The prevalence of obstructive sleep apnea in patients with difficult-to-treat asthma

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Summary

Objectives: **Obstructive sleep apnea (OSA) occurs more commonly in asthma patients than in the general population and can complicate asthma management. The aim of this study was to evaluate the presence of OSA in patients with difficult-to-treat asthma (DTA) and to investigate the sleep quality in these patients.**

Methods: **Patients with DTA were recruited from the adult allergy clinic of a tertiary care hospital. After completing the Sleep Questionnaire and Epworth Sleepiness Scale, all participants underwent overnight polysomnography. The demographic and asthma severity assessments included the following measures: the age at diagnosis, duration of illness, smoking and atopy status, results of pulmonary function tests, number of asthma control medications used, and number of hospitalizations and emergency room visits because of asthma and analgesic hypersensitivity according to apnea–hypopnea index (AHI) scores.**

Results: **We analyzed 47 (M:9/F:38) DTA patients with a mean age of 48.74±9.45 years. The mean duration of asthma was 9.17±6.5 years. Twenty-four (51.1%) patients were atopic. The analgesic hypersensitivity rate was 27.7%. Fourteen patients (29.8%) were former smokers and 2 patients were current smokers. Sleep quality was impaired in all patients. Thirty-five patients (74.5%) had OSA, 11 of whom had mild OSA, and 24 patients had moderate-severe OSA. The presence of OSA was not statistically correlated with asthma characteristics.**

Conclusion: **The study showed that there is a remarkably high prevalence of OSA in DTA. Although no statistically significant relationship between the presence of OSA and clinical asthma characteristics was identified, all DTA patients should be assessed for OSA.** ***(Asian Pac J Allergy Immunol 2014;32:153-9)***

Key words: *asthma, difficult-to-treat asthma, obstructive sleep apnea, polysomnography, sleep quality*

Introduction

Most patients with asthma have mild-to-moderate disease that can be easily controlled with conventional treatment. However, some patients have uncontrolled asthma despite moderate to high doses of inhaled corticosteroids and long acting β2 agonist and/or leukotriene modifier combinations. Uncontrolled asthma has serious impacts on morbidity, quality of life, and economic burden. Factors that influence asthma control, such as environmental exposure, comorbidities, adherence, and inhalation technique, should be identified and adequately addressed in managing severe asthma.[1]

The awareness of the determinants of asthma control may help to achieve better disease control. However, while treatment adequacy, treatment adherence, and patients' perception of their own asthma control have been studied, other determinants for asthma control have not been assessed as thoroughly.[2]

Obstructive sleep apnea (OSA) syndrome has a high prevalence of 4% in men and 2% in women.[3] OSA is characterized by recurring episodes of upper airway obstruction during sleep. Airway obstruction leads to reduced (hypopnea) or absent (apnea) airflow at the nose/mouth, resulting in periodic arousal and episodic oxyhemoglobin desaturation during sleep.[4] Asthma and OSA have similar

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nocturnal symptoms and airway obstruction is the hallmark of their pathophysiology.[5] The relationship between OSA and asthma has been previously shown; most studies have focused on the prevalence of snoring and other OSA symptoms in asthma patients.[6,7] Patients with asthma have a higher prevalence of snoring and apnea than patients without asthma. Polysomnography is the gold standard for diagnosing OSA, but population-based studies in patients with asthma have not been reported, perhaps because of the costs.[8,9] The presence of OSA makes it difficult to control asthma, and asthma symptoms can be improved after initiating continuous positive airway pressure (CPAP).[10-12]

Asthmatics have impaired sleep quality because of nocturnal asthma attacks, co-existing sleep-disordered breathing, bronchial hyper-reactivity, and existing allergic rhinitis.[12-14]

The primary aim of this study was to investigate the prevalence of OSA in patients with difficult-to-treat asthma (DTA) and, secondarily, to examine the sleep quality in these patients.

Methods

Study population

This prospective study was designed at a tertiary care adult allergy clinic and sleep disorder center. The study subjects were patients with asthma who had been observed by an asthma specialist for at least 6 months. The study included 47 DTA patients. Written informed consent was obtained for 46 of the 47 patients. The study was performed after receiving approval from the institutional review board.

Asthma diagnosis

Asthma was diagnosed based on a history of recurrent wheezing, shortness of breath, cough, and the demonstration of objective signs of reversible airway obstruction as characterized by an average of a more than 12% minimum increase in FEV_1 after 15 minutes with an inhalation of 400 μg salbutamol according to the Global Initiative for Asthma (GINA) guidelines.[15]

DTA Definition

DTA was defined as asthma that could not be controlled by a combination of high-dose inhaled corticosteroids and long-acting β2 agonists or another controller medication.

Allergy skin tests

Skin prick tests (SPTs) were performed using a common panel including *Dermatophagoides pteronyssinus, Dermatophagoides farina,* grass, tree, and weed pollens, and cat, dog, *Alternaria*, *Cladosporium,* and cockroach allergen extracts (Stallergenes, Anthony, France). The positive and negative controls were histamine (10 mg/ml) and phenolated glycerol saline, respectively. Skin testing was performed using the puncture method. The test was considered positive if the mean wheal diameter was 3 mm greater than the wheal generated by the negative control solution.

Sleep apnea questionnaire

The sleep apnea questionnaire (SAQ) includes questions about 4 OSA symptoms: loud snoring, breathing pauses during sleep, nocturnal sweating, and daytime sleepiness.

Epworth sleepiness scale

On the night of polysomnography, each subject completed an Epworth Sleepiness Scale (ESS). The ESS is a compact and easily self-administered scale. Subjects report a value on a scale of 0 to 3 to indicate their likelihood of falling asleep in 8 different scenarios (0 = would never doze; 3 = high chance of dozing). The ESS has a total score range of 0-24. Scores equal or more than 10 are associated with excessive daytime sleepiness.[16]

Polysomnography

All participants underwent overnight polysomnography from 11 pm to 7 am using the Compumedics Voyager Digital Imaging E-series System (Compumedics®, Melbourne, Victoria, Australia) or the Alice 5 system (Respironics, PA, USA). The polysomnography recordings included 4-channel electroencephalography, 2-channel electrooculography, 1-channel submental electromyography, oxygen saturation via an oximeter probe, respiratory movements via chest and abdominal belts, nasal pressure via a pressure sensor, electrocardiography, and leg movements via tibial surface electrodes. Body position was monitored by a sensor attached to a thoracic belt. Sleep stages and respiratory parameters were scored according to the standard criteria of the American Academy of Sleep Medicine (AASM). Based on the AASM guidelines published in 2007, apnea was defined as a minimum 10-second equal to or more than 90% reduction in airflow relative to the basal amplitude. Hypopnea was defined as a minimum 10-second equal to or more than 50% reduction in airflow amplitude relative to the baseline values with either an associated oxygen desaturation of equal to or more than 3% or arousal.[17] The apnea-hypopnea index

(AHI) was defined as the number of apneas and hypopneas divided by total sleep time. OSA was defined by an overall AHI equal or more than 5. Patients were categorized based on overall AHI. Patients were considered to have mild OSA with an AHI=5-15 and moderate-severe OSA with an AHI equal or more than 15. Rapid eye movement (REM)-AHI was calculated as the number of apneas and hypopneas during REM sleep divided by total REM sleep.[18,19]

Body mass index (BMI)

BMI was calculated by dividing body weight in kilograms by the square of the height in meters. Subjects were classified according to the following BMI parameters: equal or more than 30 kg/m^2=obese, 25.0 - 29.9 kg/m^2=overweight, and 18.5 - 24.9 kg/m^2=normal.[20]

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 11.0 for Windows; SPSS Inc.; Chicago, IL) for Windows. Means and standard deviations (SDs) were determined for the continuous variables, and percentages were determined for the categorical variables. The significance of the differences between 2 groups was analyzed with Student's t-test. Categorical data were analyzed by the chi-squared and Fisher's exact probability tests. All statistical analyses were performed using statistical software. Differences were considered significant at $p < 0.05$.

Results

Table 1 shows demographic and clinical characteristics of the 47 patients. The mean age of the population was 48.74 years, and 66% of the patients had never smoked. All patients were on at least moderate-to-high doses of ICS with LABA. The mean number of controller medications used was 3.22 ± 0.814.

Sleep apnea questionnaire: All patients had at least 1 significant OSA symptom, such as loud snoring, witnessed apnea, or daytime sleepiness.

ESS: Daytime sleepiness as detected by ESS was more pronounced in asthmatics with OSA ($p < 0.001$). The ESS score was equal or more than 10 in 22 asthmatics with OSA, whereas only one subject without OSA had an ESS score of equal or more than 10 (62.86% and 8.33%, respectively, $p < 0.001$*). When the entire group was analyzed, a moderate but statistically significant correlation between ESS and AHI was detected (r = 0.410 $p = 0.004$).

Table 1. Demographic and clinical characteristics of the study population.

Characteristics	n (%)
Gender (Male/Female)	9 (19) / 38 (81)
Mean age ± SD (min-max), years	48.74 ± 9.45 (30-75)
Mean age at diagnosis of asthma±SD (min-max), years	40.98 ± 11.55 (15-69)
Mean duration of asthma±SD (min-max), years	9.17 ± 6.5 (1-25)
No of controller medication±SD (min-max),	3.22 ± 0.814 (2-5)
BMI ±SD (min-max), (kg/m^2)	31.67 ± 6.04 (19.59-44.07)
Normal weight (BMI=20-24.99)	13 (27.7)
Overweight (BMI=25-29.99)	5 (10.6)
Obese (BMI≥30)	29 (61.7)
Smoking history	
Never smoker	31 (66)
Ex-smoker	14 (29.8)
Current smoker	2 (4.3)
Skin prick / intradermal test positivity	24 (51.1)
Drug hypersensitivity	
None	32 (68.1)
Analgesic	13 (27.7)
Antibiotic	1 (2.1)
Radiocontrast media	1 (2.1)
Allergic rhinitis	13 (27.7)
Chronic rhinosinusitis	31 (66)
Hospitalization due to asthma	
Ever	33 (70.2)
Last Year	28 (59.6)
Emergency department visit due to asthma	
Ever	40 (85.1)
Last Year	29 (61.7)
Mean FEV_1, %predicted±SD (min-max)	62.82 ± 20.58 (29-112)
Mean FEV_1/FVC±SD (min-max)	73.3±11.6 (51-107)
Mean PEF, %predicted±SD (min-max)	65.26±23.04 (17-107)
Mean FEF25-75, %predicted±SD (min-max)	48.17±28.03 (9-147)
ESS score±SD (min-max)	8.08±3.77 (1-16)

Abbreviations: SD, standard deviation; BMI, body mass index; ESS, Epworth Sleepiness Scale.

However, when only the OSA group was tested, the results showed no correlation between ESS and AHI (r = 0.248, p = 0.151).

Polysomnography results

Polysomnographic results for the study group are presented in Table 2. All patients had decreased rapid eye movement (REM) sleep and non-rapid eye movement (NREM) stage 3 sleep rates.

Thirty-five asthmatic patients had OSA with an AHI value equal to or more than 5. Eleven (31.43%) of these patients had mild OSA, and 24 (68.57%) had moderate to severe OSA. Table 3 shows the patients' demographic and clinical characteristics according to OSA status, and Table 4 includes the polysomnography details.

Factors related to OSA

There was no correlation between either the patient demographics or asthma characteristics and the presence of OSA.

Although obesity rates were not different between the asthmatics with or without OSA, there was a significant correlation between BMI and OSA severity, as expected (r = 0.320, p = 0.028).

Discussion

In this study, overnight polysomnography showed that the prevalence of OSA in the DTA population was up to 74.5%. There was no relationship between the clinical asthma characteristics and the presence of OSA. All DTA patients had at least 1 of the cardinal clinical symptoms of OSA, such as loud snoring, witnessed sleep apnea or excessive daytime sleepiness. In addition, although the entire study group demonstrated poor sleep quality, this measure was worse for OSA subjects.

Table 2. Polysomnographic results for the study group.

Parameters	Mean±SD (min-max)
Sleep latency (minute)	17.48±19.32 (0.5-91)
REM latency (minute)	113.50±52.67 (43-299)
REM sleep %	14.40±3.80 (5.50-22.60)
NonREM stage 1 sleep %	7.44±3.93 (1.10-18.20)
NonREM stage 2 sleep %	63.64±5.96 (51.20-78.30)
NonREM stage 3 sleep %	14.38±4.65 (2.20-26.70)
Awake SpO_2 (%)	94.51±1.37 (91-97)
Mean SpO_2 (%)	92.49±2.47 (84-96)
Lowest SpO_2 (%)	85.19±6.89 (65-93)

Abbreviations: SD, standard deviation; REM, rapid eye movement; SpO_2, oxygen saturation by pulse oximeter.

OSA is common in the general adult population, with an estimated prevalence of 2% in females and 4% in males.[3] Polysomnography is still the gold standard for diagnosing OSA; however, because of the cost, population-based studies in patients with asthma have not been reported. Consequently, most of the existing studies are based on questionnaires.[8,9] Several studies have shown that OSA symptoms, such as snoring and witnessed apnea, are also common in the asthmatic population.[21,22] Auckley et al. used the Berlin Questionnaire to compare snoring rates and OSA risk between patients with asthma and an internal medicine group. The study found higher snoring rates (18.5% vs. 8%, p < 0.001) and higher OSA risk (39.5% vs. 27.2%, p = 0.004) in the asthma group.[8] Kalra et al. found a high prevalence of snoring in young women with atopy and a significant association between snoring and asthma.[23] In a questionnaire study by Janson et al. that surveyed a group of 2202 subjects, including 267 asthmatics, the presence of asthma was a stronger predictor of self-reported apnea than the other common risk factors, such as male gender, BMI, and age.[24] In a study performed by Larsson et al., snoring was detected in 17% of subjects, and witnessed apnea was detected in 14.3% of patients with physician-diagnosed asthma.[25]

In their questionnaire study, Auckley et al. found that the risk for OSA did not correlate with asthma severity.[8] Teoderescu et al. reported that a high risk of OSA was independent of known asthma triggers and was unrelated to asthma control questionnaire scores.[26] Yigla et al. have shown that patients receiving continuous oral corticosteroid therapy had higher RDI values at PSG than patients receiving frequent bursts of oral corticosteroid therapy.[27] Julien et al. did not identify any significant correlations between the severity of sleep-disordered breathing and asthma severity, rhinitis, atopy, nasal polyposis, or the use of oral prednisolone, high-dose inhaled corticosteroids, long-acting-β2 agonists, or leukotriene modifier drugs among asthmatics. They also did not find any significant correlation between the severity of OSA and asthma control measures.[13]

Using full night home PSG, Julien et al. compared 3 groups: severe asthmatics, moderate asthmatics, and non-asthmatic controls. They reported OSA

Table 3. Demographic and clinical characteristics according to the OSA status of the study group.

Characteristics		Asthma without OSA n (%)	Asthma with OSA n (%)	*p*
Mean age±SD (min-max), years		46.67±6.44 (31-54)	49.46±10.27 (30-75)	0.471
Gender (Male/Female)		2/10	7/28	1
Mean age at diagnosis of asthma±SD (min-max), years		40.08±10.08 (21-51)	41.29±12.14 (15-69)	0.912
Mean duration of asthma±SD (min-max), years		7.25±6.82 (2-21)	9.83±6.40 (1-25)	0.174
No of controller medication±SD (min-max),		3.27±0.786 (2-4)	3.20±0.833 (2-5)	0.795
BMI (kg/m^2)		29.64±6.17 (23.14-42.35)	32.37±5.92(19.59-44.07)	0.143
Smoking history	Never smoker	9 (75)	22 (62.86)	0.443
	Ever smoker	3 (25)	13 (37.14)	
Drug hypersensitivity	Absent	10 (83.33)	22 (62.86)	0.189
	Present	2 (16.67)	13 (37.14)	
Allergic rhinitis		3(25)	10(28.6)	0.657
Chronic rhinosinusitis		6 (50)	25 (71.43)	0.289
Hospitalization due to asthma	Ever	10 (83.33)	23 (65.71)	0.302
	Last Year	8 (66.67)	20 (57.14)	0.256
Emergency department visit due to asthma	Ever	11 (91.67)	29 (82.86)	0.328
	Last Year	7 (58.33)	22 (62.86)	0.540
Skin prick / intradermal test positivity		5 (41.66)	19 (54.28)	0.517
Mean FEV_1, %predicted±SD(min-max)		58.17±20.76 (31-97)	64.43±20.58 (29-112)	0.380
Mean FEV_1±SD (min-max)		1.49±0.55 (0.80-2.37)	1.79±0.61(0.62-3.01)	0.147
Mean FVC, %predicted±SD (min-max)		67.67±18.22 (44-101)	73.80±15.44 (41-102)	0.227
Mean FEV_1/FVC±SD (min-max)		72.42±10.74 (56-89)	73.60±12.02 (51-107)	0.760
Mean PEF, %predicted±SD (min-max)		60.58±24.17 (17-103)	66.86±22.78 (26-107)	0.510
Mean FEF25-75, %predicted±SD (min-max)		45.25±26.64 (12-75)	49.17±28.80 (9-147)	0.807
ESS±SD (min-max)		3.75±2.34 (1-11)	9.57±2,92 (1-16)	**<0.001***

Abbreviations: SD, standard deviation; BMI, body mass index; ESS, Epworth Sleepiness Scale.

rates of 88% in severe asthmatics, 58% in moderate asthmatics, and 31% in the control group.[13] Teodorescu used the Sleep Disorders Questionnaire to evaluate the relationship between OSA risk and asthma control in adults. They found a 23% risk for OSA and a 2.87-fold increased risk for poorly controlled asthmatics.[26] Yigla et al. used PSG to study 22 patients with DTA. They found a 95.5% prevalence of OSA in the study group.[27] In this study, we confirmed that OSA prevalence, as measured by overnight PSG, ranged up to 74.5% in the DTA population.

However, asthma is a common disease and affects patients of all ages and both genders. Unfortunately, there are still some asthmatics whose symptoms are poorly controlled despite aggressive therapy.[15] Once the diagnosis of asthma is confirmed and adherence to the treatment plan with appropriate inhaler technique is assessed, it is important to thoroughly examine other factors or comorbidities that can contribute to poor asthma control. OSA is one contributing factor, particularly in patients with nocturnal symptoms. A high prevalence of OSA, ranging from 50% to 96%, has been reported by both questionnaires and PSG in patients with severe asthma.[28]

The present study also found a significant difference in sleep quality for the DTA population. It has been previously shown that sleep quality is impaired in asthmatics compared to those without asthma. Poor sleep quality can result in excessive daytime sleepiness.[12-14] Repetitive obstructive events in OSA result in sleep arousal. Recurrent sleep arousal leads to sleep fragmentation and impaired sleep architecture; as a result, there is marked reduction in rapid eye movement and slow-

Table 4. Polysomnography results according to OSA status of the study group.

Parameters	Asthma without OSA Mean±SD (min-max)	Asthma with OSA Mean±SD (min-max)	p
Sleep latency (minute)	25.88±21.18 (1-91)	14.60±12.53 (0.5-48.5)	0.526
REM latency (minute)	116.08±66.64 (43-299)	112.61±48.08 (48.5-220.5)	0.981
REM sleep (%)	16.75±3.58 (9.40-22.20)	13.59±3.57 (5.50-22.60)	**0.012***
NonREM stage 1 sleep (%)	6.35±3.25 (1.80-13.40)	7.82±4.11 (1.10-18.20)	0.300
NonREM stage 2 sleep (%)	60.01±4.09 (52.70-65.90)	64.89±6.03 (51.20-78.30)	**0.009***
NonREM stage 3 sleep (%)	17.07±1.68 (13.90-19.70)	13.45±4.99 (2.20-26.70)	**0.001***
Awake SpO_2 (%)	95.00±1.41 (93-97)	94.34±1.33 (91-97)	0.192
Mean SpO_2 (%)	93.83±1.70 (90-96)	92.03±2.54 (84-96)	**0.018***
Lowest SpO_2 (%)	89.25±2.92(82-93)	83.80±7.32 (65-93)	**0.009***

Abbreviations: SD, standard deviation; REM, rapid eye movement; SpO_2, oxygen saturation by pulse oxymeter.

wave sleep.[29] Nocturnal asthma and existing OSA are factors causing impaired sleep quality. However, concurrent allergic rhinitis and the controller medication taken for allergic rhinitis are also notable underlying causes of poor sleep quality.[30,31] In the present study found impairment of sleep quality in both asthmatic groups. Although the entire study group had lower rates of REM and non-REM stage 3 sleep, the rates were significantly lower in the OSA group. The lower rates may be a result ofaccompanying allergic rhinitis, as the rate is the same for both groups. The ESS scores were significantly higher in patients with OSA, dependent upon impaired sleep quality.

Full-night polysomnography is the gold standard for diagnosing SDB. Nightly variations in PSG limit diagnosis, particularly in mild OSA. It would be valuable to conduct the analysis over the course of several nights; however, cost and time considerations limited the study to single night evaluations.

The 'first night effect' in the laboratory can alter sleep parameters. All participants had similar sleep parameters, such as increased stage 1 and 2 sleep and decreased stage 3 and REM sleep; the OSA patients seemed to have more of these variations. This result demonstrates that all participants are likely influenced by the first night effect, which commonly occurs in patients evaluated in a sleep laboratory.

This study evaluated 12 DTA patients with AHI less than 5; however, increased obstructive respiratory events during REM (AHI_{REM} equal or more than 5) were observed in half of these patients. REM-related OSA in these patients may represent an early sign of impaired neuromuscular responses to upper airway obstruction.[32] These patients may have an increased likelihood of developing OSA in the future.

In conclusion, given the high prevalence of OSA in DTA asthmatics and a lack of correlation to clinical asthma characteristics, sleep-related symptoms should be routinely be enquired about and polysomnography should be performed to make a definitive diagnosis in the DTA population.

References

1. Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet LP, et al. Severe asthma in adults: what are the important questions? J Allergy Clin Immunol. 2007;119:1337-48.
2. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126:926-38.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 19939;328:1230-5.
4. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. J Appl Physiol. 1978;44:931-8.
5. Kasasbeh A, Kasasbeh E, Krishnaswamy G. Potential mechanisms connecting asthma, esophageal reflux, and obesity/sleep apnea complex--a hypothetical review. Sleep Med Rev. 2007;11:47-58.
6. Larsson LG, Lindberg A, Franklin KA, Lundbäck B. Symptoms related to obstructive sleep apnoea are common in subjects with

asthma, chronic bronchitis and rhinitis in a general population. Respir Med. 2001;95:423-9.

7. Shigemitsu H, Afshar K. Nocturnal asthma. Curr Opin Pulm Med. 2007;13:49-55.
8. Auckley D, Moallem M, Shaman Z, Mustafa M. Findings of a Berlin Questionnaire survey: comparison between patients seen in an asthma clinic versus internal medicine clinic. Sleep Med. 2008;9:494-9.
9. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J Jr, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28:499-521.
10. Lafond C, Sériès F, Lemière C. Impact of CPAP on asthmatic patients with obstructive sleep apnoea. Eur Respir J. 2007;29:307-11.
11. Alkhalil M, Schulman E, Getsy J. Obstructive sleep apnea syndrome and asthma: what are the links? J Clin Sleep Med. 2009;5:71-8.
12. Ciftci TU, Ciftci B, Guven SF, Kokturk O, Turktas H. Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome. Respir Med. 2005;99:529-34.
13. Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemière C, et al. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma. J Allergy Clin Immunol. 2009;124:371-6.
14. Luyster FS, Teodorescu M, Bleecker E, Busse W, Calhoun W, Castro M, et al. Sleep quality and asthma control and quality of life in non-severe and severe asthma. Sleep Breath. 2012;16:1129-37.
15. NHLBI/WHO Workshop Report: From the Global Strategy for Asthma Management and Prevention, Issued January, 1995, NIH Publication No. 02-3659. The 2012 Global Initiative for Asthma (GINA) Report is Available from: http://www.ginasthma.org/.
16. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep. 1992;15:376-81.
17. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. For the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
18. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22:667-89.
19. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, et al. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5:263-76.
20. National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. Obes Res. 1998;6 Suppl 2:51S-209S.
21. Teodorescu M, Consens FB, Bria WF, Coffey MJ, McMorris MS, Weatherwax KJ, et al. Correlates of daytime sleepiness in patients with asthma. Sleep Med. 2006;7:607-13.
22. Ekici A, Ekici M, Kurtipek E, Keles H, Kara T, Tunckol M, et al. Association of asthma-related symptoms with snoring and apnea and effect on health-related quality of life. Chest. 2005;128:3358-63.
23. Kalra M, Biagini J, Bernstein D, Stanforth S, Burkle J, Cohen A, et al. Effect of asthma on the risk of obstructive sleep apnea syndrome in atopic women. Ann Allergy Asthma Immunol. 2006;97:231-5.
24. Janson C, De Backer W, Gislason T, Plaschke P, Björnsson E, Hetta J, et al. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. Eur Respir J. 1996;9:2132-8.
25. Larsson LG, Lindberg A, Franklin KA, Lundbäck B. Symptoms related to obstructive sleep apnoea are common in subjects with asthma, chronic bronchitis and rhinitis in a general population. Respir Med. 2001;95:423-9.
26. Teodorescu M, Polomis DA, Hall SV, Teodorescu MC, Gangnon RE, Peterson AG, et al. Association of obstructive sleep apnea risk with asthma control in adults. Chest. 2010;138:543-50.
27. Yigla M, Tov N, Solomonov A, Rubin AH, Harlev D. Difficult-to-control asthma and obstructive sleep apnea. J Asthma. 2003;40:865-71.
28. Sumin K, Djukanovic R, Castro M. Evaluation of the difficult-to-treat severe asthma patient in the clinic. In: Chung KF, Bel EH, Wenzel SE editors. European Respiratory Monograph (51) Difficult-to-Treat Severe Asthma. Sheffield, UK: ERS Journals Ltd; 2011. p. 16-27.
29. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res. 2002;11:1-16.
30. Janson C, Gislason T, Boman G, Hetta J, Roos BE. Sleep disturbances in patients with asthma. Respir Med. 1990;84:37-42.
31. Fitzpatrick MF, Martin K, Fossey E, Shapiro CM, Elton RA, Douglas NJ. Snoring, asthma and sleep disturbance in Britain: a community-based survey. Eur Respir J. 1993;6:531-5.
32. Patil SP, Schneider H, Schwartz AR, Smith PL. Adult obstructive sleep apnea: pathophysiology and diagnosis. Chest. 2007;132:325-37.