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REVIEW

Metabolic Dysfunction and Asthma: Current Perspectives

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Abstract: The increasing knowledge of the mechanisms involved in metabolism is shifting the paradigms by which the pathophysiology of many pulmonary diseases is understood. Metabolic dysfunction is recognized in obesity-associated asthma, but other metabolic conditions have been shown to be independently related to asthma. Novel insights have also recently been brought by metabolomics in this filed. The purpose of this review is to discuss current perspectives regarding metabolic dysfunction in asthma, from obesity-related asthma to other metabolic conditions and the role of current pharmacological therapeutic strategies and lifestyle interventions. Obesity is a well-recognized risk factor for asthma across the lifespan, which is generally associated with poorer response to current available treatments, rendering a more severe, refractory disease status. Besides the epidemiological and clinical link, untargeted metabolomics studies have recently supported the obesity-associated asthma phenotype at the molecular level. Not only obesity-related, but also other aspects of metabolic dysregulation can be independently linked to asthma. These include hyperinsulinemia, dyslipidemia and hypertension, which need to be taken into account, even in the non-obese patient. Untargeted metabolomics studies have further highlighted several other metabolic pathways that can be altered in asthma, namely regarding oxidative stress and systemic inflammation, and also suggesting the importance of microbiota in asthma pathogenesis. Considering the reduced response to corticosteroids, other pharmacologic treatments have been shown to be effective regardless of body mass index. Non-pharmacologic treatments (namely weight reduction and dietary changes) may bring substantial benefit to the asthmatic patient. Taken together, this evidence points towards the need to improve our knowledge in this filed and, in particular, to address the influence of environmental factors in metabolic dysfunction and asthma development. Personalized medicine is definitely needed to optimize treatment, including a holistic view of the asthmatic patient in order to set accurate pharmacologic therapy together with dietary, physical exercise and lifestyle interventions.

Keywords: asthma, diet, inflammation, metabolic, metabolomics, obesity

Introduction

The increasing knowledge of the mechanisms involved in metabolism is shifting the paradigms by which the pathophysiology of many pulmonary diseases is understood.[1] Metabolic dysfunction is recognized in obesity-associated asthma, although the underlying mechanisms are still not fully understood. Besides and beyond obesity, other metabolic conditions that are part of the metabolic syndrome (ie, a cluster of at least three conditions that occur together, including obesity, increased blood pressure, high blood sugar and abnormal cholesterol or triglyceride levels),[2] have been shown to be independently related to asthma. These conditions may contribute or even confound the epidemiological and clinical link of obesity

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and asthma. Novel insights have recently been brought by metabolomics in this filed. The purpose of this review is to discuss current perspectives regarding metabolic dysfunction in asthma, from obesity-related asthma to other metabolic conditions and the role of current pharmacological therapeutic strategies and lifestyle interventions.

Methods

The search for articles was carried out in MEDLINE database to assess the link between metabolic dysfunction and asthma using studies in English up to January 2020. The search terms included were: "asthma" OR "wheezing" OR "airway hyperreactivity" AND "metabolism" OR "metabolic" OR "metabolomics". The following terms were also considered: "obesity", "hypertension", "diabetes", "glucose", "insulin", "hypercholesterolemia", "cholesterol", "hypertriglyceridemia" and "triglyceride". Original articles and systematic reviews were included. The references of these initial studies were hand searched and possibly eligible studies were also included for review and discussion.

Literature Review and Discussion

Linking Obesity and Asthma

The association between obesity and asthma is firmly established.[3] In children, higher and faster weight gain is associated with higher risks of preschool wheezing and school-age asthma, as well as bronchial hyperresponsiveness at school age and adolescence.[4] In general, asthma prevalence increases with children's body mass index (BMI) percentile.[5] This effect seems to occur very early in life, including during pregnancy, as significant associations of maternal obesity, gestational weight gain and asthma development in the offspring have been confirmed by meta-analysis.[6] In adults, the odds of developing asthma also increase with increasing BMI,[7] if BMI is over 30Kg/m^2 in women, the risk of developing asthma rises by more than 2.5 fold.[8]

Besides the epidemiological link, obesity-associated asthma has been recognized as a distinct clinical phenotype. In early childhood, it may be characterized by increased disease severity and persistence, with lower response to corticosteroids.[9–11] The same features have also been described in obese asthmatic adults, with increased healthcare utilization and reduced quality of life.[12] Typically, obesity-associated asthma is defined as a late-onset non-type 2 phenotype. This is not specific to adults, as many obese children with asthma also have a predominance of the non-type 2 phenotype.[13] However, a severe form of allergic, eosinophilic, type 2 asthma has also been acknowledged to be associated with obesity.[14] Thus, obesity-associated asthma may be currently summarized into two forms, both associated with more severe asthma: a) a late-onset non-type 2 phenotype (where late-onset includes adults and older children); b) an early-onset type 2 phenotype (perhaps a pre-existing asthma complicated by obesity).[15,16]

Besides and Beyond Obesity: Metabolic Conditions and Their Link to Asthma

Not only obesity but also other metabolic syndrome conditions have been independently linked to asthma (Figure 1). The metabolic syndrome is not only associated with an increased risk of heart disease, stroke and type 2 diabetes but also with other low grade systemic inflammatory diseases. A prospective cohort study including more than 23,000 adults has shown that a person with metabolic syndrome has over 50% higher risk of asthma incidence with an average of 11 years of follow-up.[17] An increased risk of asthma in the elderly has also been recently shown in patients with metabolic syndrome, with a positive linear association between the number of metabolic syndrome components and the prevalence of asthma.[18] However, study results have been heterogeneous and metabolic syndrome per se was not an independent predictor of asthma when BMI was adjusted.[19] In fact, the recent study in the elderly has shown that, among metabolic syndrome components, abdominal obesity is most significantly related to asthma.[18] It must be considered though that metabolic syndrome conditions interact (eg, hyperinsulinemia may be a causal factor in the development of obesity),[20] and there may be a bias in the literature as many of these studies analyzing asthma outcome were based on selected cohorts of obese children and adults.[5] The link between these metabolic conditions and asthma may be important to better understand the role of metabolic dysfunction in asthma and ultimately to establish effective therapeutic interventions. If obesity is indeed the phenotypic manifestation of more comprehensive metabolic alterations that may contribute to asthma development, any intervention aimed at reducing weight without directly impacting these metabolic pathways is likely to be only partially effective in preventing and controlling asthma.[21] In fact, in the study by Park and col, the mediation analysis has suggested that the metabolic syndrome is significantly associated with asthma through insulin resistance and systemic inflammation.[18]

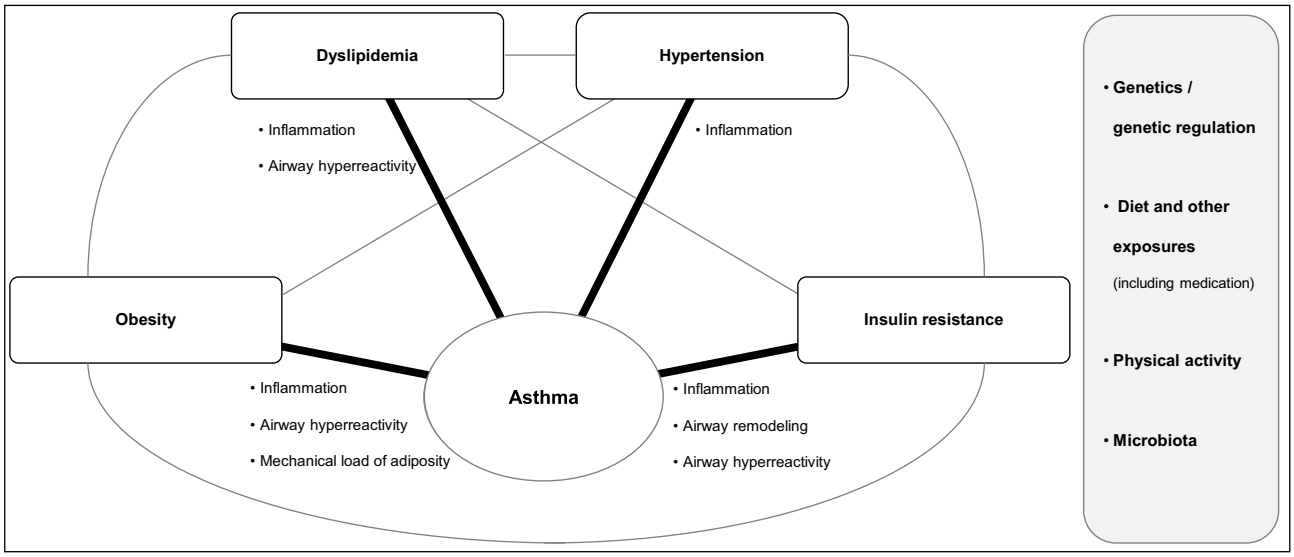

Figure 1 Schematic representation of the metabolic syndrome-asthma link.
Notes: Not only obesity-related but also other aspects of metabolic dysregulation can be independently linked to asthma, including dyslipidemia, hypertension and insulin resistance. Most commonly recognized mechanisms linking metabolic syndrome conditions and asthma involve inflammation and airway hyperreactivity. Metabolic syndrome conditions are associated in a complex multidirectional network and their link with asthma development or progression generally depends on the composite interaction between host genetics, diet and other exposures (environmental, medication, etc), physical activity and microbiota."

Insulin resistance can be broadly defined as an impaired biologic response to insulin. This broad definition remains elusive as there is no generally accepted test for insulin resistance. In clinical practice, insulin resistance usually refers to a state in which a given concentration of insulin is associated with a subnormal glucose response.[22] Insulin resistance is associated with asthma risk in children,[23,24] and adults.[25–27] It has been described, in nondiabetic adults, as a risk factor for lower lung function or accelerated lung function decline, even when controlled for BMI.[28,29] Direct exposure of the airways to insulin is associated with smooth muscle hypertrophy, bronchial hyperresponsiveness and lung remodeling.[30] Adults inhaling human insulin (now discontinued) may exhibit cough, dyspnea, along with reductions in lung function and diffusing capacity of the lung for carbon monoxide.[31] Insulin resistance may increase bronchial reactivity through inhibition of presynaptic M2 muscarinic receptors, while hyperinsulinemia may interfere with the anti-inflammatory effects of insulin.[32] It is also associated with skeletal muscle weakness, including the respiratory system,[24] by reducing glucose utilization and inducing abnormal fat metabolism in the muscle, which may impair energy production in the mitochondria. In fact, excessive weight gain in early life is associated with increased risk of insulin resistance and asthma development during school years.[33] Similarly, both visceral fat accumulation and insulin resistance have been associated with the development of asthma in type 2 diabetic adults.[27]

Dyslipidemia and hypertension are also risk factors for lower lung function or accelerated lung function decline.[34,35] In the study by Park and col low high density lipoprotein cholesterol has been associated with asthma in the elderly.[18] Higher prevalence of asthma has been found in children with high serum cholesterol and triglyceride levels.[5,36,37] Asthma and hypertension coincide more frequently than expected by chance. Its comorbidity with asthma persists after consideration of excessive weight, smoking and use of specific drugs (including non-selective beta-blockers and systemic corticosteroids), although it becomes weaker.[38,39] There are several shared genes associated with asthma and hypertension that form modules on interaction networks, suggesting that this comorbidity could be at least partly explained by concordantly altered genetic regulation.[39,40] Another possible explanation relates to medication side effects, particularly the use of non-selective beta-blockers.[39] Interestingly, lower doses of inhaled corticosteroids (ICS) may confer a "protective" association, while the opposite is applicable for higher doses of inhaled or systemic corticosteroids.[39,41,42] This may suggest that adequate control of lower airway inflammation at appropriate doses of ICS may attenuate cardiovascular risk.

Thus, hyperinsulinemia, dyslipidemia and hypertension need to be considered as they may also be associated with asthma development or progression. Furthermore, this may contribute or even confound the epidemiologic link between asthma and obesity.[5] Children whose weight is within or even below the healthy range may still be more susceptible to develop asthma because of metabolic derangements.[5] In fact, children with diagnosed asthma tend to have higher serum triglyceride levels and higher rates of insulin resistance. These associations are independent of gender, tobacco smoke exposure and BMI.[5]

Inflammation is a common feature in most studies addressing metabolic dysfunction in asthma. Asthma is a heterogeneous disease that is usually characterized by chronic airway inflammation. However, there is increasing appreciation of asthma as a systemic disease. Inflammation is not restricted to the airways, with profound cross-communication with other organs at distance through inflammatory mediators. In obesity-associated asthma, adipose tissue increases pro-inflammatory cytokines that lead to systemic inflammation since very early in life. Dietary imbalances with caloric excess and the resultant metabolic-associated inflammation profoundly affect the immune system.[5] A non-type 2 mechanism that comprises the NLRP3 inflammasome has been described. Mice fed with hypercaloric diet develop airway hyperreactivity independent of adaptive immunity but dependent on NLRP3 (just as it appears to regulate type 2 diabetes) and interleukin (IL)-17A produced primarily by type 3 innate lymphoid cells.[16,43] Considering this pathway, a role for brodalumab (anti-IL-17RA) has been suggested in obesity-associated asthma, which has not been yet explored.

An increase in IL-6, tumor necrosis factor (TNF)-alfa and leptin has also been described in obese asthmatic patients (versus healthy controls and versus non-obese asthmatic patients), linked to macrophage proliferation and differentiation in the lung tissue.[44] IL-6, a biomarker of systemic inflammation and metabolic dysfunction (positive associations with BMI, hypertension and diabetes), is associated with severe asthma in obese and non-obese patients. In particular, significantly higher IL-6 levels were found in asthmatics with worse lung function and more frequent asthma exacerbations.[45] Persistently elevated TNF-alfa in supernatants of lipopolysaccharide-stimulated peripheral blood mononuclear cells at birth and three months in offspring of mothers with excessive gestational weight gain is described associated with subsequent asthma development.[46] Furthermore, adiponectin is decreased in obesity, a mediator that is able to reduce airway inflammation.[47] Lower levels of anti-oxidants have been described in asthmatics.[48] Obesity has also been associated with an increase in systemic oxidative stress, further contributing to a pathological imbalance.[49]

Beyond obesity, both dyslipidemia and hyperinsulinemia per se can influence innate and adaptive defense mechanisms in the respiratory tract, with proinflammatory cytokines and chemokines production and increased bronchial tone.[5]

An Innovative View: Inputs from Metabolomics in Asthma

Metabolomics has provided unique and novel insights into asthma profiling at the molecular level. In particular, composite signatures in untargeted studies have brought innovation into the field of metabolic dysfunction in asthma.[50] This opens the possibility of having distinct biomarkers, which may better reflect the complexity and dynamics of genome-environmental interaction networks in asthma and even outmatch single or biomarker panels in asthma diagnosis and management. It also opens the possibility of new treatment targets and personalized care in asthma treatment and prevention.[50]

Distinct metabolic signatures have been found in asthma, unrelated to obesity and other metabolic syndrome conditions. Currently, several clinical studies using untargeted metabolomics approaches have yielded distinct results and suggested a broad number of metabolites associated with asthma. Common altered individual metabolites identified by different research groups include amino acids, lipids, purines, salts and alcohols (Table 1). More interestingly, these studies suggest that several metabolic pathways are altered in asthma. This preliminary data supports that further insights can contribute to increased knowledge in asthma. In particular, there is considerable consistency in identifying amino acids metabolism as significant. Amino acids can have antioxidant functions; in particular glycine, glutamine and glutamate may have potentially protective effects, whereas phenylalanine can have adverse effects.[51] Oxidative stress has a significant role in asthma pathophysiology and lung damage.[52] Oxidized compounds that significantly distinguish asthmatics from healthy subjects have been identified in untargeted metabolomics studies.[53] Metabolic pathways associated with oxidative stress in asthma involve not only amino acids, including essential components in glutathione metabolism, but also lipids peroxidation.[54] Furthermore, the influence of the microbiome on asthma pathogenesis has recently gained much interest with

Table 1 Metabolites Associated with Asthma in at Least Two Independent Studies in Humans Comparing Untargeted Metabolomics Profiles of Asthmatics with Non-Asthmatics

Identified Metabolite	Class*	Metabolomics Analysis	Samples	Difference (Asthmatics versus Healthy Subjects)	Participants
Adenosine	Purine	MS,[56,57,110] NMR[58]	EBC,[56,58] Plasma,[57] Serum[110]	↑	Children,[56] Adults[57,58,110]
Arginine	Carboxylic acid (amino acid)	MS,[110,111] NMR[58,59]	EBC,[58] Plasma,[111] Serum[59,110]	(conflicting results)	Children,[111] Adults[58,59,110]
Phenylalanine	Carboxylic acid (amino acid)	MS,[110,112] NMR[58]	EBC,[58] Serum[110,112]	↓ EBC ↑ Serum	Adults[58,110,112]
Tyrosine	Carboxylic acid (amino acid)	NMR[58,64,113]	EBC,[58,64] Urine[113]	(conflicting results)	Children,[113] Adults[58,64]
Taurine	Organic sulfonic acid (sulfur amino acid)	MS[57,110]	Plasma,[57] Serum[110]	↑	Adults[57,110]
Butyrate	Fatty acyls (fatty acid)	NMR[64,114,115]	EBC,[64,114] Feces[115]	(conflicting results)	Children,[114,115] Adults[64]
Acetate	Carboxylic acid	NMR[58,59,64,114]	EBC,[58,64,114] Serum[59]	↓(#)	Children,[114] Adults[58,59,64]
Formate	Carboxylic acid	NMR[58,59,64,114]	EBC,[58,64,114] Serum[59]	(conflicting results)	Children,[114] Adults[58,59,64]
Propionate	Carboxylic acid	NMR[58,64,114]	EBC[58,64,114]	↓	Children,[114] Adults[58,64]
Glucose	Organooxygen compound (carbohydrate)	NMR[59,64]	EBC,[64] Serum[59]	↑ EBC ↓ Serum	Adults[59,64]
Ethanol	Organooxygen compound (alcohol)	NMR[58,64]	EBC[58,64]	↓	Adults[58,64]
Methanol	Organooxygen compound (alcohol)	NMR[58,59,64,114]	EBC,[58,64,114] Serum[59]	↓	Children,[114] Adults[58,59,64]
Urocanate	Azole (imidazole)	MS,[116] NMR[58]	EBC,[58] Urine[116]	↑ EBC ↓ Urine	Children,[116] Adults[58]

Notes: *Classification according to the human metabolome database.[117] ↑ - higher levels reported in asthmatics (versus healthy subjects); ↓ - lower levels reported in asthmatics (versus healthy subjects); #variable results according to EBC collecting temperature.
Abbreviations: EBC, exhaled breath condensate; MS, mass spectrometry; NMR, nuclear magnetic resonance.

novel evidence being added, namely regarding short chain fatty acids produced by intestinal microbiota and its role in oxidative stress and inflammation.[55] Changes in the energy metabolism with increased tricarboxylic acid-cycle metabolism have been associated with an enhanced requirement for energy in asthma exacerbations and uncontrolled asthma, with a more hypoxic, acidic and oxidizing environment. In this setting, purine metabolism has also been identified in untargeted metabolomics studies in humans. Although adenosine is well known for its bronchoconstrictor and inflammatory effects, not only adenosine but also other related molecules have been detected as significantly altered in asthma, including deoxyadenosine, adenosine monophosphate and inosine.[56–58] Finally, metabolites related to the epigenetic pathways have also been reported.[58,59] In particular, epigenetic methylation has been suggested to skew immune responses towards a type 2 inflammation phenotype.[60–62]

Metabolomics also supports obesity-associated asthma phenotype at the molecular level. In this field, distinct respiratory and urinary metabolic profiles have been

reported in obese and non-obese asthmatics, supporting not only a unique phenotype but also unique pathophysiologic mechanisms.[63–65] The identified specific biomarkers are involved in energy metabolism (methane) and carbohydrate metabolism (pyruvate and glyoxylate and dicarboxylate metabolic pathways). An association between exhaled methane due to excessive colonization of the gastrointestinal tract with methanogen archaea and greater BMI and body fat percentage has been reported.[66,67] Furthermore, subjects with increased methane production might present with alteration in glucose metabolism and altered glycemic control.[68] Likewise, the pyruvate pathway is the sum of all biochemical reactions involving pyruvate and is at the intersection of pathways important for glucose and energy homeostasis. Furthermore, the alteration of glyoxylate and dicarboxylate metabolism in aged human female subjects has been related to mitochondrial dysfunction that would result in decreased ability to detoxify reactive oxygen species.[69] These are examples of how these untargeted metabolic studies combining high throughput technologies with bioinformatics can bring totally innovative views, which are complementary to our previous knowledge on the disease and its mechanisms.

Current Therapeutic Interventions: Where Do We Stand?

Currently, the pharmacologic treatment of asthma relies on ICS (or ICS–long-acting beta2-agonists associations) as the main preferred therapeutic controller option. Although this strategy is effective for many asthma patients, not all patients are controlled and no cure/long-lasting effect can be assured. Treating an obese-asthmatic patient is often more challenging as obese and overweight asthma patients tend to have poorly controlled asthma that does not respond as well to controller therapy with ICS compared to normal-weight patients.[3] However, it is likely that individual responses to therapy may vary significantly according to the predominant airway inflammation pattern in obesity-associated asthma, namely type 2 or non-type 2 involved mechanisms. Contrary to ICS, the response to montelukast does not seem to be affected by BMI,[70] although it is acknowledged that this drug is generally less effective than ICS, even in obese asthmatics.[71,72] Of note, tiotropium, a drug pointed as a controller therapy in step 4/5 in asthma, leads to improvements in asthma control, exacerbations and lung function that have been reported to be independent of BMI.[73] The predominance of neutrophilic airway inflammation may correlate with better response to tiotropium in asthmatics,[74] which may thus particularly benefit some obese patients with non-type 2 asthma.

Regarding the currently available biologic treatments approved for asthma, the anti-immunoglobulin E (IgE) antibody omalizumab has significantly reduced asthma exacerbations and improved asthma control in obese patients with severe allergic persistent asthma,[75] but obesity may reduce the effectiveness of this monoclonal antibody.[76] Interestingly, a supervised cluster analysis has suggested that the subgroup of asthmatic patients that benefited the most from the more recently approved anti-IL-5 monoclonal antibody mepolizumab is characterized by raised blood eosinophils, obesity and a mean duration of disease of 18 years, which could thus represent the early-onset type 2 obese-asthmatic patients.[77] A recent meta-analysis has shown, however, that a fixed dose of mepolizumab reduces exacerbations in patients with severe eosinophilic asthma, irrespective of body weight/BMI.[78] Contrary to fixed doses, the anti-IL-5 antibody reslizumab is dosed according to body weight. Thus, patients with obesity may require higher doses. Similarly to mepolizumab, for patients with severe, uncontrolled eosinophilic asthma, recent evidence shows that fixed doses of anti-IL5R benralizumab also decrease asthma exacerbations and increase lung function regardless of BMI value, but improvements, particularly in lung function, may be less robust for obese patients.[79] Finally, it has been recently suggested that dupilumab (anti-IL-4RA) reduces severe exacerbations and improves lung function in patients with uncontrolled, moderate-to-severe asthma, regardless of BMI.[80] Besides reduced asthma exacerbation rates and improved lung function, several clinical controlled trials show that these biological therapies allow reductions in corticosteroids use. However, a recent study on factors associated with omalizumab response suggested that obesity (versus normal weight) is a determinant condition for unchanged/increased level of concomitant asthma medication.[76] This has not been confirmed by others.[75] Data comparing regular corticosteroid-sparing effect of all available monoclonal antibodies in obese versus non-obese severe asthmatics is lacking. Nevertheless, these therapeutic interventions are particularly important to avoid the burden of systemic corticosteroids, namely in asthma exacerbations, which may overall reduce inflammation but have profound metabolic adverse effects and therefore a very significant unfavorable risk-benefit ratio.

The potential role for other medications that modify metabolic syndrome conditions to serve as therapeutic options for asthma has been recognized. The peroxisome proliferator-activated receptors (PPAR) were initially recognized for their functions in lipid regulation and glucose

metabolism but accumulating experimental findings support their anti-inflammatory properties and potential clinical benefits of PPAR-gamma agonists in the treatment of asthma.[81] However, these drugs efficacy remains controversial and larger randomized clinical trials (RCTs) are lacking. PPAR-gamma agonists are also associated with important side effects, which may be possibly minimized by administration via inhalation rather than systemic delivery, or through combination of drugs at lower concentrations.[81] Likewise, the metabolic and immunomodulatory properties of statins, traditionally used to manage cholesterol levels, have led to several studies evaluating its role for the treatment of asthma. Epidemiological and observational studies pointed towards therapeutic benefits in asthma, but RCTs using oral statins yielded conflicting results.[82–84] RCTs in severe asthma are lacking and studies using statins delivered by inhalation are also warranted.[84] Evidence of clinical benefit of metformin in asthma is also growing,[85–87] although it has seldom been investigated in real-life clinical settings. In particular, a decrease in asthma exacerbations in response to metformin has been reported in different populations.[88,89] This warrants further investigation. Future research may also address whether the effects of metformin are limited to patients with diabetes or whether it could bring advantage also in case of obesity, insulin resistance or the metabolic syndrome. Currently, the role of these and other pharmacological strategies addressing metabolic syndrome conditions in asthma needs appropriate study design and careful analysis to avoid biases and allow successful results to the individual patient.

Complementary to medication, non-pharmacological interventions have an important role in asthma management. In general, weight loss (both non-surgically and surgically) improves a number of clinical asthma outcomes in obese patients.[3,90-92] Weight reduction in obese asthmatics improves asthma control, quality of life and airway hyperreactivity,[93–95] but may have more limited effects in early-onset disease with high IgE levels,[93,96] and in patients with metabolic syndrome.[97] Bariatric surgery does not reduce airway eosinophilia, even when symptoms and airway hyperreactivity improve.[93] On the contrary, increased airway lymphocyte counts and peripheral blood lymphocyte function have been reported after the surgery, unrelated to airway hyperreactivity.[93] Other biomarkers of systemic and pulmonary inflammation, such as blood C-reactive protein, blood IL-6 or sputum TNF-alpha decrease after surgery.[95,98] Bariatric surgery also decreases leptin and increases adiponectin levels.[98–100] Overall, weight loss is associated with improvement in global health status and quality of life in obese patients, and even a 5% to 10% weight loss may produce significant improvements in asthma control.[101] Weight reduction may improve asthma control through mechanical unloading the respiratory system or reduced inflammation, but changes in dietary composition and lifestyle, including exercise, must be also considered.[101] In fact, the role of diet cannot be underestimated. A dietary pattern of high red and processed meats, fats and fried foods, that is low in fiber and high in sugar is associated with low lung function and increased respiratory symptoms, even when controlled for BMI.[102,103] Changing dietary quality can be effective for improving asthma control in obese and non-obese patients.[101] In particular, both dietary fiber composition and gut microbiota population influence the production of short-chain fatty acids, which can change airway inflammation. Most of these observations have been elegantly shown in mice, suggesting dietary fiber effects as early as during in utero development. However, there are only very few controlled trials in this field, and the same holds true for low-fat diet.[101] A diet high in fruits and vegetables or Mediterranean diet has been associated with improved asthma control and asthma quality of life, although the studies are rather small and heterogeneous.[104–106]

Dietary intervention studies are often included in more general lifestyle interventions. Physical exercise can also improve symptoms and asthma control, especially when combined with dietary intervention.[3,101] Although lifestyle interventions are complex and implementation challenging, these approaches may bring substantial benefit to asthma patients, given the fundamental role of environmental exposures. Of note, it is not just obese patients who seem to benefit from improved dietary quality and exercise.[101]

Another potential approach is to modify the microbiome to prevent and treat asthma. Microbiota changes have been pointed in the early development of asthma.[21] However, specific advice on the most effective regimes cannot yet be given, considering the high heterogeneity between the studies and low quality of evidence.[107–109] Taken together, these interventions will likely be more effective if combined.

Conclusion

Current evidence has largely expanded our view on metabolic dysfunction and asthma. Obesity is a well-recognized risk factor for asthma across the lifespan, which is generally associated with poorer response to current available treatments, rendering a more severe, refractory disease status. However, not only obesity-related, but also other aspects of metabolic dysregulation may be independently

linked to asthma. These include hyperinsulinemia, dyslipidemia and hypertension, which need to be taken into account, even in the non-obese patient. The recent untargeted metabolomics studies bring additional novel insights, supporting an obesity-associated asthma phenotype at the molecular level. They also highlight several other metabolic pathways that can be altered in asthma, likely associated with systemic inflammation. Taken together, this evidence points towards the need to improve our knowledge in this filed and, in particular, to address the importance of environmental factors in metabolic dysfunction and asthma development. Personalized therapeutic approaches are definitely needed that comprise not only classical pharmacological treatments but also more profound lifestyle interventions for disease prevention and treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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