Role of Sleep Apnea and Gastroesophageal Reflux in Severe Asthma

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KEYWORDS

• Asthma • Obstructive sleep apnea • Gastroesophageal reflux
• Continuous positive airway pressure • Comorbidity

KEY POINTS

- Treatment of gastroesophageal reflux (GER) with proton pump inhibitors (PPIs) has a limited impact on symptoms and lung function in patients with asthma and symptomatic GER.
- Treatment with PPI of GER identified by pH probe in the absence of GER symptoms does not improve asthma control.
- The impact of treatment of severe GER on asthma has not been fully explored in existing clinical trials.
- Multiple potential mechanisms suggest a relationship between obstructive sleep apnea syndrome (OSA) and asthma, but the directionality of cause and effect is unclear.
- Limited data suggest that treatment of OSA may improve asthma, but further exploration of clinical outcomes and mechanism of benefit are warranted.

INTRODUCTION

Historically, asthma guidelines recommend assessing and treating comorbid conditions in order to achieve asthma control. Recent guidelines from the European Respiratory Society/American Thoracic Society propose the term difficult to control asthma for those in whom treatment of comorbid conditions will presumably improve asthma control.[1] In this review, the author reviews evidence linking obstructive sleep apnea syndrome (OSA) and gastroesophageal reflux (GER) to "difficult to control" asthma and looks critically at the evidence base supporting that evaluation and treatment of these conditions impacts asthma control.

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IS THERE A LINK BETWEEN ASTHMA AND GASTROESOPHAGEAL REFLUX?

The prevalence of GER may be present at a higher rate in those with asthma than what would be expected based on general population prevalence of GER alone. Diagnosis of GER by pH probe in those with asthma with or without typical reflux symptoms has identified prevalence rates of 40% to 60%.[2–4] Despite coexistence of these conditions, it is unclear whether GER impacts asthma control or whether asthma increases the likelihood of GER.

DOES GASTROESOPHAGEAL REFLUX IMPACT ASTHMA CONTROL OR DOES ASTHMA CONTRIBUTE TO GASTROESOPHAGEAL REFLUX?

A classic hypothesis linking asthma and GER involves the direct microaspiration of acidic gastric contents into the lower airways triggering epithelial damage, neurogenic inflammation, and bronchoconstriction.[5–8] Because of shared embryologic origin and innervation of the esophagus and airways via the vagus nerve, reflux in the upper esophagus can trigger bronchoconstriction without direct aspiration. These two hypotheses have been referred to as *reflux theory* and *reflex theory* and are illustrated in **Fig. 1**. Nonacid reflux with bile acids and pepsin has been associated with GER symptoms, although a relationship with extraesophageal manifestations of GER is less clear.[3] Findings suggestive of laryngopharyngeal reflux by laryngoscopy or bronchoscopy is common in refractory asthma and may potentially impact asthma via reflux or reflex pathways.[9]

Contrarians have argued that the presence of asthma impacts lower esophageal sphincter (LES) tone and, thus, promotes GER rather than GER triggering asthma.[10] Swings in intrathoracic pressure and/or descent of the diaphragm due to hyperinflation may reverse the normal thoracoabdominal pressure gradient, drawing the LES into the chest and altering its barrier function. Asthma may lower LES tone and promote GER via direct effects of beta agonists and theophylline.[11]

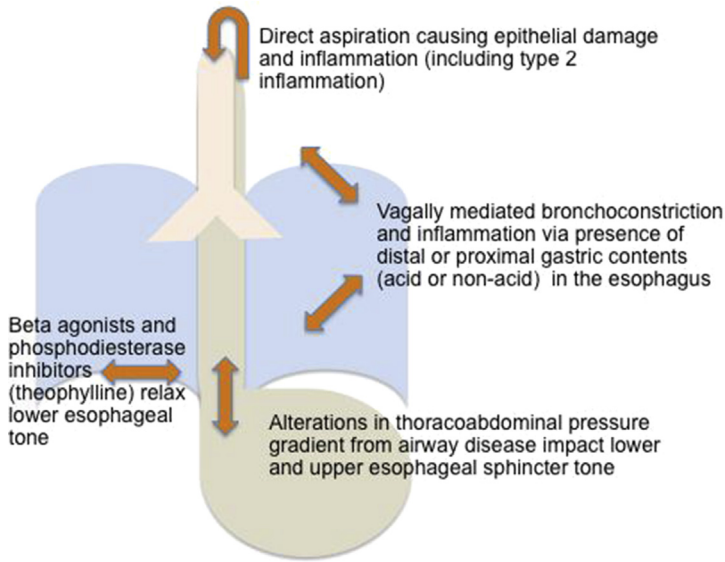

Fig. 1. Potential mechanisms explaining the interrelationship between GER and asthma.

DOES TREATMENT OF GASTROESOPHAGEAL REFLUX WITH PROTON PUMP INHIBITORS HELP CONTROL ASTHMA?

GER as a proposed cause of poorly controlled nonallergic or intrinsic asthma has been proposed for more than 50 years.[9,12–14] Several randomized clinical trials performed in the 1980s to 1990s examining the effect of GER treatment on asthma had significant methodological limitations, including small sample size, use of H_2 blockers alone, failure to use clinically effective doses of proton-pump inhibitors, and short duration of followup.[15–21] In 2003, a systematic review pooled a small group of modest-sized randomized controlled trials, but a significant treatment effect was not identified.[22] Since 2005, several large randomized placebo-controlled clinical trails directly examining this issue were conducted; the largest ones are presented in **Table 1**.

Littner and colleagues[23] performed a 24-week study of symptomatic GER and asthma treated with proton pump inhibitors (PPIs). Although reduced exacerbations and improved quality of life were noted in the PPI-treated patients, there was no difference in the primary outcome of daily symptoms. Kiljander and colleagues[24] studied patients with asthma and nocturnal symptoms, GER symptoms, or both and found no effect of PPI treatment on most asthma-related end points but found modest effects on peak flow in those with nocturnal asthma and GER. In the Study of Acid Reflux and Asthma (SARA) of participants with GER symptoms less than twice weekly, 24 weeks of high-dose PPIs did not impact the primary end point of episodes of poor asthma control, a composite score including step-up of treatment, lung function, urgent care, and exacerbations requiring steroids, despite the presence of GER by pH probe 40% of participants.[4] The same investigators also looked at the specific role of proximal reflux by use of dual pH probe testing and found no difference in lung function or asthma symptoms with PPI treatment of proximal reflux, although greater oral corticosteroid use and worse asthma-related quality of life were observed in those with proximal reflux.[25] In the Study of Acid Reflux in Children with Asthma, testing and treatment of clinically occult GER did not improve asthma control in children with uncontrolled asthma despite the presence of GER by pH probe in 43% of children. Moreover, a higher rate of adverse effects was noted in PPI-treated children, including increased respiratory tract infections.[26] The modest benefit observed in studies of patients with symptomatic GER does not exclude some benefit in these patients or a potential impact of treatment of severe or uncontrolled GER in asthma, a group excluded from the SARA study as the they would have an indication for treatment based on gastrointestinal issues alone.[23,24,26,27] A more recent systematic review looking at this issue in adults identified 11 trials containing 2524 patients and found a small effect of PPI on morning peak flow that was statistically significant but of unclear clinical significance (mean difference 8.68 L/min [95% confidence interval, 2.35–15.02]).[28] There was no effect on symptom scores, evening peak flow, asthma quality of life questionnaire (AQLQ), or forced expiratory volume in 1 second. Interestingly, a large case control study using the National Veterans Affairs and Centers for Medicare and Medicaid Services Databases found that a GER diagnosis was associated with a decreased risk of asthma-related events across all ages by 13% to 28%.[29]

UNRESOLVED ISSUES SURROUNDING THE RELATIONSHIP BETWEEN GASTROESOPHAGEAL REFLUX AND ASTHMA

The failure of PPIs to significantly impact asthma measures in existing clinical trials does not completely exclude a possible role of acid or nonacid reflux in asthma. In a systematic review, lifestyle modification including weight loss and elevation of the head of the bed impacted GER.[30] It is possible that use of PPI in the absence of

Table 1
Large randomized placebo-controlled trials of proton-pump inhibitor therapy in asthma and suspected comorbid gastroesophageal reflux

Author	Treatment Group (n)	Control Group (n)	GER Symptoms/GER Diagnosis	PPI Dosage	Duration	Results of Primary End Point	Other Outcomes
Kiljander et al,[18] 1999	52	52	Yes pH probe (GER 53%)	Omeprazole 20 mg 1 × daily	8 wk	Not described	Improved nocturnal symptoms and FEV_1[a]
Littner et al,[23] 2005	99	108	Yes Symptoms (pH probe optional)	Lansoprazole 30 mg 2 × daily	24 wk	Asthma symptom diaries: no difference	Reduced exacerbations and improved quality of life
Kiljander et al,[24] 2006	387	383	With and without GER symptoms[b]	Esomeprazole 40 mg 2 × daily	16 wk	Modestly improved PEF in those with GER and nocturnal asthma	No difference in symptoms or exacerbations
Mastronarde et al,[4] 2009	200	193	No pH probe GER 40%	Esomeprazole 40 mg 2 × daily	24 wk	No difference in episodes of poor asthma control[c]	No difference in lung function or other measures
Kiljander et al,[27] 2010	632	328	Yes GER symptoms >2 d/wk	Esomeprazole 40 mg 1–2 × daily	26 wk	Modest improved PEF in both esomeprazole groups	Modest improvement in FEV_1 and AQLQ
Holbrook et al,[26] 2012	157	149	No pH probe subgroup (n = 115) GER 43%	Lansoprazole 15 or 30 mg daily	24 wk	ACQ: no change	No change in lung function or episodes of poor asthma control

Abbreviations: ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; PPI, proton pump inhibitor.

[a] Crossover study.

[b] Study participants stratified by the presence of GER symptoms and/or nocturnal asthma.

[c] Episodes of poor asthma control defined by a decrease of 30% or more in the morning peak expiratory flow rate on 2 consecutive days, as compared with the patients' best rate during the run-in period; an urgent visit, defined as an unscheduled health care visit for asthma symptoms; or the need for a course of oral prednisone for treatment of asthma.

lifestyle modification accounted for lack of benefits in clinical trials. Patients with severe GER or motility disorders were largely excluded from these clinical trials, and a potential benefit of treatment in these patients cannot be excluded. PPIs do not address nonacid reflux including bile acids and pepsin; whereas impedance monitoring can detect nonacid reflux, controversy persists regarding optimal therapy for nonacid reflux.[3] Lastly, the possible risks of PPIs include enteric and respiratory infections (including *Clostridium difficile*), osteoporosis, B12 deficiency, electrolyte abnormalities, malabsorption, and diarrhea; thus, long-term treatment with these agents may not be justified given modest effects in asthma in the absence of significant gastrointestinal indications.[31]

The American College of Gastroenterology's current guidelines do not recommend surgery for those with presumed extraesophageal manifestations of GER that do not respond to PPI.[32] Nevertheless, several uncontrolled case series suggest a benefit of surgery for concomitant asthma and GER.[3,33] A systematic review of antireflux surgery in asthma found that surgery may improve asthma symptoms but not pulmonary function.[34] A 2-year unblinded randomized controlled trial comparing medical and surgical reflux therapies suggested superiority of surgery compared with medical therapy, with 75.0% of surgical patients showing an improvement in nocturnal asthma symptoms compared with 9.1% and 4.2% of patients on medical therapy and controls, respectively.[35]

A case series of sequential treatment with high-dose PPI followed by fundoplication in patients with asthma who were carefully evaluated at baseline, after PPI treatment and after fundoplication, found an improvement in cough and dyspnea after fundoplication in the absence of changes in objective measures, such as fraction of exhaled nitric oxide, spirometry, and bronchial hyperreactivity.[36] Use of prokinetic agents have also been advocated in refractory GER, but to date there is no high-quality evidence supporting this practice.[37] A new minimally invasive procedure for GER treatment, Stretta, uses catheter-applied radiofrequency energy to the LES, muscle, and gastric cardia to ameliorate GER. The role of this procedure in GER-associated asthma remains to be determined.

In summary, current evidence suggests that the presence of GER symptoms should largely drive how GER is treated when present along with uncontrolled asthma. Current evidence does not support investigation for occult GER as a cause of uncontrolled asthma in children or adults because treatment does not clearly improve asthma outcomes. Large placebo-controlled trials of symptomatic GER in asthma have shown modest effects on symptoms and lung function. A role of the treatment of severe GER in uncontrolled asthma and the impact of prokinetic agents, antireflux surgery, and novel radiofrequency procedures on asthma control in those with comorbid GER remain unclear.

WHAT IS THE RELATIONSHIP BETWEEN OBSTRUCTIVE SLEEP APNEA SYNDROME AND ASTHMA?

OSA is highly prevalent in difficult-to-treat asthma, with rates of more than 85% reported in some case series.[38,39] As large studies using polysomnography are expensive and not always feasible, population-based studies of OSA and asthma are largely based on symptom reports, diagnosis codes, and standardized questionnaires. The accuracy of prevalence rates in these studies has been questioned, as nocturnal dyspnea and wheeze from asthma can overlap significantly with symptoms of OSA.[40,41] In the population-based Wisconsin Sleep Cohort Study, participants without OSA by polysomnography at baseline were more likely to develop polysomnographically identified OSA after 8 years if they had a diagnosis of asthma.[42]

Epidemiologic studies suggest that OSA may be associated with uncontrolled asthma. In those with severe asthma, OSA by polysomnography is linked to frequent asthma exacerbations.[43,44] In children with severe asthma, 63% have concomitant OSA.[45,46] A population-based study in China found that OSA was twice as common in those with asthma than in controls, and those with more than one emergency department visit for asthma had the highest likelihood of OSA.[47] Julien and colleagues[38] found that patients with more severe asthma had a higher apnea-hypopnea index and more severe OSA compared with those with milder asthma. The presence of both GER and OSA was associated with poor control of asthma in local residents and responders to the World Trade Center terrorist attack.[48] In the Severe Asthma Research Program Cohort, those with a high risk of OSA based on standardized questionnaires had more asthma symptoms, greater β_2-agonist use, and greater health care utilization for asthma.[49]

PATHOPHYSIOLOGY OF THE INTERRELATIONSHIP BETWEEN ASTHMA AND OBSTRUCTIVE SLEEP APNEA SYNDROME

The relationship between asthma and OSA may be bidirectional as illustrated in **Fig. 2**. There may be a direct impact of one condition on the other or their relationship may be mediated via common comorbidities, including GER, rhinitis, and obesity. Allergic and nonallergic rhinitis, present in most patients with asthma, cause increased nasal resistance to breathing during sleep and negative oropharyngeal pressure during inspiration and may predispose to upper airway collapse.[50]

OSA may affect resting lung volumes during sleep, cause direct effects on smooth muscle and airway hyperreactivity, or trigger localized upper airway or systemic inflammation. Vagal stimulation from upper airway collapse may trigger bronchial hyperreactivity.[51] Tissue vibration with snoring, repeated upper airway obstructive events causing mechanical trauma, and cyclical hypoxemia with apneic events may trigger a local and/or systemic inflammatory response with cytokines, including interleukins 6 and 8 (IL-6, IL-8), vascular endothelial growth factor, tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP).[52–54] In an animal model, chronic intermittent hypoxia skewed an allergic immune response toward a more Th-1-predominant

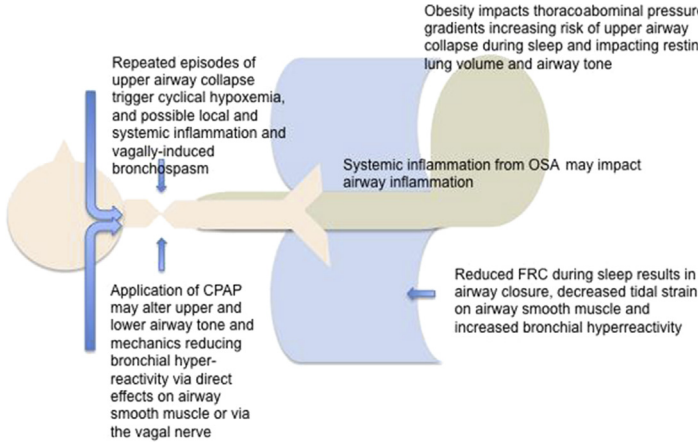

Fig. 2. Mechanisms by which OSA or continuous positive airway pressure (CPAP) may impact asthma. FRC, functional residual capacity.

cellular phenotype.[55] In humans, a recent study identified increased neutrophilic airway inflammation in patients with asthma and OSA.[55]

A cardinal feature of asthma is an intrinsic defect in airway smooth muscle function.[56] A reduction of periodic stretching of airway smooth muscle can lead to bronchial hyperreactivity, and hyperinflation and maintenance of elevated end inspiratory lung volumes is a mechanism of defense against this in asthma.[57] This effect is diminished with the reduction of functional residual capacity that occurs during sleep, resulting in a loss of airway parenchymal interdependence and loss of the ability of deep inspiration to dilate airways.[58] This mechanism may be at play in obesity-related asthma as well as in comorbid OSA and asthma. This mechanism may also have potential therapeutic implications, as the use of continuous positive airway pressure (CPAP) might impact this intrinsic smooth muscle dysfunction of asthma even in the absence of OSA.

DOES TREATMENT WITH CONTINUOUS POSITIVE AIRWAY PRESSURE WITH OR WITHOUT OBSTRUCTIVE SLEEP APNEA SYNDROME IMPACT ASTHMA CONTROL?

Several unblinded cohort studies of CPAP in those with asthma and OSA suggested improvement in symptoms, reduced rescue β-agonist use, and improved peak flow rates.[51,59–61] Three months of CPAP in patients with moderate to severe persistent asthma reduced serum inflammatory markers, including CRP, TNF, and IL-6.[62]

CPAP is currently being explored as a treatment of asthma in the absence of OSA. In several animal models, chronic lung inflation via CPAP reduces airway smooth muscle contractility in vivo and in vitro, including in a rabbit model of allergic airway inflammation.[63,64] Lin and colleagues[65] observed a decrease in methacholine responsiveness when treating participants with documented bronchial hyperreactivity in the absence of clinical asthma with nasal CPAP. In a pilot sham-controlled study of adults with mild asthma, use of nocturnal CPAP (8–10 cm H_2O) was associated with a 2.7-fold increase in the provocative concentration of methacholine resulting in a 20% decrease in forced expiratory volume in 1 second compared with control.[66] This study led to a subsequent randomized controlled trial involving 194 participants designed to assess 12 weeks of treatment with CPAP 1 cm H_2O (sham CPAP), 5 cm H_2O (medium level CPAP), or 10 cm H_2O (high-level CPAP) on bronchial hyperreactivity in asthma. This trial will be one of the largest prospective clinical trials looking at the impact of CPAP on asthma and may shed important light on mechanisms by which CPAP might improve asthma but will not directly examine the role of OSA as an asthma comorbidity and whether CPAP improves asthma when both conditions are present. Moreover, concerns regarding the ability of those with uncontrolled asthma with or without a diagnosis of sleep apnea to tolerate CPAP remain.[67]

In summary, there is a gathering body of evidence that asthma predisposes to development of OSA and that this likelihood increases with increasing asthma severity.

Similarly, asthma and commonly related conditions, including GER, rhinitis, and obesity, may increase the likelihood of development of OSA. There are several plausible mechanisms by which asthma and OSA may be related and by which each condition may impact the outcome of the other. There is a lack of controlled, prospective clinical trials supporting the contention that treatment of OSA impacts asthma outcomes. An exploration of the impact of CPAP treatment of asthma, specifically targeting treatment of bronchial hyperreactivity even in the absence of OSA, may potentially lead to a nonpharmacologic adjunct in management of asthma and may help promote understanding of disease mechanisms that have not been the target of pharmacologic

therapy. Similar to the relationship between asthma and GER, symptomatic GER and OSA warrant treatment in and of themselves when present as comorbid conditions with asthma regardless of the likelihood of impact on asthma; a better understanding of whether this in turn impacts asthma control, particularly in severe asthma, remains to be determined.

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