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THEORETICAL REVIEW

Potential mechanisms connecting asthma, esophageal reflux, and obesity/sleep apnea complex—A hypothetical review

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Summary Obstructive sleep apnea (OSA) and asthma are potentially linked at several levels. The pathophysiology of these two conditions seems to overlap significantly, as airway obstruction, inflammation, obesity, and several other factors are implicated in the development of both diseases. Gastroesophageal reflux disease (GERD), cardiovascular complications, obesity itself, and the underlying inflammatory processes are all complex contributory factors that provide hypothetical links. Furthermore, a collateral rise in prevalence of both OSA and asthma has been noticed during the past few years, occurring in association with the emerging epidemic of obesity, a common risk factor for both conditions. OSA and asthma share many other risk factors as well. We propose a hypothetical OSA–asthma relationship that has implications on the diagnosis and management of patients presenting with either condition singly. Clinicians should be aware that OSA might complicate asthma management. Based on this hypothesis, we suggest that the treatment of the individual patient who experiences both asthma and OSA needs to be multidisciplinary and comprehensive. This hypothetical association of asthma and OSA, though described anecdotally, has not been systematically studied. In particular, the influence of continuous positive airway pressure therapy (for sleep apnea) on asthma outcomes (such as quality of life, steroid utilization, emergency room visits) and fatality needs to be studied further.

Introduction

There is circumstantial, possibly suggestive evidence of a close relationship between obstructive sleep apnea (OSA) and asthma. Both OSA and asthma involve airway obstruction as the cornerstone of their pathophysiology, being at different

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Nomenclature

ACE	angiotensin converting enzyme
AHI	apnea-hypopnea index
APAP	autotitrating positive airway pressure
ASCVD	athersclerotic cerebrovascular disease
BMI	body mass index
BPD-DS	biliopancreatic diversion with duodenal switch surgery
CAD	coronary artery disease
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CS	corticosteroid
CT	computed tomography
EED	extraesophageal disease
FEV1	forced expiratory volume in 1 second
GERD	gastroesophageal disease
HTN	hypertension
IL-6	interleukin-6
IHD	ischemic heart disease
LES	lower esophageal sphincter
LPR	laryngopharyngeal reflux
LVD	Left ventricular dysfunction
MI	myocardial infarction
NERD	nonerosive esophageal reflux disease
NO	nitric oxide
NSAID	nonsteroidal antiinflammatory drugs
OSA	obstructive sleep apea
PHTN	pulmonary hypertension
PMN	polymorphonuclear leukocytes
PNDS	postnasal drip syndrome
PPIs	proton pump inhibitors
UPPP	uvulopalatopharyngoplasty
VIP	vasoactive intestinal peptide

levels in each condition. Inflammation, a condition characteristic of asthma, was recently implicated in the progression and consequences of OSA, a traditionally all-mechanical problem. Recent studies have also found obesity, a significant risk factor in both OSA and asthma, to be associated with a systemic low-grade state of inflammation.

OSA and asthma are seemingly common conditions. Approximately 4% of middle-aged men and 2% of middle-aged women suffer from symptomatic OSA.[1] The prevalence is higher (24% for men and 9% for women) when only an apnea–hypopnea index (AHI) of 5 or more is used as indicative of sleep-disordered breathing, regardless of coexistent daytime somnolence.[1] The prevalence in elderly (age $\geqslant$65 years) has been reported to be as high as 62%[2]. OSA is also being recognized by physicians more frequently. In the United States, there was a 12-fold increase in the annual number of patients diagnosed with OSA between 1990 and 1998, from 108,000 to over 1.3 million.[3] Asthma prevalence varies in different age groups but has been reported to be as high as 5.3% in the United States in some reports. Furthermore, the prevalence of asthma appears to be increasing.[4] Moreover, obesity rates are increasing rapidly in the United States. In 2000, approximately 20.1% of the adult population was obese.[5] Because of their high prevalence, OSA and asthma may coexist in a large number of patients and recent studies have shown a strong link and coexistence. A study by Yigla et al.[6] demonstrated a higher than expected prevalence of OSA in steroid-treated patients with asthma. Some clinicans, such as Thomas PS and Millman RP, suggest that OSA should be included in the differential diagnosis of difficult-to-control asthma.[7,8]

Due to this close relationship between OSA and asthma, management of either condition may warrant treatment of the patient with the other disease. Based on the above discussion, a detailed evaluation of the OSA–asthma association is needed to further understand the correlation between the two diseases as well as other existing co-morbidities, and to possibly set forth further management goals and future areas of research.

Overview

OSA is characterized by repeated episodes of upper airway occlusion that result in brief periods of breathing cessation (apnea) or a marked reduction in tidal volume (hypopnea) during sleep (Table 1). This is followed by oxyhemoglobin desaturation, persistent inspiratory efforts against the occluded airway, and termination by arousal from sleep. These episodes are associated with excessive daytime sleepiness and abnormalities in cardiovascular, pulmonary, neurocognitive, and metabolic function.[9] Asthma on the other hand, is a complex syndrome with many clinical phenotypes. Its major characteristics include a variable degree of airflow obstruction, bronchial hyperresponsiveness, and airway inflammation. The following sections discuss the possible associations between asthma and OSA and the clinical implications of these associations.

Why would asthma be a problem in a patient with OSA?

A large amount of data concerning the interaction between OSA and asthma has been accumulated in

Table 1 Definitions.

Airflow obstruction	
Apnea	Cessation of airflow for $\geqslant$10 s
Hypopnea	At least 30% reduction in airflow for 10 s associated with a 4% decrease in oxygen saturation
Severity of apnea	
Mild OSA	AHI: 5–15/h
Moderate OSA	AHI: 15–30/h
Severe OSA	AHI: >30/h

AHI: Apnea–hypopnea index.

Table 2 Risk factors for OSA.

Relevance to
General risk factors
Obesity*
Male sex
Positive family history*
Postmenopausal state*
Genetic/congenital factors
Down's syndrome
Pierre–Robin syndrome
Marfan's syndrome
Nasopharyngeal abnormality
Nasal congestion*
Nasal polyposis*
Adenoidal or tonsillar enlargement
Deviated nasal septum
Medical conditions
Acromegaly
Hypothyroidism
Structural upper airway disorders
Large neck (circumference >40 cm)
Temporomandibular joint dysfunction
Micrognathia
Retrognathia
Macroglossia
Palatal abnormalities
Craniosynostosis

*Disorder also of relevance to asthma.

recent years. Studies have shown decreased quality of sleep defined as reduced sleep time, altered sleep quality, snoring, early morning awakening, difficulty in maintaining sleep, and daytime sleepiness in asthma,[10] and as reviewed by Bonekat and Harding,[11] OSA may coexist with asthma. Sleep deprivation, upper airway edema, and systemic inflammation associated with OSA could complicate the course of asthma.[11] Also, steroid therapy in patients with asthma leads to the development of alkalosis which could contribute to greater hypoventilation during sleep.

OSA and asthma share several risk factors as listed in Table 2. The discussion that follows will seek to describe the association between asthma and OSA, and develop hypothetical mechanisms that could explain how such an association might exist clinically. Obesity can contribute to the development of both OSA[12] and asthma.[13] In addition, OSA, and obesity-associated GERD can also contribute to bronchial asthma and airway inflammation.[14,15] Several of these risk factors may occur concomitantly in both OSA and asthma and may explain their occurrence in a given patient.

Prior studies, although limited in numbers, have shown some relationship between OSA and asthma. For example, in one study, bronchial hyperresponsiveness was found among OSA patients with neither asthma nor allergies, unrelated to the severity of OSA.[16] The same study found that administration of nasal continuous positive airway pressure (CPAP) decreased this hyperreactivity. Two other studies[17,18] showed better nocturnal asthma control with the use of nasal CPAP in those individuals suffering from OSA, demonstrating the close relationship between the two conditions. These two studies also showed improvement in the nocturnal worsening of asthma, by the use of nasal CPAP, in those individuals treated for coexisting sleep apnea, further illustrating the close connection.

Shipley et al.[19] suggested a link between exposure to abnormal levels of endogenous corticosteroids (CS) and a high prevalence of OSA among patients suffering from Cushing's disease and syndrome, through parapharyngeal fat deposition and upper airway myopathy. He concluded that the link applies regarding exposure to abnormal levels of exogenous CS as well. Because body mass index (BMI) changes of $\pm$10% were associated with enormous AHI changes among the general population,[20,21] it is highly probable that Shipley's study population acquired or worsened OSA in association with CS therapy-induced BMI gain. The proposed mechanism is reduction of the pharyngeal cross-sectional area due to circumferential neck fat deposition, thereby increasing the tendency of the upper airway to collapse. A possible mechanism is chronic CS therapy-induced upper airway muscle myopathy.[22] Another study[23] showed an unexpectedly high prevalence of OSA among patients with unstable asthma receiving long-term chronic or frequent bursts of oral CS therapy. It may be

assumed that prolonged and especially continuous oral CS therapy in asthma increases airway collapsibility. However, it remains unclear to what extent there is evidence supporting a role for cortisol in OSA in the general population and to what extent CS therapy increases the prevalence of OSA among asthmatic patients. These issues need to be further resolved by well-conducted studies.

Hypothetical mechanisms linking obesity, asthma, and sleep apnea

We hypothesize on potential ways in which OSA can cause asthma or hyperreactive airway disease. Obesity, inflammation, cardiac disease, and esophageal reflux can all have effects on airway disease. Inflammation in turn could be triggered by either hypoxia, which can also induce reflex bronchoconstriction through stimulation of carotid bodies,[24] or by other mechanisms. Bohadana et al.[25] suggested that asthma can promote OSA. Proposed mechanisms include chronic disruption of sleep architecture,[26] and anatomical abnormalities that tend to decrease the pharynx cross-sectional area, such as chronic inflammation and pharyngeal wall fat deposition,[27] could increase upper airway collapsibility, a factor contributing to the development of OSA.

The following sections review possible hypothetical mechanisms underlying the worsening of asthma in a patient with OSA. These could include obesity, activation of inflammatory pathways, esophageal disease, and cardiac pathology that could occur in patients with OSA and lead thereby to asthma.

Obesity

Obesity is steadily becoming the greatest health problem in the developed world. Obesity represents a significant risk factor for OSA. For both men and women whose BMI exceeds 40, OSA is at least 10 times as common as the community norm of 2–4%.[28] Obesity has been linked to asthma in many ways. Also, both obesity and OSA act to aggravate existing asthma making it more difficult to control.[23] Young et al.[13] reported parallel findings in adults. Furthermore, Tantisira and Weiss[29] noted that asthma becomes more difficult to control among obese patients and that weight reduction improved asthma control. It may be safe to assume that patients with asthma receiving oral corticosteroid therapy are at increased risk for BMI gain and development of OSA, and their disease becomes more difficult to control.[23] Preventing weight gain or weight reduction in this group of patients receiving long-term oral CS is critical for better control of their disease.

The hypothesis that obesity could affect a person's atopic status, explaining its association with asthma, is yet to be confirmed or validated. Xu et al.[30] found an association between atopy and BMI, but a large European study found no similar association.[31] Simard et al.[32] found the prevalence of atopy to be similar to that found in the general population. The prevalence of atopy among obese asthmatic subjects was quite high (46%), which is close to what is usually found in non-obese asthmatic patients.[33]

In a review of four studies in which severe obesity was treated surgically, Tentisira and Weiss[29] reported that asthma improved after the surgery, with many patients even being able to discontinue medication.[33] In a study[34] that included data gathered when patients had regained weight, there was an increased incidence of asthma attacks that resolved when successful surgical revision resulted in weight loss.

There is marked improvement in asthma and OSA after bariatric surgery for morbidly obese patients.[35] Two years after biliopancreatic diversion with duodenal switch (BPD-DS) surgery (following which mean BMI reduced from 51.4 to 30.5 kg/m^2), asthma was reported to have improved in 79.3% of patients and sleep apnea syndrome was improved in nearly all with this condition.[32]

Inflammation and OSA

Studies have implicated inflammation, both local and systemic, in the pathophysiology of OSA, a traditionally all-mechanical problem.[9] It is postulated that these inflammatory changes occur due to snoring that evokes vibration frequencies associated with soft tissue damage and local inflammation.[9] Furthermore, evidence of systemic inflammation is present in patients with OSA.[9] The circadian rhythm of TNF-α secretion in patients with OSA is markedly different compared with healthy volunteers.[36] CPAP therapy does not change this abnormal circadian pattern. This implies a role for inflammation independent of mechanical obstruction in pathogenesis of OSA. Another marker for systemic inflammation, C-reactive protein, is increased in patients with OSA when compared with control subjects.[37] It can be hypothesized that some of these inflammatory changes could worsen coexisting airway inflammation.

Reactive oxygen species such as superoxide anion and hydroxyl radical are deleterious to cells, and are implicated in ischemia reperfusion injury that occurs in conditions such as myocardial infarction (MI) and stroke. There is increased production of reactive oxygen species from inflammatory cells in patients with OSA.[38]

Similar to hypoxia/reperfusion injury, the recurring hypoxic events in OSA initiate oxidative stress, affecting energy metabolism, redox-sensitive gene expression and expression of adhesion molecules.[39] Adhesion molecule-dependent increased avidity of OSA monocytes to endothelial cells, combined with diminished nitric oxide (NO) bioavailability, lead to exaggerated endothelial cell damage and dysfunction. Recent studies have also found obesity, a significant risk factor in both OSA and asthma, to be associated with a systemic low-grade state of inflammation. Visceral fat in particular is a source of a group of molecules that are collectively known as adipokines. These include leptin, adiponectin, tumor necrosis factor-alpha, and interleukin 6. These molecules have the capacity to provoke a proinflammatory state and oxidative damage, which might lead to some of the observed complications of OSA, most importantly the cardiovascular sequelae.[40]

Upper airway inflammation has been shown to be associated with OSA. Olopade et al.[41] have shown an increase in exhaled pentane, a marker of airway inflammation, in OSA subjects in the morning suggesting the development of airway inflammation during sleep. Carpagnano et al.[42] have shown an increase of two markers of inflammation and oxidative stress, Interleukin–6 (IL–6) and 8-isoprostane in the breath condensate of OSA patients, suggesting that inflammation and oxidative stress occur in the airways of OSA patients. Salerno et al.[43] have shown that OSA patients present a variable degree of neutrophilic bronchial inflammation. Rubenstein[44] showed an increase in the percentage of polymorphonuclear leukocytes (PMN) in the nasal mucosa of patients affected by OSA, as well as an increase in other mediators of inflammation such as bradykinin and vasoactive intestinal peptide (VIP). In addition, Sekosan et al.[45] have shown, in OSA patients, that the uvula is thicker than normal and that in the lamina propria there is an increase in the number of leukocytes. Bronchial inflammation may contribute to the pathogenesis of OSA by determining further reduction of the airway caliber. Further studies are necessary in order to assess the effect of therapeutic interventions such as CPAP and anti-inflammatory agents on the degree of the OSA-induced bronchial-inflammation. Furthermore, sleep deprivation (which may occur in severe asthma and OSA) may have an adverse impact on immunological function.[46]

Airway component: the role of the linked/unified airway

Allergic and non-allergic rhinitis affect more than 20% of the US population.[47] Scharf and Cohen[48] found that nasal obstruction contributes to sleep-disordered breathing in predisposed individuals. Nasal congestion, and consequently upper airway obstruction, may be caused by a number of conditions. The most common are allergic rhinitis, vasomotor rhinitis and chronic sinusitis. Nasal and nasopharyngeal polyps may also be associated with nasal congestion and upper airway obstruction.[49] In addition to OSA, allergic rhinitis may contribute to asthma as well.[11] A strong relationship was found between chronic bronchitis and asthma, on one hand, and snoring as a problem, and relatives' concern of witnessed apneas and daytime sleepiness on the other.[50] Recent developments suggest that airway disease can be a linked process (unified or linked airway) in selected patients.[51] The coexistence and hypothetical link between Cough/asthma, Obesity/OSA, Rhinosinusitis, and Esophageal reflux could be referred to as the "CORE" syndrome. In asthmatic patients refractory to therapy, CORE components must be considered in the management. OSA may co-exist with chronic obstructive pulmonary disease (COPD) and respiratory failure in some patients, a condition known as the "overlap syndrome".[52]

Cardiac component

Various aspects of cardiovascular sequelae of OSA could lead to a worsening of airway obstruction (Table 3). First, left ventricular dysfunction (LVD) induced by hypertension and/or ischemia related to OSA could lead to worsening of asthma by causing pulmonary edema ("cardiac asthma"). Sleep apnea has been shown to result in hypertension. Hypertension is a potential etiology of ischemic heart disease (IHD) and LVD. LVD could hypothetically lead to pulmonary edema and worsening of the bronchial asthma. Second, hypertension is a strong risk factor for stroke and, thus, could cause cognitive deterioration and possibly failure of compliance with asthma medications (Table 3). Third, it must also be recognized that certain medications used in the treatment of hypertension (especially beta-adrenergic antagonists and angiotensin converting enzyme inhibitors)

Table 3 Cardiovascular complications of OSA and how they may relate to asthma.

Complication	Resultant effect	Asthma relation
HTN	LVH, IHD, LVD	Pulmonary edema Asthma worsening
IHD	Ischemia	Asthma worsening Cough worsening
ASCVD, Arrhythmia, HTN	Stroke, cognitive decline	Poor compliance with medication
PHTN	Dyspnea	Asthma mimic
Medication	Beta–blockade ACE-inhibitor	Asthma worsening Cough worsening

HTN: hypertension; LVH: left ventricular hypertrophy; IHD: ischemic heart disease; LVD: left ventricular dysfunction; ASCVD: atherosclerotic coronary vascular disease; PHTN: pulmonary hypertension; ACE = angiotensin-converting enzyme.

could worsen asthma and cough (Table 3). They should be used with caution or not at all in patients who have combined sleep apnea and asthma.

Esophageal component

Esophageal diseases that complicate obesity and OSA could include GERD/NERD (non-erosive reflux disease) and laryngopharyngeal reflux (LPR). These conditions could be complicated by airway disease, as acid reflux into the airway or enhanced vagal activity induced by reflux can trigger asthma in some individuals.

GERD is a common condition that affects approximately 20–30% of the adult population, presenting with a broad spectrum of symptoms.[53,54] Several studies have reported an increased prevalence of GERD in patients with OSA. Some risk factors of OSA, particularly age and obesity, are shared with GERD. Sleep per se can contribute to GERD, through a decrease in the lower esophageal sphincter (LES) tone and other pharmacologic and gastric factors.[55] Additionally, sleep is associated with a prolongation of acid clearance.[56] Moreover, upper airway obstruction during sleep is associated with an increased transdiaphragmatic pressure gradient and may lead to gastric content reflux into esophagus.[57] Penzel et al.[58] reported that 15 consecutive OSA patients who underwent esophageal pH monitoring studies all had GERD. Graf et al.[59] found that 11 of 17 OSA patients had evidence of abnormal GERD. Another study[60] found that five of six patients with OSA who underwent pH monitoring had abnormal nocturnal GERD. Ing et al.[61] compared nighttime pH monitoring results in patients with AHI of <5 to those with indices that were >15. Patients with an AHI >15 experienced more GERD events, and their esophageal pH was <4 for a greater period compared to those with lower AHI values. Studies have suggested that OSA may lead to the development of nocturnal GERD. This is most likely because apneic episodes are associated with increased transdiaphragmatic pressure and decreased intrathoracic pressure, favoring gastroesophageal reflux.[61,62] In addition, in these patients with combined asthma-OSA complex, it is possible that the air trapping may lead to flattening of the diaphragm, possibly weakening the antireflux barrier.[63]

GERD can lead to worsening of airway reactivity by directly inducing airway inflammation or indirectly by enhancing vagal tone. When gastric contents reach the larynx (a condition known as acid laryngitis or LPR) patients present with a distinct group of signs and symptoms, including hoarseness, chronic cough, globus, and a persistent desire to clear the throat.[64] It is now known that GERD and postnasal drip syndrome (PNDS) along with asthma are among the three most common causes of chronic cough.[65]

Favorable effects of CPAP in patients with GERD have been reported.[60,61] Field and Sutherland[66] reported marked improvement in asthma symptoms and reduced asthma medication use in asthmatic patients on antireflux therapy for concurrent GERD. A literature review of 24 trials reported between 1966 and 1998[67] included a total of 417 patients with asthma who underwent antireflux surgery for asthma symptoms. Similar to medical therapy, fundoplication improved GERD symptoms, asthma symptoms, asthma medication use and pulmonary function in 90%, 79%, 88%, and 27% of patients, respectively.

Diagnostic and management of the obesity–GERD–OSA–asthma complex

Details of the diagnosis and management of OSA and its complication are not within the scope of this study. The following is a brief discussion of the diagnostic and management approaches of OSA and its potential sequelae as summarized in Table 4.

Diagnostic considerations

Sleep apnea should be suspected in patients who are obese, hypertensive, habitual snorers, and hypersomnolent. A high clinical suspicion for OSA is particularly indicated in asthma patients who are refractory to standard medication treatments. Polysomnography is the recommended method of assessing patients with suspected sleep disorders, including sleep apnea.[68] It is worth mentioning that physicians should not make decisions about treatment solely on the basis of the AHI, as it correlates poorly with the severity of OSA and quality of life[69] and does not help to determine the risk of a motor vehicle collision.[70] Traditional evaluation of patients with OSA may change by adding investigations to detect its recently-discovered potential sequelae, such as GERD, cardiovascular disease and asthma among other complications (Table 4). When the patient suspected of having GERD presents with heartburn alone, the diagnostic evaluation begins with a therapeutic trial. Barium examination, endoscopy, and esophageal pH monitoring could be used in selected patients. Pulmonary function tests are pivotal to the diagnosis and management

Table 4 Constituents of the OSA–asthma relationship.

Constituent	Diagnosis	Treatment
(I) Sleep apnea-related		
OSA	Polysomnography	CPAP, oral appliances, weight loss, surgery
GERD	Barium examination Endoscopy Esophageal pH study	Weight loss Diet, smoking cessation PPIs Surgery
LPR	Same as GERD, Laryngoscopy	Treat as GERD
Cardiac dysfunction	Stress testing Echocardiography	Treatment of HTN, cardiac risk factors and heart failure Avoid ACE-I and BAAN
Neurocognitive decline	Neuropsychiatric monitoring Medication compliance	Oxygen
Obesity	BMI Body fat measurement	Diet, exercise, pharmacotherapy, surgery
(II) Airway-related		
Airway inflammation	Pulmonary function tests Exhaled breath NO Sputum and serum eosinophilia	Inhaled steroids, leukotriene antagonists, immunotherapy, anti-immunoglobulin E (omalizumab)
Rhinosinusitis	Examination Allergy skin test	Nasal steroids, leukotriene antagonists, antihistamines, immunotherpy
Nasal polyps	Examination Sinus CT scan	Oral prednisone, nasal steroids, antibiotics, avoid NSAIDs

OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure; GERD: gastroesophageal reflux disease; LPR: laryngopharyngeal reflux; PPIs: proton pump-inhibitors; HTN: hypertension; ACE-I: Angiotensin-converting enzyme inhibitor; BAAN: beta-adrenergic receptor antagonist; BMI: body mass index; NO: nitrous oxide; CT: computed tomography; NSAIDs: non-steroidal anti-inflammatory drugs.

of asthma. Peak expiratory flow rate and spirometry are the two pulmonary function tests most often diagnostic of asthma. The use of cardiovascular tests such as transesophageal or transthoracic echocardiography may be indicated in the occasional patient in whom a cardiac component for dyspnea or asthma worsening is suspected.

Management

The approach to therapy of a patient with obesity, GERD, OSA, and asthma has to be multidisciplinary. Exercise and/or diet should be strongly recommended in obese patients suffering from OSA. Bariatric surgery is a practical option for weight reduction for patients with morbid obesity. In addition, in obese patients suffering from asthma, weight loss has been associated with a reduction in the severity of both asthma and of OSA.[71] In one study, a 10% weight loss was associated with a 26% decrease in the AHI.[72] Patients who have severe symptoms or who have coexisting morbidity require a lower threshold for initiating treatment than an otherwise healthy person. In its early stages OSA can be managed by general practitioners conservatively, by means such as weight loss, treating nasal congestion, avoiding sedating drugs/alcohol, and use of a lateral sleeping position, as studies have shown that the OSA worsens with intake of a benzodiazepine[73] or alcohol,[74] and with a supine sleeping position.[75] It should be realized that optimal management of the patient with OSA and concomitant asthma is often multidisplinary and should address the various facets mentioned in the earlier discussions.

The therapy of choice for OSA is CPAP, which prevents upper airway closure by creating a ''pneumatic splint''.[76] CPAP has been shown to decrease somnolence and to improve the quality of life and mood.[77] Autotitrating positive airway pressure (APAP) devices are novel positive airway pressure devices available for use in OSA. These have the ability to detect and respond to changes in upper airway resistance. Compliance with APAP was found to be the same as or slightly better than CPAP in most studies.[78] CPAP therapy was found to improve asthma[17,18] and GERD[60,61] control when given to patients suffering from OSA. Additionally, therapy of OSA with CPAP results in a significant decrease in cardiovascular complications of OSA, most importantly systemic blood pressure[79] and ASHD.[80] For patients undergoing bariatric surgery, therapy with CPAP perioperatively would supposedly prevent hypoxic complication associated with OSA. For that reason, surgeons should have a low threshold for ordering a polysomnography as part of the preoperative evaluation for bariatric surgery. In addition, surgeons should consider preoperative empiric CPAP therapy in patients who cannot complete a polysomnography prior to surgery.[81]

Is nasal CPAP therapy acceptable in asthma? Some studies have suggested that nasal CPAP therapy can be used safely in treating patients with OSA and coexisting bronchial asthma.[18] Furthermore, CPAP treatment improves asthma control, particularly nocturnal attacks.[17] In one study, nasal CPAP therapy effectively eliminated bronchial hyperresponsiveness in patients with OSA who initially had a positive methacholine challenge test.[16] Interestingly, the use of CPAP (bilevel) to supplement the management of acute respiratory failure in status asthmaticus appears highly effective in correcting gas exchange abnormalities using a low inspiratory pressure.[82,83] Moreover, the application of CPAP in acute asthma reduces respiratory rate and dyspnea with no untoward effects on gas exchange, expiratory airflow, or hemodynamics.[84]

Many types of oral appliances have been used for the treatment of sleep apnea. These are designed to reposition the mandible and thereby modify the retropalatal and retrolingual airway space. Surgical procedures for sleep apnea include uvulopalatopharyngoplasty (UPPP), laser-assisted uvulopalatoplasty, partial resection or ablation of the tongue, tonsillectomy, major reconstruction of the mandible or maxillae and tracheostomy.

No pharmacologic therapy for OSA has been found to be successful enough to be recommended as standard therapy. Lifestyle changes should be recommended for patients suffering from GERD: for example, avoiding bedtime snacks, eating low-fat foods, elevating the head of the bed, cessation of smoking, and reduction of alcohol consumption. Antacids, histamine-receptor blockers or proton-pump inhibitors can also be used. Surgical therapy of reflux is undertaken when medical therapy has failed or is not desired by the patient. Most important surgeries are fundoplication and gastropexy. One report suggests that treatment with omeprazole improves acid laryngitis.[85]

Management of the cardiovascular complications of OSA would begin with disease-modifying lifestyle changes, namely weight loss, which would have significant effects in treating hypertension particularly. In addition, specific cardiovascular complications need to be addressed. For example, hypertension is treated, as it would be with other patients keeping in mind that beta-blockers and/or angiotensin converting enzyme inhibitors might exacerbate cough or concomitant asthma. The

same principles would apply to treating the other cardiovascular complications of OSA, for example IHD, congestive heart failure, arrhythmias, and pulmonary hypertension.

Management of asthma is primarily pharmacologic, using medications such as inhaled steroids, leukotriene antagonists, immunotherapy, anti-immunoglobulin E, and cytokine antagonists. Avoidance of allergens is appropriate when rhinitis is related to allergy. Pharmacotherapy with antihistamines, topical intranasal CSs, leukotrienes, and immunotherapy may also be of benefit. Later-generation antihistamines are favored as classic antihistamines (e.g., diphenhydramine, chlorpheniramine, promethazine) are lipophilic and cause sedation. Therefore, administration of classic antihistamines may worsen underlying OSA.[48] Some asthma patients fail to respond to treatment with bronchodilators and oral glucocorticoids. Such refractory cases should be evaluated and treated for co-morbidities such as OSA and GERD, as these may be the cause of steroid therapy failure (a condition known as pseudo-steroid resistant asthma).[7]

Surgical approaches, such as correction of septal deviation to correct nasal obstruction could also be of help. Table 4 summarizes the diagnostic and therapeutic approaches to OSA and its complications.

Current state of knowledge and future reseach needs

OSA and asthma can coexist leading to enormous morbidity. Patho-physiologically, the two conditions seem to overlap significantly, as airway obstruction, inflammation, and obesity are pivotal aspects of both disorders. Complications, such as GERD, cardiovascular disease (especially ventricular dysfunction), obesity itself and the underlying inflammatory processes can compound the disease pathology seen in both conditions. The acronym "**CORE**" syndrome (**C**ough, **O**bstructive sleep apnea/**O**besity, **R**hinosinusitis and **E**sophageal reflux) could be used to describe this important association and disease entities.[86,87] It is important for the clinician taking care of these complicated patients to be aware of this association, and to carry out appropriate diagnostic and treatment strategies. The association of asthma and OSA, though described anecdotally, has not been systematically studied.

We anticipate these studies will be conducted in the next few years. The areas needing further studies are summarised in the research agenda box.

Practice points

1. Obstructive sleep apnea (OSA) and asthma can coexist in the same patient for various reasons and should promote the physician to carry out a more thorough evaluation.
2. Rhinitis, nasal polyposis and obesity can be common risk factors for both asthma and OSA and need to be looked for and treated aggressively.
3. The roles of inflammation, esophageal reflux (GERD), cardiac disease (ventricular dysfunction), and neurocognitive dysfunction in asthma outcomes and controls need careful evaluation and study.
4. Management of these patients is often multidisciplinary, requiring multiple approaches including behavioral/psychosocial, pharmacological, mechanical (CPAP), and surgical therapies. While no evidence exists to suggest improved outcomes with these measures, further studies are anticipated.

Research agenda

1. The influence of CPAP therapy (for sleep apnea) on asthma outcomes (such as quality of life, steroid utilization, emergency room visits) and fatality needs to be studied further.
2. The role of inflammatory mediators (cytokines, NO, leukotrienes, etc.) in OSA and their relationship to airway inflammatory responses need to be evaluated.
3. The effects of treatments for OSA (CPAP, surgery) on the output of inflammatory mediators (either systemic or on lung lavage samples in patients with concomitant asthma) need to be studied.
4. The effects of cardiovascular pathology (hypertension, ventricular dysfunction) on pulmonary function (FEV_1 or methacholine challenge) need to be evaluated.

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Glossary

Obstructive sleep apnea: A disease characterized by repeated episodes of upper airway occlusion that result in brief periods of apnea hypopnea, associated with excessive daytime sleepiness and abnormalities in cardiovascular, pulmonary, neurocognitive and metabolic function.

Continuous positive airway pressure

Apnea: Cessation of airflow for more than 10 s.
Hypopnea: At least 30% reduction in airflow for 10 s associated with a 4% decrease in oxygen saturation.
Apnea–hypopnea index: the total number of apnea and hypopnea events per hour of sleep.
CORE syndrome: a syndrome with the coexistence of cough/asthma, obesity/OSA, rhinosinusitis and esophageal reflux in a certain patient.
Overlap syndrome: a syndrome where obstructive sleep apnea coexists with chronic obstructive pulmonary disease and respiratory failure.