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Diet and Metabolism in the Evolution of Asthma and Obesity

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Summary

Obesity is a major risk factor for asthma. This association appears related to altered dietary composition and metabolic factors that can directly affect airway reactivity and airway inflammation. This article discusses how specific changes in the western diet and metabolic changes associated with the obese state affect inflammation and airway reactivity, and reviews evidence that interventions targeting weight, dietary components, lifestyle and metabolism might improve outcomes in asthma.

Keywords

Diet; obesity; asthma; microbiome; airway reactivity; metabolic syndrome; immunometabolism

Introduction

The world is in the midst of a major obesity epidemic, and in the United States nearly 40% of the adult population is obese.¹ Obesity is a major risk factor for asthma, and is particularly associated with poorly controlled asthma.² While many different factors could contribute to the pathogenesis of asthma in obesity, changes in dietary composition and metabolic factors directly affect airway reactivity and airway inflammation.³ This article discusses how specific changes in the western diet and metabolic changes associated with the obese state affect inflammation and airway reactivity, and reviews evidence that interventions targeting weight, dietary components, lifestyle and metabolism might improve outcomes in asthma.

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Diet

The obesity epidemic is associated with a shift in the quality and composition of food in the diet, not simply increased calories. Diets that produce obesity are typically high in red and processed meats, high in fats and fried foods, low in fiber, and high in sugar. Such a dietary pattern is associated with low lung function and increased respiratory symptoms, even when controlled for BMI.^{4,5} These effects on the respiratory system are likely to occur because such nutrients can have profound effects on the immune system and the pathophysiology of asthma, as outlined in detail below.

Effects of dietary fiber on asthma

Dietary fiber is metabolized by bacteria in the gut to produce short chain fatty acids. Short chain fatty acids (SCFA) enter the circulation, and can affect a variety of cellular processes, including the pathogenesis of asthma in obesity. Both the composition (type and amount) of fiber in the diet, and the population (species and relative quantity) of the gut microbiome influence the production of short chain fatty acids. For example, diets high in soluble fiber produce high levels of the short chain fatty acids acetate, propionate and butyrate. These short chain fatty acids enter the circulation and can signal through two major receptors: Free Fatty Acid Receptors 2 and 3 (also known as G-Coupled Protein Receptors 43 and 41).⁶ These receptors are expressed by many cell types, including those of the immune system, and affect immune responses. The effect of dietary fiber on allergic airway disease has been studied in animal models. A low fiber diet increased airway inflammation in a mouse model of allergic airway disease. This increased inflammation occurred because the low fiber diet changed the gut microbiome, decreasing production of the circulating short chain fatty acid propionate; propionate inhibited the ability of dendritic cells to promote allergic inflammation, and so the lower propionate in the low fiber diet augmented allergic airway inflammation.⁷ Another study showed that a high fiber diet increased circulating levels of acetate, and suppressed allergic airway inflammation in mice: circulating acetate altered acetylation of the FoXP3 promotor, reducing T reg cell function, and suppressing allergic airway inflammation. Remarkably, the high fiber diet fed to pregnant animals produced an epigenetic change and resistance to allergic airway inflammation in offspring.⁸ These elegant studies in mice suggest dietary fiber modulates allergic airway inflammation through effects on circulating short chain fatty acids, and that these effects may occur as early as during in utero development.

There have, as of yet, been few studies of dietary fiber in people with asthma, and so the clinical relevance of these observations in mice remains to be determined. However, in a pilot study of 29 people with asthma randomized to either a high fiber or low fiber meal challenge, there were some interesting observations: four hours after the meal, those who received the high fiber challenge had decreased cellular inflammation in sputum, decreased exhaled nitric oxide and improved lung function. These changes were associated with increased expression of receptors for short chain fatty acids in sputum.⁹ There have been no other interventional studies in humans targeting fiber alone, though this is often a component of the lifestyle interventions for asthma discussed below.

Effects of a high fat diet on asthma

A number of publications have reported the effects of a high fat diet sufficient to produce obesity on airway disease in animal models: whether the effects on airway disease relate directly to the dietary fat (and the specific dietary fat) or the other myriad complications induced by obesity is not entirely clear. However, these studies have shown that high fat diet induced obesity leads to airway reactivity even in the absence of allergen or other challenge, increases response to pollutants such as ozone, but has a variable effect on allergic airway inflammatory responses.^{10–13} Some of the reported differences likely reflect strain differences in mice, but could also reflect differences in the specific composition of the high fat diets.

Consumption of a high fat diet increases circulating levels of free fatty acids. Free fatty acids can stimulate innate immune responses, through activation of nuclear factor κ -light-chain enhancer of activated B cells (NF- κ B), and the nucleotide-binding and oligomerization domain–like receptor, leucine-rich repeat and pyrin domain–containing 3 (NLRP3) inflammasome.^{14–16} A high fat diet might contribute to airway disease even without causing obesity, as illustrated by studies both in mouse models, and in humans. Mice fed a high fat compared with normal chow diet for only two weeks develop increased airway reactivity, and higher levels of IL-1 β in lung tissue, although this is not associated with overt pulmonary inflammation.¹⁷ In humans, a single high fat diet meal challenge increased airway neutrophilic inflammation, and decreased response to bronchodilator.¹⁸

Targeting dietary components to treat asthma

Studies of dietary and lifestyle interventions in asthma could transform our approach to patients with asthma. As of yet there is a paucity of controlled trials in this field -- lifestyle interventions are complex and implementation challenging -- but there are some studies which suggest that targeting diet and lifestyle can improve asthma control. Wood et al compared a diet high in fruit and vegetables (2 servings of fruit and 5 of vegetables) with one low fruit and vegetables (1 serving of fruit, and up to two servings of vegetables): participants on the high fruit and vegetable intervention had reduced asthma exacerbations over the 16 weeks of the study. Some of the participants in the low fruit and vegetable arm received an anti-oxidant supplement, but this did not mitigate the increased risk of asthma exacerbations, suggesting that the whole food dietary component was more important than anti-oxidant supplementation.¹⁹ Ma et al performed a 6-month controlled study targeting improved dietary quality versus maintaining usual diet. In this pilot study with 90 participants, better dietary quality tended to improve asthma control and asthma quality of life.²⁰ Sexton et al performed a small 12 week pilot study in 38 patients with asthma, and found that implementing a Mediterranean diet might have some efficacy in asthma, though it did not achieve statistical significance in this small study.²¹ Of note, it is not just obese patients that seem to benefit from improved dietary quality and exercise: Toennesen et al studies the effects of an 8 week intervention of high intensity exercise versus diet (high protein, low glycemic index) versus combination of both: 125 participants completed the study – only participants in the combined intervention experienced a significant benefit in terms of asthma control and quality of life. This was not associated with significant changes in airway reactivity or inflammation.²²

Effects of weight loss on asthma

Lifestyle Interventions—Weight loss can be achieved with lifestyle interventions. There have been a few studies of this in children and adults with asthma (Table 1). These studies suggest that a weight loss of 5–10% may produce a significant improvement in asthma control,^{16–19,30–32} Exercise may have an additional benefit on asthma control, but it is not clear whether this is attributable to a direct effect of exercise on asthma control, or whether it is related to greater weight loss.²³

Weight loss surgery—There have now been a number of studies suggesting that bariatric surgery produces dramatic improvements in asthma control and lung function.^{23–31} Bariatric surgery is an expensive, complex procedure, but it may have a significant public health impact: Hasegawa et al found approximately 22% of patients with asthma had an asthma exacerbation leading to an Emergency Department visit or hospitalization annually prior to bariatric surgery, this decreased to 11% annually after surgery.³² The mechanisms by which bariatric surgery improves asthma control likely include mechanical unloading of the respiratory system, reduced metabolic inflammation, and changes in dietary composition.³³

Exercise—There are no published studies of the effects of exercise in obese animal models of asthma, though a number of reports in lean mouse models of asthma suggest favorable effects on a variety of parameters pertinent to allergic asthma, these include:

- Decreases chemokine responsive migration to lung: lean OVA mouse model³⁴
- Enhanced Tregulatory cell number and function in the lung: lean OVA mouse model³⁵
- Decreased airway smooth muscle thickness: lean OVA mouse model³⁶
- Decreased airway inflammation, airway reactivity and remodeling: lean OVA mouse model^{37,38,39}
- Decreases airway inflammation, increases epithelial modeling: lean OVA guinea pig model⁴⁰

The effects of exercise on asthma in people has been studied in the context of both obese and non-obese asthma. In contrast to animal studies, these reports have not shown effects on airway inflammation – perhaps because they have included multiple phenotypes of asthma -- but in general do seem to improve symptoms and asthma control, especially when combined with a dietary intervention, even in those non-obese patients with asthma (Table 2).^{22,23,27,41–45}

Metabolism

Metabolic Syndrome

Metabolic syndrome (MetS), a condition defined by a grouping of clinical factors, including abdominal obesity, poor glycemic control, dyslipidemias (elevated triglycerides and/or reduced high density lipoprotein cholesterol levels), and hypertension, is present in about 2/3 of the obese population.^{46,47} Although not a specific disease per se, MetS increases the risk

for diabetes, cardiovascular diseases, hepatic steatosis and cancer, to name a few. Given obese subjects that concomitantly have this condition have a greater propensity for developing chronic diseases in multiple organs, it is reasonable to speculate that MetS can also affect the lungs, and to some extent, potentially explain why obesity is associated with asthma. The question of whether in fact MetS is independently associated with changes in lung function or asthma diagnosis and morbidity has been evaluated in several epidemiological studies (See Table 3). In a large cross sectional studies of adults and children, MetS diagnosis was associated with reduced FEV₁ and FVC,⁴⁸⁴⁹⁵⁰ and increased respiratory symptoms after adjusting for potential confounders. Longitudinally, it is associated with steeper loss of lung function over time and increased risk for asthma diagnosis; however, it remains unclear how much of this incidence is confounded by BMI.⁵¹ Individual MetS components are also associated with asthma in adult and children, particularly poor glycemic control, dyslipidemias and abdominal girth.⁵²

The mechanisms by which MetS relates to asthma are likely multifactorial and involving several pathways.⁵³ Poor glycemic control, associated with insulin resistance and hyperinsulinemia, could explain deficits in lung function and greater respiratory symptoms. Insulin may induce hypercontractility in airway smooth muscle (ASM) via phosphoinositide 3-kinase and Rho-kinase-dependent pathways, and through vagally mediated bronchoconstriction with loss of inhibitory muscarinic receptor 2 functionality on parasympathetic nerves.⁵⁴⁵⁵⁵⁶ Epidemiological and clinical data support a role for insulin by showing an inverse association between insulin resistance and lung function decrements and by the fact that subjects inhaling human insulin (now discontinued Exubera) exhibited more respiratory symptoms, including cough and mild dyspnea, along with reductions in FEV₁ and diffusing capacity of the lung for carbon monoxide.⁵⁷

Oxidative Stress

Compared to their leaner counterparts, obese asthmatics have increased levels of airway and systemic biomarkers of oxidative stress, associated with increased asthma morbidity and reduced response to inhaled corticosteroids.^{58–60} Oxidative stress is a complex process involving a fine balance between many potential oxidative sources and the function of antioxidant mechanisms. While MetS has been widely associated with greater systemic oxidative stress & inflammation,⁶¹ it is unclear if it has similar effects in the airways of asthmatics. However, animal models and epidemiological studies suggest that altered L-arginine and nitric oxide (NO) metabolism as a potential pathway by which obesity, metabolic syndrome and airway oxidative stress are linked. Compared to mice fed regular chow, those taking high-fat or high-fructose diet for 18 week, developed MetS and had increased iNOS (inducible nitric oxide synthase) protein and nitrotyrosine lung levels (a marker for oxo-nitrative stress) while having lower NO in the absence of increased airway inflammation.⁶² The unexpected lack of NO increase while iNOS is upregulated suggests a NO redox imbalance, which was explained by the fact that diet induced MetS reduced the lung L-arginine/ADMA (asymmetric di-methyl arginine and a methylated product of L-arginine catabolism) ratio levels. When this imbalance occurs, iNOS becomes uncoupled, producing anion superoxide at the expense of NO production.⁶³ These results have been replicated in primary human airway epithelial cells of asthmatics treated with ADMA.

Interestingly, the clinical relevance of these results were recently validated in a cross sectional study of participants from the Severe Asthma Research Program (SARP), which showed that obese subjects had lower L-arginine/ADMA ratios, which were associated with lesser exhaled NO levels, reduced lung function, and more frequent respiratory symptoms.⁶⁴ Having greater ADMA levels in obesity and MetS coupled with increased levels of allergic inflammatory mediators, such as IL-4, can have synergistic effects in producing mitochondrial dysfunction, which is a common feature of these conditions and also associated with asthma.⁶⁵

Dyslipidemias immunometabolism

Elevated triglycerides and/or reduced HDL are MetS factors, which have independently been associated with greater asthma prevalence, respiratory morbidity and reduced lung function in children and adults.^{66,67} These dyslipidemias are not only indicative of adipose metabolic dysfunction but are also related to immune changes that may explain the underlying mechanism supporting these associations.⁶⁸ Obesity is a low-grade inflammatory state in which adipocytes secrete cytokines activating and recruiting macrophages that play pivotal roles in systemic inflammatory responses, including activation of Th cells, in particular Th1 polarization, which has been described in obese asthmatic children.⁶⁹ A large cross sectional study of obese and normal weight adolescents with and without asthma, showed that having reduced HDL was significantly associated with increased Th1/th2 (Th1 [CD4⁺IFN γ ⁺] / Th2 [CD4⁺IL4⁺] cells) cell responses to phytohemagglutinin, and inversely associated with percent patrolling monocytes but directly associated with CCR2 expression on patrolling and resident monocytes. These associations suggested a role for obesity-mediated dyslipidemia in monocyte activation among obese subjects with asthma and may explain why these lipid disorders are associated with asthma in the context of MetS and obesity.⁶⁷ The immunological consequences of metabolic dysregulation in obesity have far reaching consequences beyond Th1 polarization. For example, obese subjects, independently of asthma, have increased odds for developing H1N1 influenza and when they do, it can be of greater severity.⁷⁰ This phenomenon may be partly explained by the fact that 12 months after vaccination, greater BMI is associated with a steeper decline in influenza antibody titers.⁷¹ Furthermore, peripheral blood monocytes cells from obese individuals challenged ex vivo with vaccine strain virus show decreased CD8. T-cell activation and decreased expression of functional proteins compared with healthy weight individuals.⁷² In addition, obese individuals also have dysfunctional Natural Killer cells and a greater degree of B-cell immune activation, which is associated with a suboptimal humoral response to vaccines.⁷³

In summary, metabolic deregulations associated with obesity are linked to changes in oxidative stress, airway function and immunological changes, all of which can confer increased susceptibility to have increased asthma morbidity, as well as having increased risk for having viral respiratory infections and pneumonia that can indirectly also worsen asthma.

Conclusions

Obesity is a complex disorder associated with altered exposures and behaviors (diet, lifestyle and physical activity). Excess adipose tissue contributes to immunometabolic disarray,

increased oxidative stress and decreased bioavailability of nitric oxide. All these factors combine to alter the pattern of established airway disease, and to produce de novo airway disease. Obesity is producing an epidemic of airway disease poorly responsive to conventional therapies, therapies developed for treatment of disease in lean patients. Understanding the interactions between altered exposures, metabolic syndrome and airway disease will yield fundamental insights into the relationship between respiration and metabolism, and to new and better treatments for patients with obesity and asthma.

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Key Points

1. Obesity is a major risk factor for asthma, and obese patients tend to have poorly controlled asthma that does not respond to controller therapy as asthma in lean patients.
2. The development of obesity occurs because of changes in the quality and composition of the diet: specific dietary factors can affect airway disease, and might be as important as excess weight in contributing to the pathogenesis of asthma in obesity.
3. Significant weight loss can improve asthma control, changing dietary quality might also be effective for improving asthma control.
4. Metabolic syndrome in obesity is associated with increased asthma severity, as metabolic dysfunction contributes to altered immune and airway function.
5. Increased oxidative stress, and decreased bioavailability of nitric oxide in the airway may result in enhanced airway closure in obese individuals.

Table 1:

Studies of the effect of diet-induced weight loss on asthma control

author	intervention	n	weight change in intervention group	effect on asthma
Freitas 2017	Diet and sham versus diet and exercise	55	Diet alone: ↓ 3.1% Diet and exercise ↓ 6.8%	Significantly greater improvement in asthma control and quality of life with addition of exercise
Pakhale 2015	Liquid meal replacement	22	↓ 19%	Significant improvement in AHR and asthma control
Ma, 2015	Diet and exercise	330	↓ 4.1% (versus ↓2.1% in enhanced care)	Improved asthma control in those who lost 5% weight
Dias-Junior, 2014	Diet and weight loss medication (controlled study)	22 adults	↓ 7.5%	Improved asthma control
Scott, 2013	Diet and exercise (controlled study)	28 adults	↓ 8.5%	Improved asthma control
Jensen, 2013	Dietary intervention versus wait list control	32 children	↓5.7% versus ↑ 1.8%	Improved asthma control in intervention group
Hernández Romero, 2008	Diet including meal replacements Diet	96 adults	↓ 10.6 % (diet + meal replacement) ↓ 6.1% (diet)	Improved symptoms, decreased medication
Johnson, 2007	Diet (single arm)	10 adults	↓ 8%	Improved asthma control
Stenius-Aarniala, 2000	Diet (controlled study)	19 adults	↓ 14.5%	Improved lung function and symptoms

Table 2:

Studies of the efficacy of exercise intervention for asthma

author	intervention	n	duration	main findings
Turk, 2017	outpatient pulmonary rehabilitation	53 obese, 85 non-obese	12 weeks	improved 6 minute walk distance and asthma control score
Freitas, 2017	weight loss versus exercise and weight loss	55 obese	12 weeks	more significant improvement in asthma control in the diet and exercise group (also lost more weight)
Toennesen, 2017	improved dietary quality, exercise and diet, exercise or control	125 non- obese	8 weeks	participants randomized to improved dietary quality and exercise had most significant improvement in asthma control and quality of life, no effect on airway inflammation or airway reactivity
Franca-Pinta, 2015	exercise versus control	58 (obese and non-obese)	12 weeks	exercise group experienced improved asthma control and decreased airway reactivity
Scott, 2013	exercise versus diet versus exercise and diet	46 obese	10 weeks	exercise not as effective as inducing either weight loss or improved asthma control as diet and diet plus exercise intervention
Boyd, 2012	usual care or walking program	19 (obese and non-obese)	12 weeks	showed feasibility of intervention, likely underpowered to see effects on clinical outcomes
Turner, 2011	exercise versus control	35 older adults	3 months	improved symptoms and quality of life in the exercise intervention group
Mendes, 2010	usual care or exercise	101 non- obese	3 months	improved aerobic capacity and asthma symptom free days in the exercise group

Table 3.**Epidemiological Studies on Lung Function Or Asthma Diagnosis And Morbidity**

Author	Exposure	Study design	population	Outcomes
Brompton et al ⁵²	Metabolic Syndrome	Prospective	23,191 Nord-Trondelag Health Study participants from 1995–2008, ages 19–55 y	Metabolic syndrome is associated with higher risk for incident asthma ; not BMI adjusted.
Assd et al ⁵¹	Metabolic Syndrome	Prospective	4,619 eligible participants in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort followed over 25 years	Metabolic syndrome predicted incident asthma among women but not men ; this association was confounded by BMI
Kuschnir, et al ⁷⁴	Metabolic syndrome	Cross sectional , multi center school survey	metabolic syndrome and asthma	Metabolic syndrome was associated with severe asthma
Forno et al ⁷⁵	Metabolic syndrome, insulin resistance	Cross sectional	1429 adolescents aged 12 to 17 years in the 2007–2010 National Health and Nutrition Examination Survey	Insulin resistance and MS are associated with worsened lung function in overweight/obese adolescents
Lee Ej, et al ⁷⁶	Metabolic Syndrome	Cross sectional	9,942 individuals (4,716 men and 5,226 women) Participating in The Korean Health and Genome Study	Metabolic syndrome was associated with asthma-related respiratory symptoms. Those with symptoms had lower lung function.
Cardet JC ⁷⁷	Obesity and insulin resistance	Cross sectional	12□421 adults, ages 18–85 years from the National Health and Nutrition Examination Survey 2003– 2012	The relationship between obesity and current asthma was stronger with increasing insulin resistance levels