] (Table 1). However, unlike normal-weight asthma, obese asthmatic children have reduced FRC with low lung volumes.[33]

These studies suggest an association among truncal adiposity, asthma, and altered lung mechanics. However, because truncal adiposity is a risk factor for metabolic dysregulation,[51] we speculate that metabolic dysregulation, not investigated in these earlier studies, may have coexisted with truncal adiposity. In keeping with this speculation, insulin resistance and dyslipidemia were found to be predictors of FEV_1/FVC ratio and ERV,[34] the 2 pulmonary function indices that are decreased among obese asthmatics, and mediated the association of BMI and waist circumference with these indices,[34] suggesting that biological factors other than mechanical fat load may mediate the influence of obesity on pulmonary function.

Ethnicity and gender may also influence these associations. Hispanics and African Americans, who bear a higher burden of obesity-related asthma, have greater truncal adiposity for the same body weight than Caucasians.[52] With regard to gender, although obese girls have more symptoms[53,54] and nonatopic inflammation compared with boys,[47] boys have a higher prevalence of metabolic syndrome.[25] Moreover, whereas one study reported an association between truncal fat and FEV_1 and FVC only among boys,[50] another study found an association between lean mass, rather than fat mass, with FEV_1, FVC, and total lung capacity (TLC) among boys,
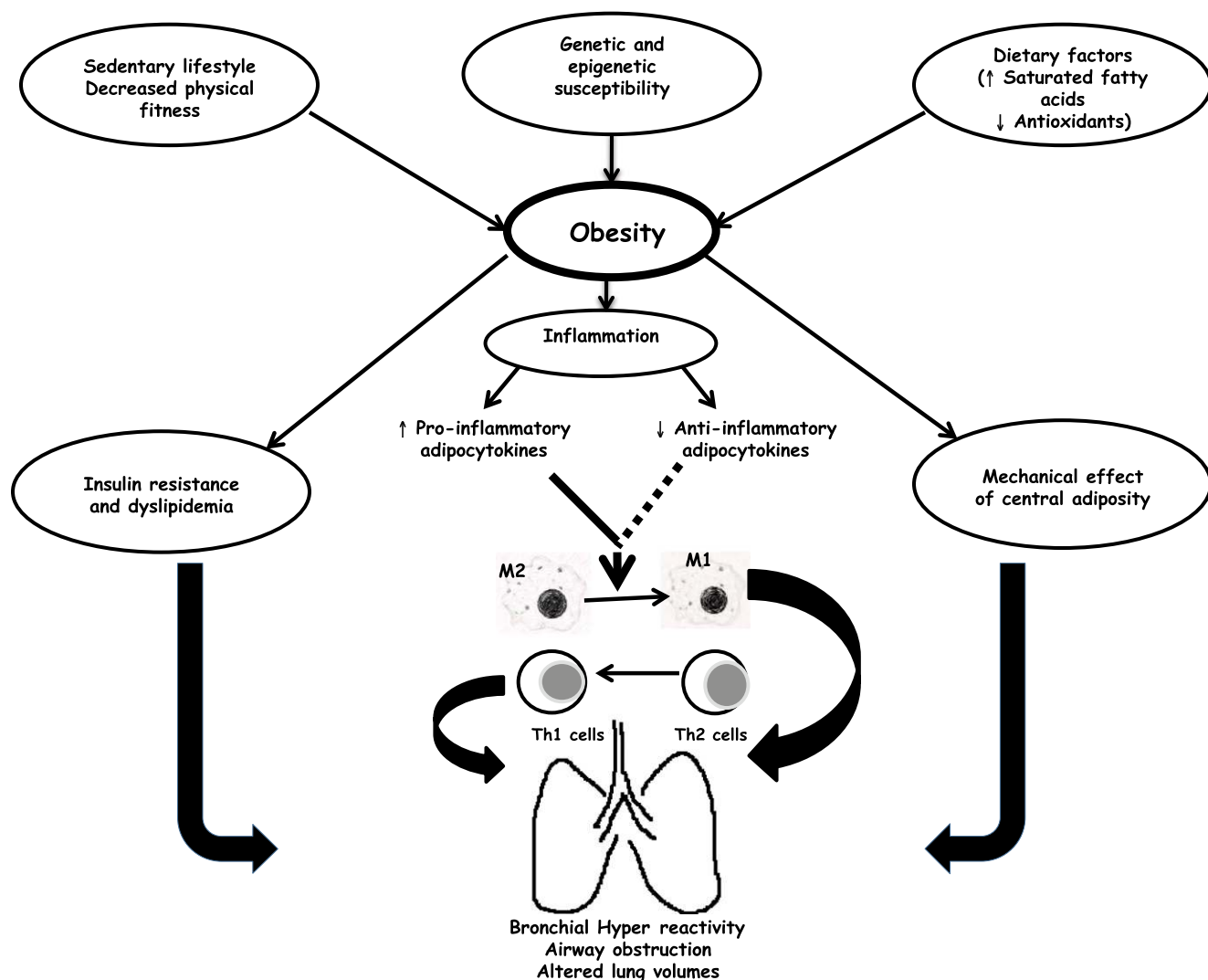
FIGURE 1
Mechanisms proposed to underlie pediatric obesity-related asthma. This figure summarizes the factors associated with obesity-related asthma in the context of obesity preceding asthma. Although several factors such as genetics and epigenetics are also associated with childhood asthma, the relationships shown in this figure are specific to those discussed in this review.

and only with TLC in girls.[48] The disparate results of these few studies highlight the need for gender as well as ethnicity-specific investigations of the associations among mechanical fat load, presence of metabolic dysregulation, and pulmonary function deficits linked with pediatric obesity-related asthma.

Weight Loss

Thus far, there are only 2 studies on the effect of weight loss on obesity-related asthma in children.[48,55] Jensen et al reported an improvement in asthma control in obese asthmatics

following diet-induced weight loss.[48] ERV and RV/TLC ratio and Pediatric Asthma Quality of Life Questionnaire (PAQLQ) symptom and emotional domain scores also improved but did not differ significantly from the change in the control group.[48] Van Leeuwen et al reported decreased severity of exercise-induced bronchoconstriction and improved PAQLQ scores, particularly in the symptoms and activity domain, after weight loss.[55] Moreover, limiting caloric intake in the normal range in obese children was also associated with improvement in

asthma control and PAQLQ scores.[56] Together, this limited literature suggests that weight loss in children is associated with improvement in clinical and quality-of-life parameters. However, there are no studies on pulmonary effects of weight loss in ethnic minority children. Because diet-induced weight loss in children, particularly among those of minority ethnic background, is often modest,[57] other therapeutic options are needed to address obesity-mediated pulmonary morbidity in the pediatric populations most afflicted by these diseases.

TABLE 1 Summary of Pediatric Studies Reporting an Association Between General or Truncal Adiposity and Asthma

Study	Study Design	Obesity Definition/ BMI Analysis	Sample Size, n	Age, y, (Range/ Mean ± SD)	Ethnicity	Finding
Tantisira et al, 2003[39]	CS	BMI >95th percentile for age and gender	1041	5–12	Whites (17%), Blacks (17.6%), Hispanic (18.8%) Others (16.6%)	Decrease in FEV_1/FVC ratio was associated with increase in BMI.
Perez-Padilla et al, 2006[42]	CS	BMI >95th percentile or BMI above limits set by International Obesity Task Force	6784	8–20	Mexican	Increase in FEV_1 and FVC but decrease in FEV_1/FVC ratio with increase in BMI. Increase more in preadolescents than adolescents.
Chu et al, 2009[40]	CS	BMI >95th percentile for age and gender	14 654	14.3 ± 0.9	Taiwanese	Higher FEV_1 and FVC but lower FEV_1/FVC ratio with higher BMI.
Musaad et al, 2009[28]	CS	BMI >85th percentile for age and gender	1123	5–18	Caucasian (57.4%), African American (33.8%), others (8.8%)	BMI and waist circumference were inversely associated with FEV_1.
Spathopoulos et al, 2009[41]	CS	BM I>95th percentile for age and gender	2715	6–11	Caucasian (Greek)	High BMI is inversely correlated with FEV_1, FVC, FEV_1/FVC ratio, and $FEF_{25\%-75\%}$.
Chen et al, 2009[43]	CS	BMI analyzed as a continuous variable	718	6–17	Caucasian (Canadian)	Waist circumference was inversely associated with FEV_1/FVC.
Consilvio et al, 2010[44]	CS	BMI >2 SD for age and gender	118	6–9	Caucasian (Italian)	Obese asthmatic children had low FEV_1/FVC ratio.
Sidoroff et al, 2011[45]	L	BMI >98th percentile for age and gender	100	4–12	Caucasian (Finnish)	Weight gain associated with decrease in FEV_1/FVC ratio.
Huang et al, 2012[46]	CS	BMI >95th percentile for age and gender	140	10–16	Mexican	No association between FEV_1/FVC ratio and BMI in asthmatics.
Rastogi et al, 2012[33]	CS	BMI >95th percentile for age and gender	120	7–11	African Americans (50%), Hispanics (50%)	FEV_1/FVC ratio, and $FEF_{25\%-75\%}$ was lower in obese asthmatics
Vo et al, 2013[32]	CS	BMI >95th percentile for age and gender	980	7–20	Whites (16%), African Americans (42%), and Hispanics (42%)	Higher FEV_1 and FVC but decrease in FEV_1/FVC ratio with higher BMI. FEV_1/FVC ratio was lower in overweight and obese African Americans and Hispanics, and obese Whites.
Jensen et al, 2013[47]	CS	BMI z score >1.64 SD	361	8–17	Caucasian (Australian)	Lung volumes reduced among obese children; ERV reduced in obese asthmatics, RV and RV/TLC ratio reduced in obese nonasthmatic children.
Jensen et al, 2014 [48]	CS	BMI z score analyzed as a continuous variable	48	11.9 ± 2.3 (Boys) 13.6 ± 2.2 (Girls)	Caucasian (Australian)	Lean mass, not fat mass, is associated with FEV_1, FVC, and TLC in boys and with TLC in girls.
Sanchez-Jimenez et al, 2014[49]	CS	BMI >95th percentile for age and gender	153	4–15	Caucasian (Spanish)	Waist circumference was inversely associated with FEV_1 and FVC.
Wang et al, 2014[50]	CS	BMI z score analyzed as a continuous variable	646	11–12	Caucasian (British)	Higher FEV_1 and FVC with higher BMI in girls. Percent truncal fat inversely correlated with FEV_1 and FVC in boys but not girls.
Rastogi et al, 2014[34]	CS	BMI >95th percentile	168	13–18	African Americans (42.1%), Hispanics (57.9%)	Truncal adiposity and general adiposity were associated with reduced FRC, RV, and RV/TLC ratio.

CS, cross-sectional; L, longitudinal.

DIET AND ASTHMA

Increased intake of processed food, high in fat and low in antioxidant content, has been associated with asthma.[58,59] Conversely, consumption of the Mediterranean diet, high in fruits and vegetables, and omega-3 fatty acids, has been found to be protective.[60–63] Therefore, the type of fat, in addition to total fat intake, may play a role in its association with asthma. Systemic inflammation linked to dietary fat intake may underlie these associations.[64–66]

Omega-6 fatty acids, including arachidonic acid (20:4 n-6) and linoleic acid (18:2 n-6), mediate inflammation,[67] whereas omega-3 fatty acids, including eicosapentaenoic acid (20:5 n-3) and docosahexaenoic acid (22:6 n-3),

are protective.[67,68] Prostaglandins and leukotrienes, both of which are arachidonic acid metabolites, have been quantified in exhaled breath condensates from children with asthma.[69] However, the extent to which asthma symptomatology and pulmonary function improve with increased intake of omega-3 or decreased intake of omega-6 fatty acids is not well known among obese children with asthma and is being investigated in ongoing randomized trials of omega-3 fatty acids supplementation.[70]

Furthermore, intake of micronutrients such as vitamins A,[59,71,72] C,[59,73] and E[73] has been inversely associated with asthma, whereas vitamin D insufficiency has been associated with higher asthma disease burden[74] and lower lung function.[75,76] Although the exact mechanism through which vitamin D influences asthma in obese children is not known, vitamin D does have immunomodulatory effects[77] and may influence intestinal microflora,[78] mechanisms that have been associated with asthma pathophysiology.[79,80] There is also evidence to suggest that maternal diet may influence incident childhood asthma and obesity, an aspect that has been previously reviewed.[81] Although these initial studies suggest that dietary intake may be linked to obesity-related asthma, more research is needed to explore the various effects of dietary macro- and micronutrients on asthma.

There is also a substantive role of parental choice[82] and feeding practices[83] in a child's dietary intake[82] and behavior,[83] including among Hispanics[84,85] and African Americans.[86] For example, among Hispanic households, >50% of the parents reported having sugar-sweetened beverages, and >80% reported having energy-dense foods including potato chips, cookies, cake, or ice cream in their home.[84] In keeping with these findings,

weight-resilient African American adolescents were those who consumed more fruits and vegetables and whose parents were in the healthy weight range and provided supervision to physical activity and accessed grocery stores with better food availability.[86] Given the complex relationships between macro- and micronutrient intake and asthma and the role of parental dietary choices and feeding practices on dietary intake, future studies are needed to define the impact of each of these aspects of nutritional intake on childhood asthma, including obesity-related asthma. These findings may elucidate a role of dietary modification rather than restriction in the management of obesity-related asthma,[18,87] particularly in those of minority ethnicities, given their higher disease burden and modest effectiveness of weight loss.

SEDENTARY LIFESTYLE, PHYSICAL FITNESS, AND ASTHMA

Obese children also tend to have a sedentary lifestyle. Increased use of electronic gadgets, television watching, and video games has decreased outdoor play time and been linked with overweight and obesity in children.[88,89] The number of hours playing video games and watching TV directly correlate with asthma incidence and prevalence among children.[19,90] Sedentary lifestyle and decreased physical fitness cause central obesity and thereby predispose children to asthma.[91,92] Moreover, the association of functional exercise capacity among obese asthmatics with BMI and not with FEV_1/FVC ratio, suggests a larger role of adiposity in exercise limitation among obese asthmatics.[93] Together these associations highlight the importance of addressing such obesogenic behaviors early in life to prevent the development of obesity and its associated pulmonary morbidities.

OBESITY-MEDIATED INFLAMMATION AND ASTHMA

Obesity is recognized to be a low-grade inflammatory state. Obesity-mediated inflammation has been associated with asthma and pulmonary function deficits.[33] Adipocyte hypoxia due to delayed neovascularization of adipose tissue is the most potent known stimulus for initiation of adipose tissue inflammation[94] and release of leptin, a proinflammatory adipokine. The proinflammatory cascade comprises a shift in the macrophage pool from the antiinflammatory M2 macrophages to the proinflammatory M1 macrophages (Fig 1).[95] Additionally, there is enhanced CD4+ T lymphocyte proliferation and differentiation into Th1 cells (Fig 1), with increased interferon-γ (IFN-γ), interleukin (IL)-6, and tumor necrosis factor (TNF) production.[95] This correlates with suppression of Th2 cells and decrease in T regulatory cells.[96] To maintain homeostasis, the proinflammatory effect of leptin is offset by antiinflammatory adipokines, including adiponectin, and omentin and the related antiinflammatory cytokine IL-10.[97–99]

Clinical studies have demonstrated elevated leptin[21] and reduced adiponectin levels in obese children[33,100] compared with nonobese children with asthma, suggesting that obesity-induced changes in the systemic adipocytokine milieu may underlie asthma in children.[101] Serum leptin levels correlate with higher Th1/Th2 cell ratio,[33,102] and higher serum IFN-γ levels,[21] indicative of nonatopic inflammation among obese asthmatic children compared with their nonobese counterparts, including in ethnic minority children.[33,103] These nonatopic systemic inflammatory patterns correlate with lower airway obstruction[33] and exercise-induced bronchoconstriction[104] among obese asthmatic children and persist into

adulthood.[105] These findings support epidemiologic reports of a lack of association between childhood obesity-related asthma and atopy[7,101,106] and higher prevalence of noneosinophilic asthma in obese children.[47] However, there are also reports of increased atopy among obese children,[53,54,107] including associations among BMI, atopic sensitization, and bronchial hyperresponsiveness,[53] as well as among BMI, atopy, cough, and wheeze,[54] particularly among girls[53,54] (Table 2). Similar disparate links among obesity, asthma, and atopy are also observed in investigations of allergic airway inflammation using fractional exhaled nitric oxide (FeNO) and obesity-related asthma. Whereas BMI was associated with asthma only among children with low FeNO,[108] BMI was associated with higher asthma disease burden among those with high FeNO[108] (Table 2). Furthermore, FeNO was not associated with asthma among obese children,[109] and a significant association between BMI and FeNO was observed only among nonasthmatic children.[110]

It is hypothesized that these disparate reports either support heterogeneity in the pathophysiology of obesity-related asthma[116] or are reflective of inherent differences in disease severity.[108] As noted in normal-weight asthma, although classic asthma is atopic, involving eosinophils and Th2 cells, severe asthma, even among normal-weight individuals, is nonatopic, mediated by neutrophils.[117] Whether similar variability in the involvement of innate immune pathways comprising Th1 cells, M1 macrophages, and neutrophils occurs in the pathogenesis of obesity-related asthma needs further investigation. Recent literature highlighting the role of metabolic dysregulation in obesity-related asthma[118] may begin to clarify these issues because differential inflammation among obese individuals with or without metabolic dysregulation may partly underlie the heterogeneity of the obese asthma phenotype.

Obese asthmatics are also less responsive to steroid treatments.[13,119] Peripheral blood mononuclear cells from obese asthmatics had lower production of antiinflammatory enzymes in response to dexamethasone,[119] and increased TNF production, which directly correlated with BMI.[119] Similar trends were also observed in bronchoalveolar lavage cells obtained from obese asthmatics.[119] On the basis of these reports, it can be speculated that obese asthmatics may respond to nonsteroidal antiinflammatory agents including montelukast or etanercept, a TNF inhibitor,[120,121] an aspect that needs further investigation.

OBESITY-MEDIATED METABOLIC DYSREGULATION AND ASTHMA

Association With Insulin Resistance

Obese children, particularly those of ethnic minorities, are predisposed to develop insulin resistance,[122] a precursor to diabetes,[123] that is associated with systemic hyperinsulinemia.[122] Our review of the recent literature highlights that metabolic dysregulation plays a role in pediatric obesity-related asthma (Table 3). Higher prevalence[124] and degree of insulin resistance[22] and higher prevalence of its surrogate marker, acanthosis nigricans,[23] and metabolic syndrome,[25] have been reported among children with asthma compared with their nonasthmatic counterparts. Insulin resistance correlates with the proinflammatory markers leptin and IL-6[124] and is found to be a predictor of both lower airway obstruction and reduced lung volumes, 2 distinct measures of lung function deficits, independent of general and truncal adiposity.[34]

Systemic inflammation, associated with insulin resistance, may be one of the mechanisms through which insulin resistance contributes to impaired lung function and asthma phenotype. In addition to its role in glucose metabolism, insulin has antiinflammatory effects.[126] Insulin supplementation has been associated with attenuation of lipopolysaccharide-induced acute lung injury in a murine model, with decreased TNF, IL-1β, and IL-6 in the bronchoalveolar lavage fluid.[127] Obesity-mediated inhibition of insulin signaling, a key mechanism underlying insulin resistance, is associated with adipose tissue inflammation with activation of Th1 cells and innate immune pathways, involving macrophages.[128] Recent studies have found that insulin resistance mediates the association of systemic Th1 polarization with obesity-mediated pulmonary function deficits among ethnic minority children.[103] Given these initial investigations into the association among insulin resistance, inflammation, and pulmonary function impairment, further study of the underlying immunometabolic pathways is needed to determine the mechanism through which insulin resistance contributes to the obese asthma phenotype.

Another mechanism is the influence of insulin on airway smooth muscle (ASM). Insulin resistance is associated with airway hyperreactivity due to increased ASM contractility.[129] Several mechanisms underlie this observation. Hyperinsulinemia increases laminin expression in bovine ASM cells via phospho-inositide-3 kinase (PI3K)/Akt dependent pathway.[129] Insulin resistance also increases free insulin-like growth factor, which is associated with ASM proliferation.[130] Furthermore, insulin may increase airway hyperresponsiveness by modulating parasympathetic stimulation, studied in an obese

TABLE 2 Summary of Pediatric Studies Reporting an Association Between Inflammatory Mediators of Obesity and Asthma

Study	Study Design	Obesity Definition/ BMI Analysis	Sample Size, n	Age Range, y	Ethnicity	Finding
Huang et al, 1999[53]	CS	BMI analyzed in quintiles	1459	13.2–15.5	Taiwanese	BMI was a significant predictor of atopy, allergic symptoms, and airway hyperresponsiveness in teenage girls.
Von Mutius et al, 2001[7]	CS	BMI analyzed in quartiles	7370	4–17	Caucasians (26.3%), African Americans (34%), Mexican Americans (35%), others (4.8%)	BMI is associated with asthma, but not with atopy, among children sampled in NHANES III.
Schachter et al, 2003[54]	CS	BMI >95th percentile for age and gender	5993	7–12	Caucasian	Higher BMI is a risk factor for atopy, wheeze and cough in girls only but not a risk factor for asthma or airway hyperresponsiveness in either boys or girls.
Leung et al, 2004[111]	CS	Body wt >120% of the median wt for height	115	7–18	Hong Kong	Obesity is not associated with FeNO or airway leukotriene levels in asthmatic children
Santamaria et al, 2007[109]	CS	BMI >95th percentile for age and gender	50	8–16	Caucasian (Italian)	No association between FeNO and obesity among asthmatic children
Huang et al, 2008[112]	CS	BMI >95th percentile for age and gender	89	10–16	Mexican	Higher markers of endothelial inflammation (sICAM) among obese asthmatics. No difference in CRP levels between obese and normal-weight asthmatic children.
Michelson et al, 2009[113]	CS	BMI z score analyzed as a continuous variable	10 140	0–19	Caucasians (60.6%), African Americans (14.4%), Mexicans (12.4%), other Hispanics (6.4%), others (6.3%)	BMI z score and CRP levels were associated with asthma severity among children in NHANES 2001–2004.
Visness et al, 2010[106]	CS	BMI >95th percentile for age and gender	16 074	2–19	Caucasians (59.9%), African Americans (14.7%), Mexicans (12.5%), others (12.9%)	Association between obesity and asthma greater among non-atopic children than atopic children. Association of CRP with asthma among nonatopics mediated by BMI.
Rastogi et al, 2012[33]	CS	BMI >95th percentile for age and gender	120	7–11	African Americans (50%), Hispanics (50%)	Obese asthmatics had systemic Th1 polarization, which directly correlated with lower airway obstruction.
Huang et al, 2012[46]	CS	BMI >95th percentile for age and gender	178	10–16	Mexican	Obese asthmatics and nonasthmatics had higher plasminogen activator inhibitor, fibrinogen, and BMI with inversely correlated with FEV_1/FVC ratio.
Khan et al, 2012[114]	CS	BMI >95th percentile for age and gender	124	12–20	African Americans (41%), Hispanics (59%)	hsCRP highest in obese asthmatics compared with obese nonasthmatics, normal-weight asthmatics, and healthy controls
Sah PK et al, 2013[115]	CS	BMI >95th percentile for age and gender	269	6–17	Whites (32.7%), nonwhites (67.3%)	Obese asthmatics with poor asthma control had lower serum levels of IL-5, IL-13, and IL-10.
Youssef et al, 2013[102]	CS	BMI >95th percentile for age and gender	70	9.3 ± 2.5 (obese asthmatics) 10.4 ± 1.3 (nonobese asthmatics) 10.7 ± 2.9 (controls)	Caucasian (Egyptian)	Obese asthmatics had high asthma severity, lower FEV_1. Serum leptin levels correlated with serum IFNγ levels, which directly correlated with asthma symptoms and inversely correlated with FEV_1 among obese asthmatic children.
Jensen et al, 2013[47]	CS	BMI z score >1.64 SD	361	8–17	Caucasian (Australian)	Noneosinophilic asthma more prevalent in obese asthmatic girls than boys.
Han et al, 2014[108]	CS	BMI >95th percentile for age and gender	2681	6–17	Caucasians (33.3%), African Americans (20.2%), Hispanics (40.2%), others (5.7%)	Adiposity indicators are associated with asthma among children with low FeNO. Adiposity indicators are associated with worse asthma morbidity in those with high FeNO among children in NHANES 2007–2010.

TABLE 2 Continued

Study	Study Design	Obesity Definition/ BMI Analysis	Sample Size, n	Age Range, y	Ethnicity	Finding
Rastogi et al, 2015[103]	CS	BMI >95th percentile for age and gender	168	13–18	African Americans (42.1%), Hispanics (57.9%)	Th1 polarization and monocyte activation correlated with metabolic abnormalities in obese asthmatics. Association of monocyte activation with pulmonary function was mediated by BMI, whereas that of Th1 polarization was mediated by insulin resistance.

CRP, C-reactive protein; CS, cross-sectional; HsCRP, high-sensitivity C-reactive protein.

TABLE 3 Summary of Pediatric Studies Reporting an Association Between Metabolic Dysregulation and Asthma

Study	Study Design	Obesity Definition	Sample Size, n	Age, y (Range/ Mean ± SD)	Ethnicity	Finding
Al-Shawwa, et al, 2006[24]	CS	BMI >95th percentile for age and gender	188	4–20	Not available	Hypercholesterolemia is associated with higher asthma frequency, independent of obesity.
Al-Shawwa et al, 2007[22]	CS	BMI >95th percentile for age and gender	415	2–18	Caucasian (40.5%), African Americans (38.5%), others (21%)	Obese asthmatics had higher levels of insulin resistance compared with morbidly obese nonasthmatics. Asthma prevalence directly correlated with insulin levels.
Arshi et al, 2010[124]	CS	BMI analyzed as a continuous variable	31	6–17.9	Caucasian (Australian)	Insulin resistance was present among atopic asthmatics, which correlated with leptin and IL-6 levels.
Del-Rio-Navarro et al, 2010[25]	CS	BMI >95th percentile for age and gender	443	12–14.2	Mexican	Prevalence of metabolic syndrome was higher among obese asthmatic boys, not girls.
Cottrell et al, 2011[23]	CS	BMI >95th–98.9th percentile for age and gender	17 994	4–12	Whites (90.7%), African American (2.3%), others (0.9%)	Asthma is associated with dyslipidemia and insulin resistance, independent of BMI.
Lee et al, 2012[58]	CS	BMI analyzed as a continuous variable	2082	8.5 ± 1.7	Taiwanese	Diet with high intake of fat and simple sugars was associated with increased risk of asthma.
Chen et al, 2013[125]	CS	BMI >95th percentile for age and gender	462	10–15	Taiwanese	Asthma was associated with higher levels of total cholesterol and low-density lipoprotein, particularly in overweight and obese children.
Rastogi et al, 2014[34]	CS	BMI >95th percentile for age and gender	168	13–18	African Americans (42.1%), Hispanics (57.9%)	Dyslipidemia and insulin resistance were predictors of pulmonary function deficits, independent of adiposity
Sanchez-Jimenez et al, 2014[49]	CS	BMI >95th percentile for age and gender	153	4–15	Caucasian (Spanish)	Insulin levels were associated with allergen sensitization among asthmatics.
Rastogi et al, 2015[103]	CS	BMI >95th percentile for age and gender	168	13–18	African Americans (42.1%), Hispanics (57.9%)	Th1 polarization and monocyte activation correlated with metabolic abnormalities. Insulin resistance mediated the association of Th1 polarization with pulmonary function.

CS, cross-sectional.

rat model.[131] These studies suggest that insulin resistance and associated hyperinsulinemia influence ASM cell function through different mechanisms, with the end result of increased bronchial hyperresponsiveness. Translational studies are now needed to study the role of each of these pathways in ASM cells obtained from obese asthmatics. We believe that better understanding of these pathways will be paradigm changing by potentially extending the use of metformin, routinely prescribed for insulin resistance, into management of obesity-related asthma.[132]

Association With Dyslipidemia

Similar to insulin resistance, links have been described between

dyslipidemia and wheezing in adults[133] and asthma among children[23] (Table 3). High-density lipoprotein (HDL) has been found to have a protective effect on pulmonary function indices in obese urban adolescents.[34] There is preliminary evidence to suggest that this effect may be mediated in part by the protective effect of HDL on monocyte activation.[103] There is also increasing evidence to suggest that the origins of the association of diet-induced metabolic dysregulation and pulmonary morbidity may start as early as in utero. For instance, altered fat intake, with low intake of poly-unsaturated fatty acids in the mother, has been associated with an increased predisposition to asthma among the offspring.[134] Thus, altered fat intake and dyslipidemia, irrespective of BMI, may be risk factors for airway inflammation and hyperreactive airways.[23]

Many mechanisms, including inflammation, may underlie the association between dyslipidemia and asthma. High fat intake in an adult cohort was associated with increased neutrophilic airway inflammation and an attenuated response to bronchodilators.[135] Similarly, a high-fat meal, associated with elevated triglycerides and reduced HDL after 2 hours, correlated with increased levels of FeNO.[136] Because high-fat diet is associated with decreased consumption of antioxidants, it may make the lung susceptible for oxidative damage and inflammation.[18] These pathways have not been studied in children, and thus the mechanisms underlying the association of dyslipidemia with asthma in children are relatively unknown.

CROSSTALK BETWEEN GENES AND ENVIRONMENT IN OBESITY-RELATED ASTHMA

The associations of asthma with obesogenic lifestyles and obesity-mediated metabolic dysregulation, inflammation, and mechanical fat load suggest that these environmentally mediated exposures and clinical states may influence the lungs via epigenetic mechanisms.[137,138] However, it is also evident that not all obese children with metabolic dysregulation or inflammation develop asthma, suggesting that differences in genetic susceptibility may also underlie the development of pulmonary morbidity in only some obese children. Although few studies have investigated the genetics or epigenetics of obesity-related asthma, we discuss the existing literature and the direction of association observed in these initial investigations.

Epigenetics of Obesity-Related Asthma

Epigenetic differences have been identified in context of both obesity[139,140] and asthma[141,142] compared with healthy controls. Among obese children, differences in DNA methylation, an epigenetic regulatory mechanism, were identified at 5 sites at the *FTO* gene, variants of which are strongly associated with obesity.[139] Similarly, hypomethylation of DNA at the *IL-4* gene promoter and hypermethylation of the *IFNγ* promoter have been observed in children with atopic asthma.[143] Genome-wide studies have also identified differential methylation of several genes associated with atopic inflammation among asthmatics.[141] However, only 1 study defined differences in DNA methylation among children with obesity-related asthma compared with children with normal-weight asthma, obesity without asthma, and healthy controls.[144] In this study, specific DNA methylation patterns were associated with childhood obesity-related asthma. Gene promoters encoding for molecules involved in Th1 polarization, chemokine (C-C motif) ligand 5 (CCL5), interleukin

2 receptor α chain (IL2RA), and T-box transcription factor (TBX21), were hypomethylated, whereas those encoding for receptors for immunoglobulin E and TGFB1, involved in Th1 cell inhibition, were hypermethylated,[144] suggesting DNA methylation plays a role in Th1 polarized systemic inflammation. Additionally, molecules such as PI3K and PPARγ, involved in glucose metabolism in T cells,[145] and lipid uptake, respectively, were hypomethylated in obese asthmatics relative to obese nonasthmatics. These findings suggest that molecules associated with both inflammation and metabolic dysregulation are differentially methylated among obese asthmatics. Because dietary intake and nutrients modify DNA methylation,[138] these pilot results highlight the need for additional studies to investigate the effect of diet modification and related weight loss on DNA methylation and its association with insulin resistance, dyslipidemia, and systemic inflammation among obese asthmatics.

Genetics of Obesity-Related Asthma

While few conclusive studies have identified susceptibility loci for development of asthma among obese children,[146] a common 16p11.2 inversion that may protect against susceptibility to asthma and obesity has been identified in adults.[147] This inversion, found in 10% of Africans and ~50% of Europeans, is associated with increased expression of obesity-associated proteins including apolipoprotein B (APOB48R) and SH2B1, which inhibit type 1 interferon and IL27. This inversion explains ~40% of the population-attributable risk for joint susceptibility to obesity and asthma. Additional genes including the β2-adrenergic receptor gene (*ADRB2*),[148,149] the TNF gene,[150,151] and the lymphotoxin-α *(LTA)* gene[152,153] have been associated in

both obesity and asthma in children. However, the limited number of these studies highlights the paucity of data on genetic susceptibility for obesity-related asthma. Moreover, given the ethnic differences in the prevalence of pediatric obesity-related asthma, studies are needed to identify the role, if any, of ancestry-specific genetic polymorphisms that may explain the greater disease burden among Hispanics and African Americans.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Together, these studies on the mechanisms underlying obesity-related asthma suggest a complex interplay among mechanical fat load of truncal adiposity, metabolic dysregulation, and inflammation. On the basis of these studies, we suggest that pediatricians consider implementing the following in their clinical practice:

1. Routine evaluation for truncal adiposity by measuring waist circumference among their patients who are overweight/obese

2. Routine evaluation for metabolic dysregulation, specifically for insulin resistance and dyslipidemia in fasting blood among obese children,[154] particularly in those with truncal adiposity

3. Elucidation of respiratory symptoms among obese children, particularly those with truncal adiposity, and/or metabolic dysregulation

4. Testing for pulmonary function deficits among obese children, especially those with truncal

adiposity, and/or metabolic dysregulation

5. Ensure good asthma control and encourage physical activity for weight control because there is no therapy specific for obesity-related asthma, and these children are suboptimally responsive to inhaled steroids

6. Encourage parents to monitor dietary intake, with increased intake of foods included in a Mediterranean diet and decreased consumption of processed foods

ROAD MAP FOR FUTURE

In summary, obesity-related asthma is an emerging health problem among children. Although it appears to be distinct from normal-weight asthma, further investigations are needed to better define its pathophysiology. The association of obesity-related asthma with insulin resistance and dyslipidemia provides directionality to future investigations into underlying pathways that may be amenable to pharmacologic modification. Because these metabolic abnormalities are obesity-mediated but do not develop in all obese children, quantification of these metabolic biomarkers may help identify obese children at risk for developing obesity-mediated pulmonary morbidity. Moreover, the association of asthma with diet, particularly fat and vitamin intake, and the association of diet with DNA methylation highlights the need for studies to better define the links between diet and epigenetics of obesity-related asthma, in the presence of insulin resistance and/or dyslipidemia. Given the modest effect of weight loss interventions

among children and lack of studies on the pulmonary effects of bariatric surgery, these future studies will identify mechanisms underlying the beneficial effects of nutrients and thereby facilitate the development of targeted diets for obese children at risk for developing obesity-related asthma, specifically those of Hispanic and African American ancestry. Identification of ancestry-specific genetic susceptibility will not only shed light on the reasons underlying increased disease burden among certain populations but may facilitate the development of primary prevention strategies for those identified to be genetically susceptible to obesity and its associated morbidities. Because obese asthmatics are suboptimally responsive to current asthma medications, identification of mechanisms underlying obesity-related asthma will provide direction for development of both preventative strategies and targeted therapy.

ABBREVIATIONS

ASM: airway smooth muscle
ERV: expiratory reserve volume
FeNO: fractional exhaled nitric oxide
FEV_1: forced expiratory volume in 1 second
FRC: functional residual capacity
FVC: forced vital capacity
HDL: high-density lipoprotein
IFN-γ: interferon-γ
IL: interleukin
PAQLQ: Pediatric Asthma Quality of Life Questionnaire
RV: residual volume
Th cells: T helper cells
TLC: total lung capacity
TNF: tumor necrosis factor

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