Obstructive sleep apnea in patients with severe asthma: Prevalence and association between severity and asthma control

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Abstract:

INTRODUCTION: Asthma and obstructive sleep apnea (OSA) are common respiratory disorders that can coexist and cause sleep disturbances. The strength of this association and the impact of OSA on asthma severity and control remain unclear. The study aims to estimate the prevalence of OSA in patients with severe asthma in Oman and to examine whether the severity of OSA contributed to the level of asthma control.

METHODS: Adult patients with confirmed diagnosis of severe asthma who attended the respiratory clinic in a tertiary hospital in Oman over a period of 19 months were enrolled in the study. Eligible participants were screened by asthma control test (ACT) and Berlin questionnaire (BQ). Patients with high risk for OSA were subjected further to level 3 sleep study. The prevalence of OSA in patients with severe asthma and the associations between the severity of OSA and asthma control were calculated.

RESULTS: We identified 312 adult asthma patients on Global Initiative for Asthma step 4 or 5 management out of 550 who were screened. The mean age of the study population was 56.59 ± 12.40 years and the mean body mass index (BMI) 40.30 ± 12.24 kg/m². The prevalence of OSA in asthma patients with severe asthma was found to be 32.4%. Out of the 138 well-controlled asthma patients (ACT ≥20), 35 had high risk of OSA based on BQ, and 32 were confirmed to have OSA (23%). Of the 174 uncontrolled patients, 80 patients had high risk of OSA and 69 patients were confirmed to have OSA (39.65%). Severe OSA was seen in 63.8% and 9.4% in uncontrolled and controlled asthma patients, respectively ($P = 0.002$). The median respiratory event index in the uncontrolled group was 43, and it was significantly higher than 12.5 in the controlled group ($P < 0.001$).

CONCLUSIONS: The prevalence of OSA was high (32.37%) in patients with severe asthma. Uncontrolled severe asthma was significantly associated with severe OSA.

Keywords:

Asthma control test, asthma, desaturation, sleep apnea

A sthma and obstructive sleep apnea (OSA) syndrome are common chronic disorders of the respiratory system. Asthma is characterized by generalized airway narrowing, while hallmark of OSA is repeated upper airway obstruction during sleep. Several studies have shown that asthma and OSA occur simultaneously and have a bidirectional relationship.[1] Clinical studies indicated that OSA has a higher prevalence in asthma patients than normal population, with the estimated prevalence figures being highly variable among studies.[2-4] With this association, treating one disorder is likely to improve the other.

In a large multicentric epidemiological study, sleep-disordered breathing was correlated with the prevalence of asthma in both children (odds ratio [OR] = 1.58, 95% confidence interval [CI]: 1.35–1.80) and adults (OR = 1.55, 95% CI: 1.42–1.67).[3] Moreover, the prevalence of OSA in a Canadian study was found to be higher in severe asthma, 88%, when compared to 58% in moderate asthma and 31% in the controls.[5] Interestingly, the prevalence of asthma in 606 patients with a confirmed diagnosis of OSA was found to be 35.1%.[6] Increasing evidence indicates that, among patients with asthma, coexistent OSA is associated with poor disease control. Many studies have shown that, compared to the patients without OSA, those with coexistent OSA have a higher asthma control questionnaire score, more severe day and nighttime symptoms, worse quality of life, more frequent exacerbations, and increased health-care utilization.[7] Likewise, OSA was found to be more severe in patients who had concurrent asthma.[6] Moreover, presence of OSA can be a risk factor for severe asthma exacerbations.[8] Analysis of large population-based data of 73,408 adult patients and 27,935 children hospitalized for acute asthma in eight U. S. states showed that the need for noninvasive ventilation and longer hospitalization was significantly higher in the patients with coexistent OSA.[7]

Over the past 25 years, the Global Initiative for Asthma (GINA) has regularly published and annually updated a global strategy for asthma management and prevention that has formed the basis for many national guidelines.[9] The classification of asthma severity has fundamentally changed over the past years and is now based on prescribed treatment. Patients requiring GINA step 1 or 2 treatment are often described as having mild asthma, step 3 as having moderate, and those prescribed steps 4–5 as having severe asthma.[9] This study aims to find the prevalence of OSA in patients with severe asthma attending a specialist asthma clinic and to explore the association between OSA severity and level of asthma control.

Methods

This is a cross-sectional study conducted in the sleep medicine unit and the pulmonology clinic in Sultan Qaboos University Hospital (SQUH). The study was approved by the Sultan Qaboos University Research Ethics Committee. All patients who attended the asthma clinic between January 01, 2015, and August 31, 2016, were included in the study with the following inclusion criteria: local adult patients with asthma >18 years of age, with confirmed diagnosis either clinically by a pulmonologist and/or consistent spirometry, followed up at SQUH, with at least 2 visits or more in pulmonology clinic, and are on GINA step 4 or 5 asthma treatment.

Patients with the following criteria were excluded: recent asthma exacerbation in the preceding month, active smoking, cardiac failure, other lung diseases such as interstitial lung diseases, chronic obstructive pulmonary disease, bronchiectasis, pulmonary embolism, and patients with disabling neurological or psychiatric diseases and those unable to give consent. Those who had been diagnosed with sleep breathing disorder before were also not included.

Sample size
The sample size was calculated as 277 subjects, considering a prevalence of OSAS in asthmatic subjects as 50% and CI of 95% and an error margin of 10% on either side of the estimate.

Data collection
Demographic and anthropometric data such as age, gender, height, and weight were all obtained from the electronic medical records system and added to study database. Other data such as responses to Berlin questionnaire (BQ), asthma control test (ACT) score, and respiratory event index (REI) score were also added while being evaluated.

Study protocols
After enrollment, subjects were assessed by Arabic version of ACT and were categorized into two groups: well-controlled asthma and uncontrolled asthma. Subjects of both the groups were assessed for OSA by a validated Arabic version of BQ and accordingly classified into two subgroups: BQ positive and BQ negative. Both ACT and BQ were done during the outpatient clinical visit or sometimes through phone calls. BQ-positive subjects in both the groups underwent sleep study to confirm the results. Patients who refused to continue providing their data or to continue with the study protocols got excluded from the study.

Asthma control test
ACT is a patient self-administered tool for identifying asthma control. It assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. It contains 5 items, with 4-week recall on symptoms and daily functioning. The scores range from 5 to 25, with higher scores reflecting greater asthma control. It has been validated in different languages, and we used the Arabic version.[10] Asthma was deemed to be well controlled if the ACT score was more than or equal to 20 and uncontrolled if the ACT was 19 or less.

Berlin questionnaire
The BQ is a tool used to screen the risk of OSA in the general population. The questionnaire consists of 10 questions

covering 3 categories snoring, sleepiness, and high blood pressure. The first is an introductory question followed by 4 questions each to address snoring and sleepiness and a single question to address high blood pressure. Patients can be classified into high risk or low risk based on their responses to each question and their overall scores in the symptom categories. This is a valid tool to screen for OSA syndrome in a source-limited setting and has been validated in native Arabic-speaking population.[11]

Sleep study

Asthma patients with high risk for OSA based on BQ were further subjected to home sleep apnea testing (ApneaLink, ResMed, Sydney, Australia) level 3 and scored according to the guidelines of the American Academy of Sleep Medicine. The study includes airway monitoring, chest and abdominal movements, and oximetry.[12] REI is calculated by the total number of respiratory events multiply by 60 divided by the monitoring time. The severity of OSA is classified based on REI: normal: <5, mild sleep apnea: 5 to <15, moderate sleep apnea: 15 to <30, and severe sleep apnea ≥30.

Statistical analysis

The study database was created in SPSS version 23.0 software (SPSS, IBM, USA). Descriptive and inferential statistics were done. Chi-square test was used to test the significance of association between the categorized variables and independent sample *t*-test has been applied to test the significance of the difference of means of the characteristics between the uncontrolled and controlled asthma patients. Multivariate regression analysis was also performed to evaluate the significance of impact of characteristics on AHI level among uncontrolled and controlled asthma patients. *P* value of 0.05 or less has been taken as significant.

Results

We identified 312 adult asthma patients out of 550 screened during the study period. All of them were on GINA step 4 or 5 management. When assessed by ACT, 138 (44.2%) had well-controlled asthma while 174 (55.8%) were uncontrolled. BQ scored as low risk in 197 subjects. High risk of OSA was noted in 35 (25%) and 80 (46%) controlled and uncontrolled asthma patients, respectively.

Five subjects refused to undergo sleep study, and therefore, home sleep study was done on 110 patients. Nine sleep studies showed REI of <5 [Figure 1]. The total number of patients who were confirmed to have OSA (REI >5) was 101, 27 (26.7%) males and 74 (73.3%) females. The mean age of the study population was 56.59 ± 12.40 years and the mean body mass index (BMI) 40.30 ± 12.24 kg/m² [Table 1].

The overall prevalence of OSA in this cohort of asthma patients was 32.4%. Out of 138 patients with controlled asthma, 35 had high risk of OSA, and 32 (23.2%) were confirmed to have OSA (REI >5). Of the 174 patients with uncontrolled asthma, 80 patients had high risk of OSA based on BQ and 69 patients were confirmed to have OSA (39.7%) by the sleep study.

Among uncontrolled asthma patients (ACT ≤19), 63.8% had severe OSA while majority (65.6%) of controlled asthma patients (ACT ≥20) had only mild OSA (*P* < 0.0001) [Table 2]. The distribution of REI is given in Figure 2. The REI was significantly higher in patients with uncontrolled asthma (*P* < 0.001). The median REI in the uncontrolled group was 43 while that in the controlled was 12.5.

The mean age of the patients with uncontrolled asthma was higher (58.72 ± 10.22 years) than the patients with controlled symptoms (50.78 ± 15.45 years), *P* = 0.002. Although the mean BMI was higher (40.39 ± 7.30 kg/m²) in uncontrolled asthma patients than in controlled cases (37.46 ± 7.97 kg/m²), the difference was not statistically significant (*P* = 0.071). Linear regression analysis indicates that REI is a significant predictor for ACT (*P* < 0.001) after controlling for age. Moreover,

Table 1: Study demographics for the controlled and uncontrolled asthma patients

Characteristic	Asthma	Mean±SD	Median	Significance
Age (years)	Uncontrolled (71)	58.45±10.83	61.0	0.016
	Controlled (28)	51.86±14.89	49.5	
ACT	Uncontrolled (71)	13.10±3.84	13.0	<0.001
	Controlled (28)	21.43±1.10	21.0	
BMI (kg/m²)	Uncontrolled (71)	41.25±13.44	40.5	0.224
	Controlled (28)	37.91±8.36	38.4	
REI	Uncontrolled (71)	48.38±30.07	43.0	<0.001
	Controlled (28)	17.36±16.09	12.5	

REI=Respiratory event index, ACT=Asthma control test, BMI=Body mass index, SD=Standard deviation

Table 2: Distribution of severity of obstructive sleep apnea in controlled and uncontrolled asthma patients and significance of their association

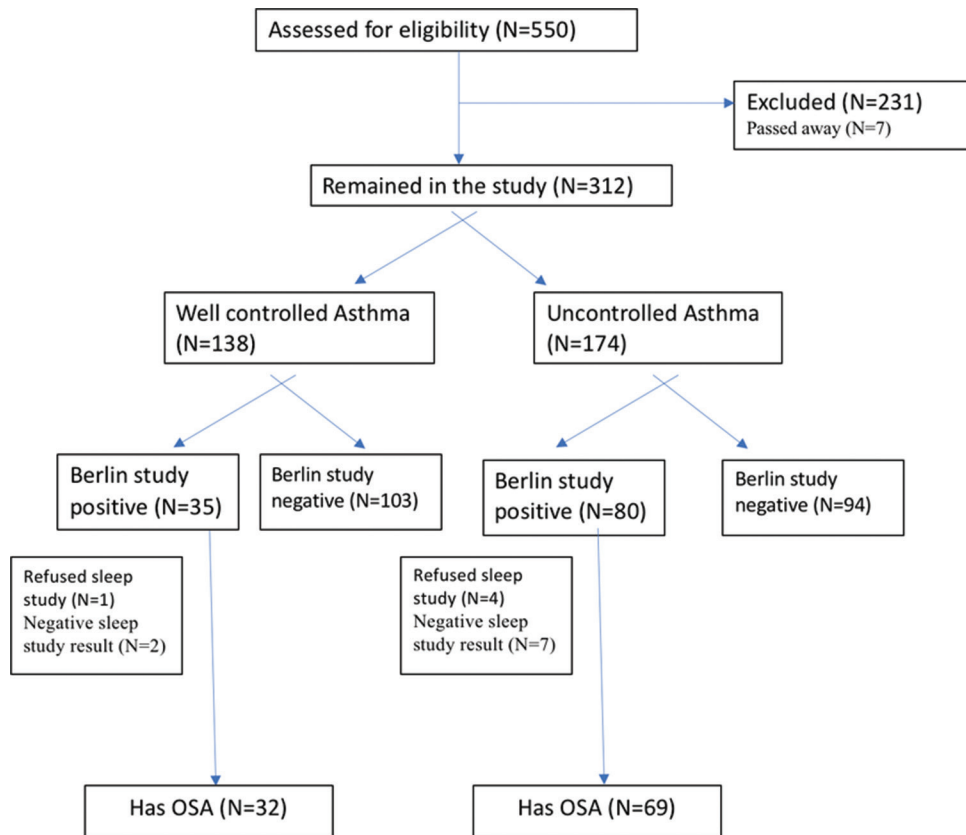| OSA severity	Uncontrolled asthma (%)	Controlled asthma (%)	Total	*P*
Mild	4 (5.6)	19 (67.9)	23	<0.001
Moderate	21 (29.6)	7 (25.0)	28	
Severe	46 (64.8)	2 (7.1)	48	
Total	71	28	99	

OSA=Obstructive sleep apnea

Figure 1: The flowchart showing the selection of patients (obstructive sleep apnea is defined as respiratory event index >5)
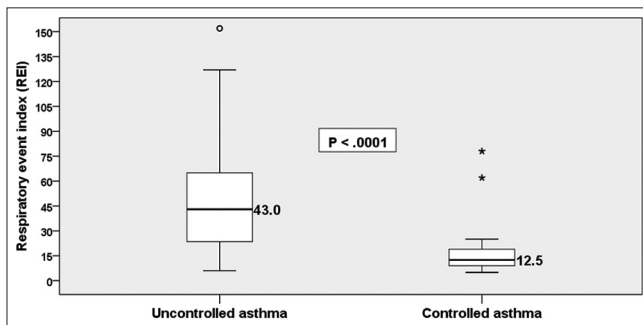

Figure 2: Difference of respiratory event index between controlled and uncontrolled asthma patients

BMI is also having a significant association with REI ($P < 0.002$) [Table 3].

Discussion

OSA is one of the causes for difficulty in controlling the symptoms in patients with asthma. We found that among patients with asthma, coexistent OSA is associated with severity and poor disease control. Nearly a third of patients with severe asthma, needing higher treatment strategies, have OSA. Moreover, OSA was present in two-thirds of patients with severe asthma whose symptoms remained uncontrolled in spite of receiving additional controllers of step 4 or 5 therapy.

The major advantage of our study was that the diagnosis of OSA was confirmed by sleep study and not only by an approximate assessment of questionnaires.

We studied patients with severe asthma needing step 4 or 5 treatment of GINA guidelines. OSA was identified in one-third of our asthma patients and that is in accord with the findings of other studies conducted worldwide. Generally, the prevalence of OSA among asthmatic populations ranges from 38% up to as high as 70%.[2] Similarly, the prevalence of OSA in adult asthma patients was found to be 50% in a meta-analysis with a 2.64-fold higher chance of having OSA than the normal people.[13] A systematic review demonstrated a prevalence of OSA in asthma in the range of 8%–52.6% in questionnaire-based studies and a higher prevalence of 19.2%–60% in studies using polysomnography with a higher rate at 50%–95% in severe asthma.[14] Moreover, other studies also suggest that the prevalence of OSA increased progressively according to severity of asthma. In another study, the prevalence of OSA in difficult-to-treat asthma (uncontrolled) patients was found to be as high as 75.5%.[15] Serrano-Pariente *et al*. showed that the presence of OSA increased from 58% in moderate asthma to 88% in severe asthma.[16] The prevalence of moderate-to-severe OSA (REI ≥15) in our asthmatic population sample was 36.59%.[17] We selected

Table 3: Multiple regression analysis showing coefficients and their significance for independent variables among controlled and uncontrolled asthma patients

	Independent factor	Regression coefficient (*B*)	Standardized coefficient	Significance
Combined (*n*=99)	Age	0.198	0.081	0.277
	ACT	−3.868	−0.654	<0.001
	BMI	0.422	0.171	0.020
Uncontrolled asthma (*n*=71)	Age	−0.147	−0.053	0.583
	ACT	−4.734	−0.605	<0.001
	BMI	0.495	0.221	0.021
Controlled asthma (*n*=28)	Age	0.612	0.567	0.003
	ACT	−3.389	−0.232	0.194
	BMI	0.185	0.096	0.584

Dependent variable: REI. REI=Respiratory event index, ACT=Asthma control test, BMI=Body mass index

patients with severe asthma who were receiving step 4 or 5 care with some of them receiving biological therapy as well.

Possible shared pathophysiological links could include mechanical effects, intermittent hypoxia, nerve reflex, inflammation, medications, nasal diseases, smoking, obesity, and gastroesophageal reflux disease.[4,6,18] In addition, vascular endothelial growth factor-induced airway angiogenesis, leptin-related airway changes, and OSA-induced weight gain may be mechanisms linking both disorders.[19] The common asthma features that promote OSA symptoms are nasal obstruction, a decrease in pharyngeal cross-sectional area, and an increase in upper airway collapsibility.[19] Moreover, epidemiologic, physiologic, and biologic evidence suggests a bidirectional interaction between asthma and OSA aside from these shared factors, indicating that the nasal, pharyngeal, and lower airways are indeed "united."[4]

Our patients with uncontrolled severe asthma had a higher BMI and REI compared to patients with controlled symptoms. However, the difference in BMI was not statistically significant, thereby obesity alone could not be the solo factor linking the association. However, Kong *et al*. noted that the BMI was significantly higher in asthma patients with OSA when compared to those who do not have.[13] Similarly, another study noted that patients with more severe OSA were significantly more likely to be at asthma treatment step 4, and this tendency was more pronounced in patients with a higher BMI.[20]

Physiologically, the evidence for severe asthma in OSA can be demonstrated. It was found in other studies that pulmonary function parameters such as peak expiratory flow, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC in asthmatic patients with severe OSA were lower than those with mild or moderate OSA.[17,21,22] Interestingly, continuous positive airway pressure (CPAP) treatment may improve FEV1 in asthma patients, especially in those with severe OSA.[22]

A systematic review reports that CPAP treatment can improve asthma-related quality of life and this effect appears more pronounced in severe OSA or poorly controlled asthma.[23] A prospective, multicenter study also showed improvement in asthma control, quality of life, and lung function after starting CPAP in asthmatics with moderate-to-severe OSA.[16]

There is enough evidence now to emphasize the need for screening and eventually treating OSA in patients with severe or poorly controlled asthma as well in those with significant nocturnal symptoms, especially when they fail to respond to guidelines recommended treatment.[16,24] In addition to these adverse health outcomes, evidence suggests that untreated OSA could be associated with increased health-care utilizations and costs. The presence of OSA was associated with longer hospitalization, need for invasive respiratory support, higher hospital charges, and health-care utilization in asthma-related hospitalizations in a US Nationwide Inpatient Sample.[25] Moreover, a review of a large population-based database of 65,731 patients hospitalized for asthma exacerbation across seven U. S. states showed that the patients with coexistent OSA had a significantly higher rate of readmissions in the 1st year.[26] Therefore, it is really important to identify coexistent OSA in this population and optimize both asthma and OSA management.

Although our findings confirm a higher prevalence of OSA in patients with severe asthma, particularly in the uncontrolled group, further study is required to assess the effect of CPAP in these patients in achieving asthma control. The advantage of our study was that sleep study was done to confirm OSA, and all patients were selected from a specialized asthma clinic in a tertiary hospital. Moreover, we used ACT which gives more insight about the nocturnal symptoms, which are of concern for both respiratory conditions. However, we did not look into the association with pulmonary function, type of medications, and comorbidities, which could be the limitations of our study.

Conclusions

The prevalence of OSA in patients with severe asthma was high, and it was much higher in uncontrolled patients. Therefore, we need to screen for any symptoms suggestive of OSA in asthma patients, especially in more severe forms and overweight individuals. Further studies are needed to address the impact of long-term treatment of OSA on the clinical outcomes of asthma management.

Conflicts of interest
There are no conflicts of interest.

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