

Asthma, GERD and Obesity: Triangle of Inflammation

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Abstract There is increasing prevalence of both asthma and obesity in children globally in recent years. Various epidemiological studies link obesity as a risk factor for asthma and suggest a possible causal association. Obesity asthma phenotype is considered as distinct in view of greater severity and poor asthma control. Various mechanisms underlying this phenotype have been suggested including mechanical effects of obesity and systemic inflammation, but still the exact mechanism is unclear. Also, the comorbidities like gastroesophageal reflux disease (GERD) and sleep disordered breathing (SDB) lead to inflammation in airways and contribute to asthma obesity association. A better understanding of mechanisms by which obesity and GERD lead to inflammation in airways and increase the risk of asthma may provide insight towards targeted treatment approach of these patients.

Keywords Asthma · Gastroesophageal reflux · Obesity · Sleep disordered breathing · Inflammation

Background

Globally, the prevalence of asthma and obesity is progressively increasing over the last few years [1, 2]. Obesity has been found to be a risk factor for asthma in various studies involving children and adults [3]. Patients with gastroesophageal

reflux (GER) and sleep disordered breathing syndrome (SDB) or obstructive sleep apnea have been reported as having increased prevalence of asthma. The relationship between obesity and asthma may be partly explained by comorbidities like GERD and SDB associated with obesity. However, obesity, SDB and GERD are independent risk factors for asthma as per various intervention studies [4]. Reduction of weight has been found to decrease airway bronchoconstriction and variability in peak flow rate [5]. On the other hand, anti-reflux measures, both medical and surgical have been shown to decrease symptoms of asthma and requirement of asthma medication but have minimal or no effect on pulmonary function [6]. Furthermore, treatment of SDB with nasal CPAP (continuous positive airway pressure) has shown considerable improvement in asthma symptoms and peak expiratory flow rate (PEFR) variability in patients with coexistent asthma and SDB [7]. In this article, authors try to explain the different mechanisms by which asthma, obesity and gastroesophageal reflux may be linked and contribute to continuous inflammatory process in airways.

Methodology

To identify the literature on relationship between asthma, obesity and gastroesophageal reflux, authors searched PubMed/Medline and Google Scholar for relevant articles from 1991 to April 2017 by using the following keywords: ‘asthma’, ‘airway hyperresponsiveness’, ‘obesity’, ‘overweight’, ‘weight gain’, ‘body mass index’, ‘gastroesophageal reflux’, ‘inflammation’, ‘obstructive sleep apnea’, ‘sleep disordered breathing’, ‘steroids’ as well as combinations of these. As it is not a systematic review, authors identified relevant articles for inclusion in this review.

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Epidemiology

The obesity epidemic has been constantly increasing for the past several decades and is being seen in all age groups including children. Globally, the prevalence of childhood overweight and obesity is 22.6–23.8% in developed countries and 12.9–13.4% in developing countries [2]. Likewise, in India, combined prevalence of childhood overweight and obesity has been reported as 19.3% till 2010, which has increased from the earlier prevalence of 16.3% reported in 2001–2005 [8]. Asthma prevalence and incidence have also increased over the past decade, affecting approximately 4–7% of the people worldwide [1], while in India the prevalence has been reported as 2.74% [9]. In the last decade, there has been increasing evidence of obesity being related to asthma and also as a risk factor for development of asthma in future as suggested by various epidemiological studies both in children and adults [3, 10]. The prevalence of GERD in children with asthma is estimated to be 43–87% as per various studies and is associated with poor asthma control [11]. There is also increased incidence of reflux in obese population, which may be one of the reasons for asthma like symptoms in them besides several other pathophysiologic mechanisms [12].

Pathophysiology

Inflammation of airways is hallmark of asthma, which is aggravated in presence of comorbidities particularly obesity and GERD. However, the exact mechanism by which obesity and GER lead to increased symptom severity and poor control in asthma is still not well understood and is an area of research.

Asthma and Obesity- Mechanism

The increased incidence and severity of asthma in obese children has several explanations. These include:

1. *Mechanical effects of obesity* – Truncal adiposity associated with obesity leads to decreased functional residual capacity (FRC), reduced residual volume (RV) and expiratory reserve volume (ERV) resulting in effortful breathing in obese subjects [13].
2. *Dietary factors* – Increased intake of processed food which is high in fat and low in antioxidant content is associated with increased risk of asthma while diet rich in fruits and vegetables and omega-3 fatty acids (Mediterranean diet) has been found to be protective [14].
3. *Lifestyle factors* – Sedentary behavior and reduced physical fitness leads to central adiposity and obesity and hence, predisposes children to asthma as observed by various studies [15].

4. *Sleep disordered breathing* – SDB may affect resting lung volumes during sleep, induce localized upper airway or systemic inflammation and has direct effects on smooth muscle, leading to airway hyperreactivity. Bronchial hyperreactivity may also be triggered by vagal stimulation due to upper airway collapse [16].
5. *Inflammatory effects of obesity on airways*

Th2 mediated allergic inflammation is a characteristic feature of atopy and hence asthma. However, various studies investigating the relationship between obesity and allergic inflammation failed to suggest obesity as a risk factor of atopy, rather asthma obesity phenotype has predominantly Th1 polarisation [17].

Obesity is considered to be a chronic low-grade inflammatory state. Obesity-mediated systemic inflammation has been shown to have effects on pulmonary functions and is associated with asthma. Adipocyte hypoxia during adipocyte proliferation and delayed angiogenesis has been associated with macrophage infiltration. These macrophages are of proinflammatory M1 phenotype as compared to anti-inflammatory M2 macrophages seen in non-obese subjects. Adipose tissue itself along with macrophages release various biologically active molecules like chemokines, cytokines, complement proteins, and other acute-phase proteins collectively known as adipokines which can affect innate and adaptive immune system. The most extensively studied adipokines are leptin and adiponectin. The proinflammatory leptin is structurally homologous to IL-6 and increases chemotaxis and phagocytosis. Additionally, it leads to naïve T cell proliferation and modulates cytokines that favour Th1 instead of Th2 response. Levels of leptin have been shown to increase in proportion to BMI [18, 19]. On the other hand, adiponectin is anti-inflammatory in nature as it inhibits production of proinflammatory cytokines like IL-6 and TNF- α , and augments expression of anti-inflammatory cytokines like IL-10 and IL-1 receptor antagonists [18, 20].

Obese children with asthma have been found to have elevated leptin and reduced adiponectin levels compared to their non-obese counterparts in various clinical studies on asthma. This finding relates obesity induced changes in the systemic adipocytokine milieu with asthma pathogenesis in children. Also, serum leptin levels correlate with higher Th1/Th2 cell ratio, and higher serum IFN- γ levels, indicative of non-atopic inflammation among obese asthmatic children [19].

Recently, there are several other inflammatory pathways recognized in obesity associated asthma like ILC3- NLRP3 inflammasome, IL-1 β and IL-17 pathway, activated by metabolic dysfunction associated with obesity. This reflects non-Th2 mechanism of obesity asthma phenotype and contribute to more severe asthma in obese population. IL-17 is released by Th 17 cells as well as by group 3 innate lymphoid cells (ILC3). Activation of ILC3 cells by NLRP3 inflammasome

and IL-1 β leads to release of IL-17 which recruit neutrophils in airways and cause airway inflammation and is central to development of asthma in obese individuals [21, 22]. However, all these pathways are described in murine models which may or may not be translated in humans, requiring more research in this field.

Insulin has several anti-inflammatory effects. However, insulin resistance associated with obesity correlates with increase in pro-inflammatory markers like leptin and IL-6 and is found to be a predictor of both lower airway obstruction and reduced lung volumes. It is also associated with adipose tissue inflammation with activation of Th1 cells and innate immune pathways, involving macrophages with M1 phenotype [23]. Insulin resistance is associated with airway hyperreactivity due to increased airway smooth muscle contractility by increasing laminin expression in airway smooth muscle cells, parasympathetic stimulation and increasing airway smooth muscle proliferation mediated by increased free insulin-like growth factor [24].

Epigenetics and genetics may also play a role in obesity related asthma. Differences in DNA methylation at 5 sites at the *FTO* gene were identified and their variants were found to be strongly associated with obesity. Genome-wide studies have also identified differential methylation of several genes like IL-4 and IFN- γ promoter genes associated with atopic inflammation among asthma children. However, differences in DNA methylation among children with obesity-related asthma compared with healthy children, those with normal-weight asthma, and with obesity without asthma were defined by only one study. In this study, specific DNA methylation patterns were associated with childhood obesity related asthma indicating its role in Th1 mediated systemic inflammation [25].

Genetic studies have shown that 16p11.2 inversion may protect against susceptibility to asthma and obesity in adults [26]. This inversion is associated with increased expression of obesity-associated proteins including apolipoprotein B (APOB48R) and SH2B1, which inhibit type 1 interferon and IL27. Other genes including the β 2-adrenergic receptor gene (ADRB2), the TNF gene, and the lymphotoxin- α (LTA) gene have been associated in both obesity and asthma in children [24].

Asthma and Gastroesophageal Reflux- Mechanism

Classically, the pathophysiology of association of asthma and GERD can be explained by two proposed mechanisms: the 'reflux' and the 'reflex' theories [7, 11].

Reflux theory: It refers to recurrent microaspiration due to retrograde reflux of gastric and/or duodenal contents into the esophagus. The reflux may get higher up leading to laryngitis and even dental erosions. Direct aspiration of gastroduodenal

contents into lung tissue stimulate and damage the epithelial cells that leads to release of various cytokines and cause chronic airway inflammation. This contributes to airway hyperresponsiveness and airway obstruction [6, 27].

Reflex theory: This mechanism is based upon the fact that both esophagus and bronchial tree have similar embryological origin and neural innervation *via* the vagus nerve. The pH sensitive receptors in distal esophagus get stimulated with reflux and lead to bronchoconstriction through vagal reflexes [27].

Besides these mechanisms, neuroinflammatory reflexes have also been described, leading to airway hyperresponsiveness via stimulation of capsaicin-sensitive C fibers and release of tachykinins like substance-P and neurokinin A which mediate the inflammation of airways [27].

Histologically, GERD-induced airway inflammation has shown infiltration with neutrophils, lymphocytes, eosinophils, and macrophages. Multiple animal studies show that GERD has been associated with release of proinflammatory Th2 cytokines and different interleukins which increase release of TNF- α [28].

Asthma itself can cause or aggravate the symptoms of GERD. Asthma, by increasing negative intrathoracic pleural pressure leads to increased diaphragmatic pressure. This pressure difference causes regurgitation of gastric contents across the lower esophageal sphincter (LES). Also, medications for asthma like beta-agonists can cause relaxation of LES and predispose to reflux [11].

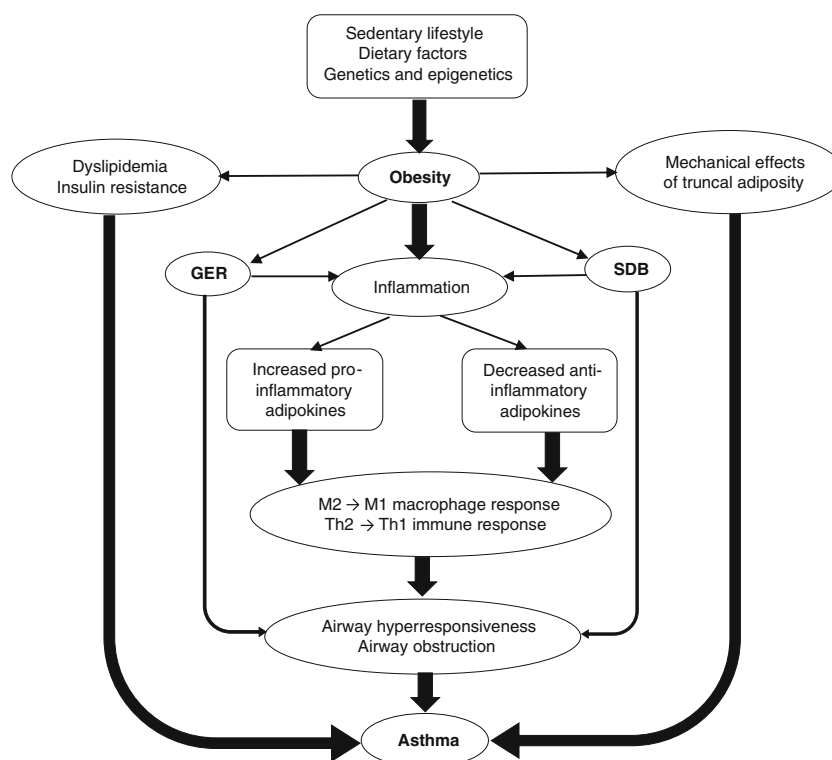
Combining All Three Together

There are several studies that suggest obesity and gastroesophageal reflux are independent risk factors for asthma. Also, obesity carries increased risk of GERD independently as well as by leading to sleep disordered breathing. While obesity and GERD are associated with Th1 immune response, SDB associated with chronic intermittent hypoxia leads to Th2-predominant allergic immune response as per animal studies but in humans, SDB leads to predominant Th1 mediated inflammation in airways [29, 30]. Figure 1 depicts the interrelationship between asthma, obesity and GERD.

Clinical Relevance

Obesity and asthma represent distinct phenotype in terms of pathophysiology and severity of asthma. Obese children have several metabolic or immunological derangements and several comorbidities (SDB and GERD) leading to increased risk of asthma. These children have poor asthma control as compared to their non-obese counterparts and also have decreased response to controller medications (steroids).

Fig. 1 Demonstration of complex interplay between obesity, gastroesophageal reflux, SDB and asthma. *GER* Gastroesophageal reflux; *SDB* Sleep disordered breathing



All these factors form the basis of studies demonstrating that loss of weight leads to improvement in asthma control. Leeuwen et al. reported decreased severity of exercise-induced bronchoconstriction and improved PAQLQ scores, particularly in the symptoms and activity domain, after weight loss [31]. Limitation of calories in obese children as per recommended intake for age and gender in normal healthy children was also associated with improvement in asthma control and PAQLQ scores.

Insulin resistance associated with obesity predisposes to asthma by inducing proinflammatory state and increasing smooth muscle hyperreactivity. Hence, metformin, usually prescribed for insulin resistance, may have a role in the management of obesity related asthma but require studies depicting the exact mechanisms of airway hyperresponsiveness (AHR) associated with insulin resistance and effect of metformin [24, 32].

Obese asthmatics often show poor response to steroid medications. One of the most important pathways associated with glucocorticoid insensitivity in obese asthmatics is MAPK pathway. In this, glucocorticoid dependent nuclear translocation is inhibited, resulting in decreased response of T cells to glucocorticoids. This finding was further supported by Sutherland et al. who demonstrated reduced induction of MKP-1 expression and enhanced TNF- α expression in both peripheral and lung immune cells of obese asthmatics, associated with reduced responsiveness to dexamethasone and its direct correlation with BMI [33, 34]. On the basis of these reports, it can be speculated that obese asthmatics need

alternative treatment strategies and may respond to nonsteroidal antiinflammatory agents including leukotriene antagonists or etanercept, a TNF inhibitor; but this needs further research [35].

Also, targeting the molecular pathways involved in obese asthma phenotype may contribute to future therapies. A monoclonal antibody against IL-17 receptor A (Brodalumab) has been studied in patients with steroid resistant severe asthma. As obesity related asthma is associated with high levels of IL-17, this therapy might be effective in this population [36].

Addressing the comorbidities like SDB and GERD is necessary for adequate control of asthma and should be sought actively in difficult to control asthma.

Several studies investigating use of CPAP in those with co-existent asthma and SDB suggested improvement in symptoms, reduced use of rescue medications, and improvement in peak flow rates. Also, serum inflammatory markers including CRP, IL-6 and TNF- α , have been shown to decline with the use of CPAP in moderate to severe persistent asthma [7, 16].

Gastroesophageal reflux has been shown to have association with asthma, however, the causal relationship is still not well established. Use of proton pump inhibitors (PPIs) in asthma is controversial. Firstly, it has been observed in various clinical trials that treatment of reflux with proton pump inhibitors has equivocal effects on asthma symptom control in children with asymptomatic GER [37, 38]. Secondly, PPIs do not have any role in non-acid reflux and optimal therapy for non-

acid reflux is still controversial. Lastly, the long term use of PPIs has been associated with the possible risks of gastrointestinal and respiratory infections (including *Clostridium difficile*), malabsorption, diarrhea, B12 deficiency, electrolyte abnormalities and osteoporosis and hence, its prolonged use in asthmatics with asymptomatic GER is not justified [11, 39]. However, PPIs lead to improvement in asthma symptoms and pulmonary function along with reduction in exacerbations in patients with symptomatic reflux [40]. The current guidelines of American College of Gastroenterology on GERD give no recommendation for surgery in patients with presumed extraesophageal manifestations of GER not responding to PPI. Indications for surgery include documented moderate to severe reflux not responding to adequate therapy with PPI and those having hiatal hernia of moderate size [41].

As per the current evidence, pediatricians and pulmonologists should regularly evaluate the asthmatic children for overweight and obesity, insulin resistance and dyslipidemia. Physical activity and diet rich in antioxidants should be encouraged for obese asthmatics as till now there is no specific therapy for obesity related asthma, and also they may be poorly responsive to inhaled steroids. In poorly controlled asthma, evaluation for SDB and GERD should be done by polysomnography and Impedance monitoring. If present, appropriate interventions like CPAP for SDB or surgical intervention and PPIs and lifestyle measures for GERD should be taken.

Conclusions

To summarize, obesity associated asthma is emerging as an important health issue among children. Addressing the comorbidities in difficult to control asthma needs to be highlighted. Though in the past decade, several studies have demonstrated the pathophysiologic mechanisms linking the two, still there are several areas that are unexplored. More studies are needed for better defining the pathophysiology, particularly related to insulin resistance and dyslipidemia which may have targeted therapies in future. Also studies are required to identify the underlying mechanisms of benefits of certain nutrients that may facilitate the development of targeted diets in obese asthmatics. Because obese asthmatics are sub-optimally responsive to current asthma medications, identification of mechanisms underlying obesity related asthma will provide direction for development of both preventative strategies and targeted therapy. The interplay between asthma and GERD is still incompletely understood and studies are needed to determine the causal relationship between GERD and asthma for appropriate treatment strategies. Future trials should also focus to determine the correlation between various doses and duration of PPIs and improvement in severity of asthma *via* pulmonary function and objective symptoms. The role of non-acidic

reflux in asthma is not fully understood and is an important area of research as there is often no response to PPI treatment in this subgroup and alternative modalities for diagnosis (whether *via* impedance monitoring) and treatment are not well defined.

Contributions SG: Literature search, analysis and manuscript writing, RL: Manuscript writing and analysis, SKK: Manuscript writing and will act as guarantor for the manuscript.

Compliance with Ethical Standards

Conflict of Interest None.

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