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Nocturnal Asthma

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Abstract

Nocturnal asthma has unique pathophysiological mechanisms, comorbid diseases, and intervention. Even though the treatments for asthma have been highly developed, there are a high number of patients with asthma whose symptoms are not well controlled, particularly those with nocturnal asthma in which symptoms occur during the night and interfere with sleep. Moreover, nocturnal asthma also causes poor sleep quality, impairs quality of life, and deteriorates daytime cognitive performance. Overall, the prevalence of nocturnal asthma is estimated to be between 44-61% of patients with asthma. Pathophysiological mechanisms of nocturnal asthma included circadian rhythmicity and diurnal variation of inflammatory process, beta 2-adrenergic receptor polymorphism, and polluted environments. Furthermore, co-morbid conditions, such as obstructive sleep apnea and gastroesophageal reflux disease, may contribute to nocturnal asthma. In addition to optimal medical treatment, management of co-morbid conditions should be considered. Utilization of continuous positive airway pressure (CPAP) has been shown to significantly improve nocturnal symptoms in patients with co-existing obstructive sleep apnea as supported by numerous studies, but improvement of pulmonary function is still controversial. In addition, several studies also demonstrate that use of proton-pump inhibitors may assist those patients with gastroesophageal reflux disease resulting in an increase of peak expiration flow rate and/or FEV_1.

Key words: nocturnal asthma, circadian, inflammatory processes, obstructive sleep apnea, gastroesophageal reflux disease

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Introduction

Asthma is a chronic respiratory disease affecting 1-18% of the population.[1] Asthmatics can display variable symptoms of wheeze, shortness of breath, chest tightness and/or cough with variable expiratory airflow limitation. Despite extensive treatments for asthma, there are a high number of asthmatic patients who cannot control their symptoms, despite the fact that treatments are used in accordance with the provided guidelines. Many of this may be due to symptoms occurring in the night, also known as nocturnal asthma.[2]

The symptoms of nocturnal asthma can range from aforementioned symptoms of wheeze, shortness of breath, chest tightness and/or cough, which occur during the night and interfere with sleep.

These symptoms can be ascribed as an indicator for the severity of the disease.[3] In one study reported that most of nocturnal asthmatic patients with bronchial hyperresponsiveness experience a fall of forced expiratory volume in 1 second (FEV_1) of more than 20% after taking normal saline inhalation in the night when compared to the daytime.[4]

There are no definite and specific criteria for the diagnosis for nocturnal asthma (other than reviewing patients' history) and this is a limitation of the diagnosis. One potential manner is with a pulmonary function test, together with the patients' history, by using the 15% decrease of peak expiratory flow rate (PEFR) when comparing the result between day and night as an indicator,[5] as the change of PEFR in normal individual when comparing between day and night is generally in the range of 5-10%.[6,7]

In 1988, there was an epidemiological study on nocturnal asthma based on questionnaires obtained from 7,729 patients with asthma and found that 74% of the patients had experienced nocturnal asthma symptoms in which 48%

of the patients had been treated with aerosol steroids.[8] In 2012, there was a research by Perry TT, et al.[9] on 109 young patients with asthma, aging between 4-17 years, in suburb area and revealed that 61% of the patients had nocturnal asthma symptom and 51% of the patients had been treated with asthma medications (inhaled corticosteroids being prescribed in 8%, leukotriene receptor antagonist being prescribed in 28%, and both inhaled corticosteroids and leukotriene receptor antagonist being prescribed in 15%).

Another study, the Study for Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE) by Levin AM, et al. published in 2014[10] used questionnaires in 5,198 asthmatic patients, aging between 12-56 years; with 65% of the cohort was African American and remaining was European American. They found 44.2% of the patients with nocturnal asthmatic symptoms were African American patients demonstrating a 3-fold higher chance to experience nocturnal asthma than European American patients (odds ratio [OR], 2.95; 95% CI: 2.61-3.34).

The importance of nocturnal asthma is recognized and listed as one of the symptoms defining asthma control according to recent GINA guideline.[1] This review is aimed to focus on underlying pathophysiology, comorbid diseases, and current evidence of nocturnal asthma treatment.

Pathophysiology

Even though, the asthma symptom can be treated by various medications, targeting to control the inflammatory processes or direct bronchodilation effect such as various type of beta-2 receptor agonist drugs, there are still remaining asthmatic patients with nocturnal symptom. These findings suggest that other factors may be associated with the nocturnal symptom. Underlying pathophysiology has been described and is reviewed below. (**Figure 1**)

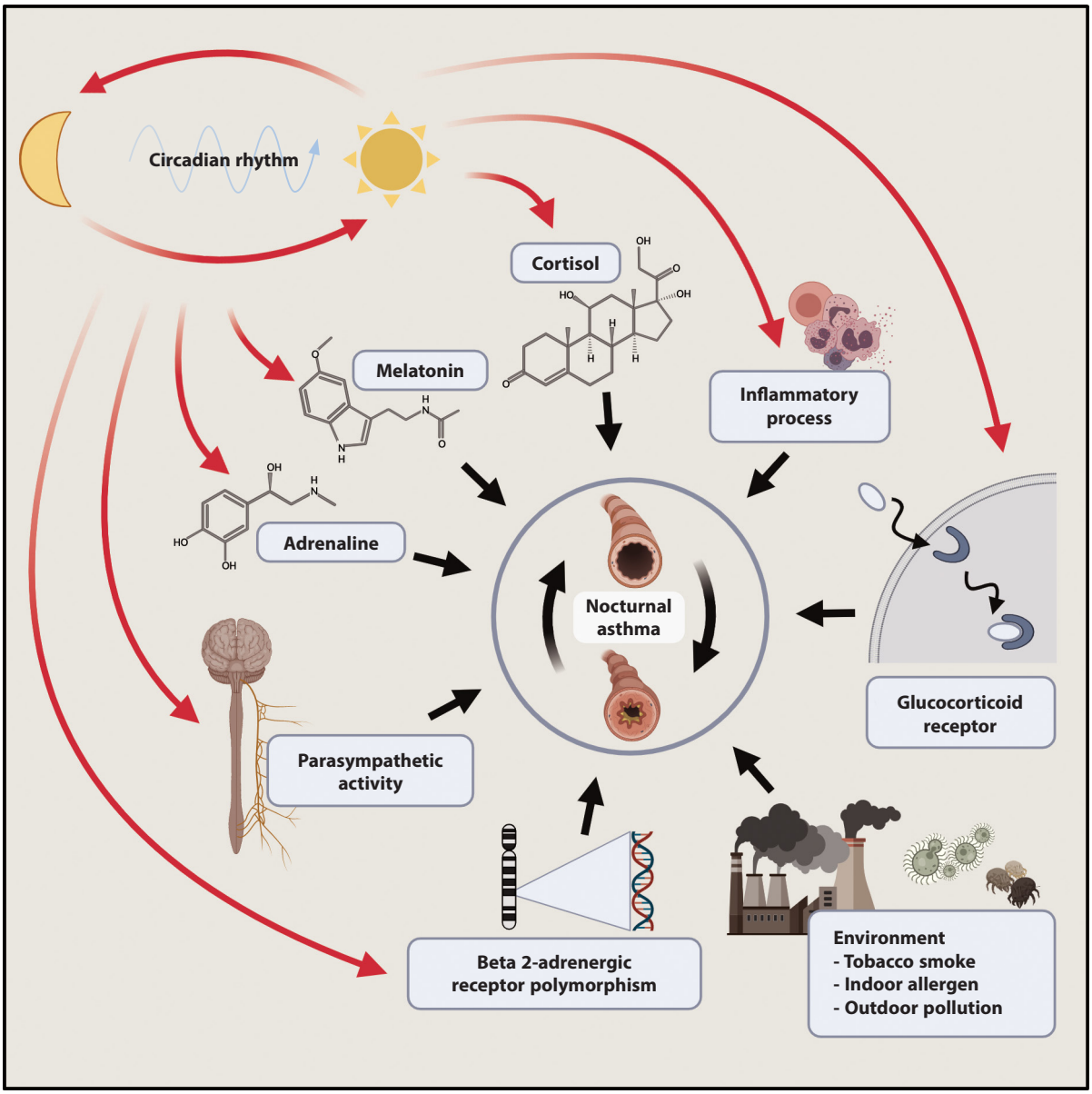

Figure 1. Pathophysiology of nocturnal asthma.

Circadian rhythm

All life forms, including human, will adopt itself to the environment which changes during the day (circadian) as the sun light, acting as a main factor, causes the change in 24-hour cycle. The sun light stimulates central circadian center at suprachiasmatic nucleus, located in hypothalamus, affect physiological and behavioral change. In healthy individuals, pulmonary function tests in many studies show circadian variation in a specific pattern where in the early morning, the parametric values of pulmonary function were lower than daytime values. Moreover, other studies, obtained from repeated pulmonary function testing in patients with asthma, showed diurnal variation of small airway as the pathological site. In healthy subjects, Goyal M, et al.[7] measured lung function including FEV_1 and mid expiratory flow rate during wakefulness and night time. Spirometry was measured at 5:00, 8:00, 11:00, 14:00, 17:00, 20:00, and 23:00 hours to observe for circadian variation. The study used Cosinor model[11] for analysis of diurnal changes. The results showed that the circadian variation follows a sinusoidal pattern in which all spirometric parameters exhibited lower values during night and higher values during daytime. Diurnal variability in terms of amplitude percent mean and standard deviation percent mean of FEV_1 were 7.1% and 2.5%, respectively. For the forced expiratory flow at 75% of the forced vital capacity (FEF_{75}), amplitude percent mean and standard deviation percent mean were 27.8% and 9.8%, respectively. The result from this study was consistent with the study performed by Troyanov S, et al.[12] In asthma patients, the study demonstrated high number of variabilities in peak expiratory flow (PEF) and further found PEF decreased between 3.00 A.M. to 7.00 A.M.[13,14] Subsequently, Spengler CM, et al.[15] studied the relationship between pulmonary function and circadian rhythm by limiting environmental and activating factors on circadian rhythm. The result of pulmonary function test demonstrated that after removing exogenous stimulus, endogenous factors can influence diurnal variation in pulmonary function in healthy subjects. The essential endogenous factors that affect circadian variation on pulmonary function include the followings:

Cortisol

Cortisol, one of the important markers that identifies the circadian. Many researchers revealed that the levels of cortisol in healthy subjects, asthmatic patients, and asthmatic patients with nocturnal asthma will be lowest at 0:00 A.M. and will be gradually increased in the morning. While the cortisol level is rising, the FEV_1 is decreased at 4:00 A.M. which is likely the delayed effect of falling cortisol level during the night time affecting airway narrowing,[16,17,18] since cortisol is known to up-regulate the expression of beta-adrenoceptors.[19]

Adrenaline

Adrenaline also fluctuates in circadian variation among healthy subjects and asthmatic patients. Studies found the adrenaline level drastically decreased during the night time together with PEF and FEV_1 level that decreased in the same period.[17,20] The adrenaline will stimulate beta 2-adrenergic receptors at airway smooth muscle resulting in decreasing of muscle tone and cause bronchodilation afterward. However, Morrison JF, et al.[21] studied the effect of adrenaline intravenous infusion in asthma patients with nocturnal asthma showed that the adrenaline intravenous infusion could not improve PEF that decreased during the night. This indicates that the adrenaline is not the primary mechanism causing the nocturnal variation.

Melatonin

Melatonin is a hormone secreted from pineal gland in which the production and release is adaptive based on light/dark cycle. The main function of melatonin is to regulate the sleep and wake cycle. Furthermore, melatonin has also been characterized as proinflammatory agent.

Sutherland ER, et al.[22] measured cytokines level via blood sampling at 4.00 A.M. and 4.00 P.M. from asthmatic patients, including those with and without nocturnal asthma symptoms, and non-asthmatic subjects. In the non-asthmatic group, the result demonstrated only significant difference in response in the level of IL-6 at 4:00 A.M. versus 4:00 P.M. (52.4% ± 10.6% versus 17.8% ± 4.8%, $p = 0.02$). In nocturnal asthmatic group, the result revealed significant and markedly increase of the level of IL-1, IL-6, and TNF-α on peripheral blood mononuclear cells (PBMCs) after mixing with melatonin at 4:00 A.M. (85.6 ± 17.1%, 129.4 ± 22.5%, 46.6 ± 10%, respectively) and 4:00 P.M. (82.5 ± 17.1%, 105 ± 19.2%, 81 ± 16.9%, respectively). However, there was no difference on cytokines level of the patients with nocturnal asthma at two time points ($p > 0.05$). The result revealed that after mixing melatonin into PBMCs, in the group without nocturnal asthma symptom, the level of cytokines, including IL-1, IL-6, and TNF-α, were largely increased at 4:00 A.M. (131.7%, 124.6%, 51.8%, respectively), compared to 4:00 P.M. (27.2%, 26.8%, and 12.8%, respectively). These findings suggested melatonin as a proinflammatory agent causing the increase of cytokines in asthmatic patients. However, the response on melatonin in the nocturnal asthmatic patients may be abnormal due to many factors including the variation of melatonin susceptibility.

Another study by Karasu-Minareci E, et al.[23] demonstrated that melatonin can worsen asthma. In their experiment, they tested the contraction and relaxation reactions of tracheal ring obtained from rats which received or did not receive intraperitoneal melatonin injection with different types of contractile (acetylcholine and serotonin) and relaxant (theophylline and papaverine) agents for 6 weeks. The study indicated that contractile reaction to both acetylcholine and serotonin were significantly increased in the trachea rings obtained from the melatonin group compared to no melatonin group. This finding suggests that melatonin, when increasing, may be important cause of asthma severity. In addition, Sutherland ER, et al.[24] reported a negative correlation between blood melatonin levels and FEV_1 in nocturnal asthmatic patients.

Inflammatory process

Airway obstruction in asthma can be caused by chronic inflammation in the airway wall, accompanied by plasma extravasation and edema, and influx of inflammatory cells such as eosinophils, neutrophils, lymphocytes, macrophages, and mast cells.[25] In nocturnal asthma, many evidence demonstrated inflammatory process in circadian variation. Kraft M, et al.[26] performed endobronchial and transbronchial biopsies at 4:00 P.M. and 4:00 A.M. 1 week apart in order to elucidate the inflammatory process in patients with nocturnal and non-nocturnal asthma. In this study, the patients also underwent spirometry prior to each bronchoscopy. The result of the study demonstrated that the number of eosinophils and macrophages were significantly greater at 4:00 A.M. compared with 4:00 P.M. in the alveolar tissue from nocturnal asthmatic group. Moreover, there was an inversely significant correlation between the percentage of fall in FEV_1 overnight and quantity of eosinophils in the alveolar tissue at 4:00 A.M. ($r = -0.54$, $p = 0.03$), but not at 4:00 P.M. Similarly, Kelly EA, et al.[27] observed the relationship between the inflammatory markers in airway and the FEV_1 in the night time, where in the night, the inflammatory markers in airway, including CD4+ lymphocyte, neutrophil and IL-5, drastically increased while the FEV_1 decreased. In addition, many evidence demonstrated the connection between the increasing of other inflammatory markers in lower airway in the night time and the decreasing of FEV_1 and PEFR.[28,29] Thus, the change of this inflammatory process may be caused by the decrease of cortisol level in the night time.

Nitric oxide

Nitric oxide (NO) is a gaseous molecule, produced from arginine by NO synthases in inflammatory cells in the human airway. NO can be measured in single exhaled breath as fractional exhaled NO (FeNO). As FeNO can detect airway eosinophilia and allergic inflammation, FeNO is predominantly used in diagnosis and monitoring treatment in asthmatic patients with allergic predominant in both upper and lower airway.[30]

There are studies on the diurnal variation of the exhaled NO (ENO) during day/night and found the ENO has been varied in diurnal variation pattern in asthmatic patients.[31,32] However, another study did not revealed association between FeNO and circadian variation. This might be due to difference in measurement technique on NO level.[30] For example, George G, et al.[32] studied the ENO in healthy subjects and asthmatic patients to gauge ENO level at 4.00 P.M., 10 P.M. and 4 A.M. by using exhalation flow rate at 80 milliliters/second. They detected highest level of ENO at 4.00 P.M. and constantly decreasing level in the night (both 10.00 P.M. and 4.00 A.M.) in the nocturnal asthmatic patients. While the study by N H ten Hacken, et al.[33] also investigated ENO in patients with asthma, nocturnal asthma, and healthy subjects using exhalation flow rate at 188 milliliters/second found not significant change in ENO on circadian variation pattern.

The study done by N H ten Hacken and L Lehtimäki observed nocturnal asthmatic patients to have ENO level higher than patients without nocturnal symptoms as this may result from the severe symptom causing more alveolar inflammation.[33,34]

Beta 2-adrenergic receptor polymorphism

Beta 2-adrenergic agonists are effective bronchodilator drugs used in the management of airway diseases such as asthma. Their potent bronchodilator effect acts on the beta 2-adrenergic receptor which promoting the relaxation of airway smooth muscle.[35] Szefler SJ, et al.[36] examined nocturnal changes in beta 2-adrenergic receptor expression in mononuclear and polymorphonuclear leukocytes used as surrogates for beta 2-adrenergic receptors expressed on bronchial smooth muscle. They demonstrated that beta 2-adrenergic receptor density was decreased by 33% at 4:00 A.M. compared to 4:00 P.M.in the patients with nocturnal asthma. However, no difference was observed in normal subjects and non-nocturnal asthma groups. Beta 2-adrenergic receptor is the product of a 1242-base intronless gene, located on the long arm of chromosome 5q31.32.[37] Substitutions of glycine for arginine at amino acid position 16 in this gene affects beta 2-adrenergic receptor expression. Three studies found that Gly16 allele of the beta 2-adrenergic receptor gene was associated with nocturnal asthma[38,39,40] however, another study revealed negative relation of Gly16 with nocturnal asthma.[41] Different population and environmental factors may explain these conflicting results.

Glucocorticoid receptor

Kraft M, et al. studied glucocorticoid receptors in asthmatic patients with nocturnal asthma[42] by comparing glucocorticoid receptor affinity from blood sample at 4.00 A.M. and 4:00 P.M. among three groups of patients: healthy subjects, patients with nocturnal asthma, and patients with non-nocturnal asthma. The study revealed that glucocorticoid receptor affinity in patients with nocturnal asthma changed according to circadian variation whereas no change was found in other two groups. Moreover, glucocorticoid receptor affinity in patients with nocturnal asthma was observed to be minimized during nighttime in comparison to daytime.

Another study from Kraft M, et al.,[43] compared the quantity of glucocorticoid receptors β and cytokines in bronchoalveolar lavage (BAL) fluid obtained during bronchoscopy at 4:00 P.M. and 4:00 A.M. from patients with and without nocturnal asthma. It demonstrated the percentage of airway cells expressing glucocorticoid receptor β was significantly increased in patients with nocturnal asthma at 4.00 A.M. In addition, BAL lymphocytes and macrophages from both groups were incubated with dexamethasone and then the production of IL-8 and TNF-α were measured. They observed in the nocturnal asthma group, dexamethasone demonstrated lower suppression of the IL-8 and TNF-α production at 4:00 A.M. as compared to 4:00 P.M. ($p = 0.0001$). In comparison to the non-nocturnal asthma group, steroid responsiveness was not significantly different at 4:00 A.M. and 4:00 P.M. following mixture with dexamethasone. Increased glucocorticoid receptor β expression with reduced steroid responsiveness suggests that fluctuation of function of glucocorticoid receptors β may be involved in mechanism of nocturnal asthma.

Parasympathetic activity

Morrison JF, et al.[44] performed vagal nerve block by atropine injection in patients with nocturnal asthma in order to study the function of the parasympathetic system related to the respiratory system. After receiving atropine at 4:00 A.M. and at 4:00 P.M., the mean PEFR increased from 260 to 390 L/min ($p < 0.0001$) and 400 to 440 L/min ($p = 0.04$), respectively. These results support the effect of the vagus nerve on bronchoconstriction with diurnal variation.

Normally, when sleep begins and the ventrolateral preoptic nucleus (VLPO) which is responsible for sleep and located at the hypothalamus, is stimulated. This sleep-promoting nuclei release neurotransmitters, mainly gamma-aminobutyric acid (GABA) and galanin to ensure the ongoing sleep and shall inhibit the tuberomammillary nucleus (TMN) and lateral hypothalamus (LH) activities, which act on awaking part. Moreover, VLPO will directly inhibit locus coeruleus (LC) activity, causing the decreased inhibitory response to airway-related vagal preganglionic neurons (AVPNs) resulting the occurrence of bronchoconstriction during sleep. In addition, LC will obtain a direct signal projection from suprachiasmatic nucleus via dorsomedial hypothalamic nucleus (DMH). The light-dark cycle control circadian variation effect on LC impulse activity which is of an effect on inhibition of AVPNs function.[45]

Environment

Environment is one of the key factors that influence nocturnal asthma. However, due to limitation of study protocol, most of the studies to date have been questionnaire based. Many studies reported that environmental tobacco smoke is a frequent environmental factor and is linked to nocturnal asthma.[46,47,48,49] Moreover, second hand smoking effect can trigger nocturnal asthma.[50] Furthermore, indoor allergens, including mold and house dust mites are key contributor to nocturnal asthma.[47,51,52,53] Indoor pollution such as nitrogen dioxide (NO_2) is also related to night time symptoms in asthmatic patients.[53] Li T, et al. reported that air pollution such as PM10, sulfur dioxide (SO_2), and NO_2 can raise the risk of nocturnal asthma.[54]

Comorbid disease

Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA) is characterized by episodic sleep state-dependent collapse of the upper airway, resulting in periodic reductions or cessations in ventilation, with consequent hypoxia, hypercapnia, and/or arousals.[55] Many studies have indicated that OSA and asthma can be co-existent.[56,57]

Teodorescu M, et al.[58] studied the relationship between nocturnal asthma and OSA in 2012 using the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) in 752 asthmatic patients with the mean age of 47 ± 14 years. The result indicated statistically significant risk (1.97 [1.32–2.94]) ($p = 0.0009$) for the asthmatic patients with elevated risk of OSA as determined by the SA-SDQ to have nocturnal asthma. Another study by Nguyen-Hoang Y, et al.[59] was conducted on 85 children (mean age of 9.5 ± 2.1 years) with asthma symptoms and observed that 65.9% of those children had OSA. In addition, the presence of nocturnal asthma symptoms significantly increased risk for OSA (OR = 4.2, 95% CI: 1.5-11.4, $p = 0.005$).

Wang TY, et al.[60] studied the relationship between OSA and asthma by investigating a group of patients with asthma and OSA for 5 years and observed lower FEV_1 than patients with asthma without OSA. After multivariate stepwise linear regression analysis, they concluded the apnea-hypopnea index (AHI) was an independent risk factor for the decline in FEV_1 (-0.033; 95% CI:-0.052 to -0.014; $p = 0.001$), while body mass index was not. The cause of this finding may be related to chronic intermittent oxygen desaturation/resaturation resulting in local airway and systemic inflammation.[61,62] Co-existence of OSA and asthma is associated with higher pro-inflammatory mediators than healthy individuals.[63]

Gastroesophageal reflux disease (GERD)

Gastroesophageal reflux disease (GERD) occurs when acid refluxes into the esophagus from the stomach. GERD is connected to many diseases of the respiratory system, including asthma.[64] Gislason T, et al.[65] studied the connection between nocturnal GERD and asthma. The study observed that group of the patients with nocturnal GERD had more prevalence of asthma than non-nocturnal GERD patients (9% vs 4%, $p < 0.05$). Moreover, they observed that nocturnal GERD was related to nocturnal asthma symptoms such as nocturnal cough (73% in nocturnal GERD and 49% in non-nocturnal GERD, $p < 0.05$). These may be explained by the study from Cuttitta G, et al.[66] They found that in each spontaneous episodes of gastroesophageal reflux during sleep could aggravate and sustain nocturnal bronchoconstriction in adult asthmatics with GERD.

Rhinitis/Chronic rhinosinusitis

The most common symptoms of allergic rhinitis are sneezing, running nose, as well as itching and nasal congestion, which can be seen in both children and adults. There was evidence about diurnal variation in patients with allergic rhinitis which symptoms worsen at nighttime and early morning. Long AA, et al.[67] revealed that most of patients with allergic rhinitis had a history of nasal congestion, sneezing, itchy eyes, runny nose, and watery eyes in the morning (6:00 A.M.). Initially, allergen stimulate mast cell in nasal area which followed by an inflammatory process, involving inflammatory mediators, cytokines, T cells lymphocyte, and eosinophils. The underlying cause of worsening rhinitis symptom from night to early morning is likely the circadian variation of certain neurohormonal agents, such as cortisol, which results in inflammation in the upper airway that directly affect the lower airway since they have the same characteristics of inflammatory cells.[68]

The presence of chronic rhinosinusitis can affect asthma in a negative direction. Ek A, et al.[69] assessed the effect of chronic rhinosinusitis in asthmatic patients. They found that the prevalence of nocturnal symptoms in asthmatic patients with chronic rhinosinusitis was significantly higher than those without chronic rhinosinusitis. Chronic rhinosinusitis was also associated with impaired quality of life,[69] which is similar

to the study by Sahay S, et al.[70] In addition to inflammatory process from chronic rhinosinusitis, infectious microbes may exacerbate the symptoms of asthma.[71]

Management

Chronotherapy

The use of chronotherapy in treatment of nocturnal asthma is aimed to target the time variation of the disease. The benefit from these measures are improvement of the efficacy and reduction in side effect from medications.

Inhaled Corticosteroids

Pincus DJ, et al.[72] compared the administration of triamcinolone 800 micrograms daily at 3:00 P.M. to 200 micrograms four-times daily on pulmonary parameters. After 4 weeks of treatments, FEV_1, morning PEFR, and evening PEFR were significantly increased from baseline with no statistically significant difference between groups.

Pincus DJ, et al. evaluated the 3 different dosing patterns of triamcinolone: a single dose of 800 micrograms at 5:30 P.M.; a single dose of 800 milligrams at 8:00 A.M. and conventional four times per day dosing in mild to moderate asthmatic patients.[73] The results showed that in the conventional group and the single dose at 5:30 P.M. group had significantly increase in morning PEFR compared to baseline (46 L/min, $p = 0.001$ and 13 L/min, $p = 0.003$, respectively).

Furthermore, Anthony D'Urzo[74] compared the efficacy of mometasone furoate 200 micrograms once daily in P.M., 400 micrograms once daily in P.M., and 200 micrograms twice a day. The result demonstrated that mometasone furoate dry powder inhaler 200 micrograms in the evening improved night time symptoms and was nearly equivalent to the other doses of mometasone furoate at 3 months of study. A Gillissen, et al.[75] evaluated the effect of beclomethasone dipropionate in hydrofluoroalkane 200 micrograms in the evenings with 100 micrograms twice a day and with placebo. Beclomethasone dipropionate at the evening time improved morning PEF and decreased nocturnal symptom and was equal to twice daily dose. The result from this study was consistent with the study performed by Gagnon M, et al.[76] There was circadian variation of cortisol level which is decreased at night along with increase of inflammatory processes. Administration of corticosteroid in the evening to nighttime may have an advantage in targeting this mechanism which resulting in reduction of inflammatory mediators.[77]

Long-acting Beta 2 agonists

In a randomized, double-blind, placebo-controlled study on the effects of salmeterol on 474 asthmatic patients, the result showed that salmeterol had significantly improved nocturnal symptoms in this group of patients.[78] In this study, the patients were allowed to continue theophylline and inhaled corticosteroids, and as-needed albuterol. The result from this study was consistent with the research performed by Kraft M, et al.[79] Another studies demonstrated the effect of salmeterol compare to theophylline. Salmeterol resulted in improvement of night-time symptom when compared with theophylline.[80,81]

Treatment of OSA

Many mechanistic effects regarding how OSA may impact asthma such as nerve reflex stimulation, intermittent hypoxia, vascular endothelial growth factors, and leptin have been proposed.[82] Razak M and Chirakalwasan N reviewed that airway inflammation are common key factors in the development of both asthma and OSA.[82] There was evidence supporting the benefit of CPAP in reduction in the local airway and systemic inflammation in OSA.[61,83] Several studies on CPAP therapy in OSA patients demonstrated improvement in asthma control (**table 1**). In asthmatic patients with concomitant OSA, many studies revealed benefit of CPAP on nocturnal symptoms and/or spirometric parameters. Chan CS, et al.[84] reported of early response of CPAP treatment in improvement of morning PEFR and reduction in night time asthma symptoms at 2 weeks. While Ciftci TU, et al.[85] revealed improvement of nocturnal symptoms, not spirometric parameters at 2 months of CPAP therapy.

Table 1. Impact of CPAP in OSA patients on nocturnal asthma.

Study, year	Subjects	Characteristics	Outcome/objective	Results
Chan CS et al., 1988[84]	- Dx OSA by nocturnal polysomnography - Dx asthma by clinical and PEFR - 9 patients with nocturnal asthma and OSA (mean apnea index = 23.75/hr in 8 patients and hypopnea index = 30/hr in 1 patient)	- A prospective study with three 2-wk periods consisting of control, CPAP, and control	- The effect of CPAP therapy on the severity of asthma	- CPAP significantly increased morning pre bronchodilator PEFR ($p < 0.01$) and morning post bronchodilator PEFR ($p < 0.001$) - CPAP improved the asthma control and the nocturnal attacks in all patients

Ciftci TU et al., 2005[85]	- Dx OSA by nocturnal polysomnography
	- Dx asthma by clinical and PFT
	- 38 asthmatic patients with nocturnal symptom
	  - 16 asthma with OSA (mean AHI = 44.25 ± 50.82/hr)
	  - 22 asthma without OSA (mean AHI = 3.9 ± 3.72/hr)
		- A prospective study with 2 months of CPAP in asthmatic patients with nocturnal symptom and concomitant OSA
		- CPAP used more than 4 hr/night
			- The association of nocturnal asthma and OSA
			- The effect of CPAP therapy on improvement in nighttime symptoms in asthmatic patients with OSA
				- No significant difference in PFT values before and after CPAP therapy in asthma with OSA
				- Nighttime symptom scores were significantly decreased after CPAP therapy (from 2.19 ± 1.07 to 1.44 ± 1.15, $p = 0.04$) in asthma with OSA

Table 1. (Continued)

Study, year	Subjects	Characteristics	Outcome/objective	Results
Kauppi P et al., 2016[98]	- Dx OSA by home polygraphy - Dx of asthma by self-reported physician-diagnosed disease - 152 patients with asthma and OSA and CPAP therapy was initiated after starting asthma medication	- Retrospective cross-sectional questionnaire study - All the patients had used CPAP therapy for 5.7 ± 4.7 years for average use of 6.0 ± 2.5 hr/night	- The prevalence of asthma among OSA using CPAP - The effect of long-term CPAP use on asthma symptoms	- Prevalence of asthma among OSA using CPAP was 13% - No night-time symptoms was increased from 28% to 55% ($p < 0.001$) after CPAP use

Shaker A, 2017[99]	- Dx OSA by an overnight polysomnography
	- Dx asthma by history and PFT
	- 50 asthmatic patients
	  - with OSA (n = 12)
	  - without OSA (n = 38)
		- A prospective study with 3 months of CPAP therapy in asthmatic patients and concomitant OSA
		- No data of compliance in CPAP usage
			- Frequency of OSA in asthmatics patients with various degrees of severity
			- The effect of CPAP on asthma symptoms and control
				- Prevalence of OSA in this asthmatic patient group was 24%
				- CPAP reduced number of asthmatic patients with daytime symptoms from 11 to 5, $p = 0.009$ and reduced number of asthmatic patients with night time symptoms from 11 to 4, $p = 0.003$
				- $\%FEV_1$ was significantly increased from 65.16 ± 10.6 to 78.08 ± 6.9, $p = 0.002$ after CPAP

OSA, obstructive sleep apnea; PEFR, Peak expiratory flow rate; CPAP, continuous positive airway pressure; PFT, pulmonary function test; AHI, apnea hypopnea index.

Treatment of GERD

Despite knowing that GERD is associated with nocturnal asthma, there is scarce evidence on the treatment of GERD and nocturnal asthma control. Goodall RJ, et al.[86] reported that cimetidine can increase PEFR, reflux symptom score ($p < 0.02$), and night time asthmatic scores ($p < 0.05$) in asthmatic patients with GERD. However, pulmonary function tests showed no significant difference.

Moreover, there was published data that revealed improvement of nighttime symptoms in coexisting asthma and GERD with the use of antireflux therapy. Improvement in pulmonary function was also observed in some trials (**table 2**).

In 2010, Kiljander TO, et al.[87] studied the effect of esomeprazole 40 milligrams once and twice daily dose compared to placebo for 26 weeks in asthmatic patients with concomitant symptoms of GERD. Asthma Quality of Life Questionnaire total score was significantly improved after administration of both esomeprazole doses compared to placebo (+0.28 in esomeprazole once daily dose ($p = 0.0006$) and +0.41 for esomeprazole twice daily dose ($p = 0.0001$)). Patients receiving 40 milligrams of esomeprazole twice daily had more improvement in mean FEV_1 when compared to placebo (+0.07 L; 95% CI: 0.02-0.12; $p = 0.0042$).

Table 2. Impact of anti-reflux therapy on nocturnal asthma.

Study, year	Subjects	Characteristics	Outcome/objective	Results
Gooddall RJ et al., 1981[86]	- Dx of asthma by clinical presentation - Dx of GER by symptoms, EGD, lower esophageal manometry, esophageal pH monitoring, acid infusion test	- A double-blind, crossover study to receive cimetidine or placebo for 6 weeks	- The effect of cimetidine on symptoms and pulmonary function in asthmatic patients with GER	- PEF was significantly increased at night (310 vs 335 L/min, $p < 0.05$) - Night time asthmatic score was significantly improved (1.1 vs 0.7, $p < 0.05$)

Kiljander TO et al., 1999[100]	- Dx of GER by ambulatory esophageal pH monitoring
	- Dx of asthma by PFT and PEF
	- 107 asthmatic patients
	  - 57 with GER
	  - 50 without GER
		- A double-blind, placebo-controlled crossover study to receive either 40 mg omeprazole once daily, or placebo for 8 weeks with 2-week washout period	- The prevalence of GER in the outpatient asthmatic population
			- The effect of omeprazole on asthma symptoms and pulmonary function
				- Pathologic GER was found in 53% of the asthmatic patients
				- PEF and FEV_1 were not improved after omeprazole therapy
				- Daytime asthma symptoms were not improved ($p = 0.14$)
				- Nighttime asthma symptoms were significantly improved ($p = 0.04$)

Kiljander TO et al., 2006[88]	- Dx of asthma by PFT and PEF
	- Dx of GER by symptoms, EGD, esophageal 24-hour pH monitoring
	- 770 moderate-to-severe asthmatic patients were divided to 3 groups
	  - NOC+/GERD- (n = 201)
	  - NOC-/GERD+ (n = 219)
	  - NOC+/GERD+ (n = 350)
		- Multicenter, randomized, placebo-controlled study to receive 40 mg esomeprazole or placebo twice daily for 16 weeks	- The change in the mean morning PEF at the end of the treatment period
			- The change in evening PEF, daytime and night time asthma symptom score, ACT, and AQLQ
				- In GERD+/NOC+, morning PEF was increased 8.7 L/min ($p = 0.03$) and evening PEF was increased 10.2-L/min ($p = 0.012$) after receiving esomeprazole compared with placebo
				- In NOC+/GERD- and NOC-/GERD+, PEF was not significantly changed after receiving esomeprazole compared with placebo
				- Daytime and night time asthma symptom score was not different among 3 groups

Table 2. (Continued)

Study, year	Subjects	Characteristics	Outcome/objective	Results

Kiljander TO et al., 2010[87]	- Dx of asthma by clinical and PFT
	- Dx of GERD by symptoms or 24-hour esophageal pH monitoring
	- 828 patients with moderate-to-severe asthma and symptomatic GERD
	  - 40 mg esomeprazole once daily (n = 273)
	  - 40 mg esomeprazole twice daily (n = 272)
	  - Placebo (n = 283)
		- Randomized, double-blind, placebo-controlled study to receive 40 mg esomeprazole once daily, 40 mg esomeprazole twice daily, or placebo for 26 weeks	- The change from baseline in morning PEF during the 26-week treatment period
			- Change in evening PEF, change in FEV_1, change in asthma symptom score (total, morning, and evening) and change in AQLQ and RDQ scores
				- No significant difference in morning PEF among 3 groups
				- 40 mg of esomeprazole twice daily significantly improved FEV_1 compared to placebo (+0.07 L; 95% CI, 0.02–0.12; p = 0.0042)
				- Esomeprazole once and twice daily significant improved AQLQ total score compared with placebo (+0.28; 95% CI, 0.12-0.44; $p < 0.001$ and +0.41; 95% CI, 0.25-0.57; $p < 0.0001$, respectively)
				- Asthma symptom scores were not different between esomeprazole once and twice daily groups

Sharma B et al., 2007[101]	- Dx of asthma by clinical and PFT - Dx of GERD by 24-h esophageal pH monitoring - 198 patients with mild-to-moderate persistent asthma and GERD	- 1:1 randomized, double-blind, placebo-controlled study to receive 20 mg omeprazole twice daily and 10 mg domperidone three times daily or placebo for 16 weeks	- Mean daily daytime and night time asthma symptom scores - Mean daily reflux symptom scores, daytime and night-time PEFR, FEV_1, and FVC	- Daytime asthma symptom score (17.4% vs 8.9%, p = 0.0002) and night-time asthma symptom score (19.6% vs 5.4%, p = 0.0007) were significantly reduced in treatment group - Morning PEFR (7.9% vs 0.2%, p = 0.005) and evening PEFR (9.8% vs 0.5%, p = 0.002) were significantly improved in treatment group

Sandur V et al., 2014[102]	- Dx of asthma by clinical and PFT
	- Dx GERD by esophageal manometry and 24- esophageal pH monitoring
	- 40 moderate-to-severe asthmatic patients
	  - 28 patients with GERD (on omeprazole)
	  - 12 patients without GERD (without omeprazole)
		- A prospective study
		- GERD group received 20 mg of omeprazole twice daily and lifestyle changes for 3 months
		- No-GERD group was not given anti-GER treatment
			- The prevalence of GER in patients with difficult to control asthma
			- The effect of omeprazole on asthma symptoms, reflux symptoms, pulmonary function, and on the requirement of asthma medications
				- In GERD group, night time asthma symptom score was improved from 6.71 ± 1.80 to 3.04 ± 1.23 ($p < 0.0001$)
				- In GERD group, FEV_1 was increased from 1.38 ± 0.57 to 1.47 ± 0.54 (p = 0.0011) and PEFR was increased from 4.14 ± 1.97 to 5.56 ± 1.72 ($p < 0.0001$)
				- In no-GERD group, night time asthma symptom score was not significantly changed from baseline (6.92 ± 1.62 vs 5.83 ± 1.19, p = 0.116)
				- In no-GERD group, FEV_1 and PEFR were not different from baseline (1.54 ± 0.64 vs 1.57 ± 0.62, p = 0.095 and 4.47 ± 2.42 vs 4.91 ± 2.13, p = 0.068, respectively)

GER, gastroesophageal reflux; EGD, esophagogastroduodenoscopy; PEFR, peak expiratory flow rate; FEV_1, forced expiratory volume in the first second; GERD, gastroesophageal reflux disease; NOC, Nocturnal Asthma; ACT, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; RDQ, Reflux Disease Questionnaire; PEF, peak expiratory flow

In addition, Kiljander TO, et al.[88] investigated the effect of esomeprazole 40 milligrams twice per day dose compared with placebo for 16 weeks in 3 groups of asthmatic patients including no GERD with nocturnal asthma (GERD-/NOC+), GERD without nocturnal asthma (GERD+/NOC-), and GERD and nocturnal asthma (GERD+/NOC+). Although, high-dose esomeprazole could not alleviate nocturnal symptom in asthmatic patients. This medication increased PEF in the morning and evening. Discrepancy in the results of these studies may be due to the difference of the dosage of the medication as well as duration of the study.

Moreover, there was a published data demonstrated the result of esomeprazole in severe asthmatic patients with minimal or no symptoms of gastroesophageal reflux.[89] The study used pH monitoring for GERD diagnosis and demonstrated a higher incidence of GERD in the group of asthmatic patients. Finally, 40 milligrams of esomeprazole twice a day did not show benefit in neither relieving severity of asthma nor nocturnal symptom in asthmatic patients. The result from this study was consistent with the study performed by Kiljander TO, et al.[88] This may be explained by aspiration non-acid reflux resulting to decreasing in efficacy of this medication.[90] The recent GINA guideline recommended that patients with poorly controlled asthma should not be treated with proton pump inhibitor except with the presence of gastroesophageal reflux symptoms.[1]

Treatment of allergic rhinitis and chronic rhinosinusitis

Asthmatic patients were observed to have more prevalence of allergic rhinitis.[91,92,93] In addition, Bousquet J, et al.[94] observed that asthmatic patients with history of allergic rhinitis had greater chance of asthmatic attack (OR = 1.35, 95%CI = 1.03–1.77) compared with asthmatic patients without allergic rhinitis. Baiardini I, et al.[95] investigated the efficacy of mometasone nasal spray in patients with asthma and allergic rhinitis. After 4 weeks of treatments, mometasone nasal spray

improved nocturnal asthma symptoms. While, Dahl R, et al.[96] could not find the benefit of intranasal fluticasone propionate in nocturnal symptoms nor morning peak-flow in asthma patients with pollen induced allergic rhinitis.

In addition, a small study by Meena RS, et al.[97] revealed the treatment of chronic rhino-sinusitis in 20 asthmatic patients in which 18 patients were administered standard medical treatments and 2 patients were treated with functional endoscopic sinus surgery (FESS). After 6 months of chronic rhinosinusitis treatments, night time symptoms were reduced altogether. Effect of allergic rhinitis and chronic rhinosinusitis treatment in asthmatic patients can reduce aspiration of nasal discharge from the upper airways down to the lower airways and can also reduce inflammation in the airways as well.

Conclusions

Nocturnal asthma is underrecognized problem and frequently underdiagnosed. Nocturnal increase in inflammatory processes, reduction in beta 2-adrenergic receptor density, alteration in function of glucocorticoid receptors β, increase in cholinergic outflow related bronchoconstriction, proinflammatory effect of melatonin, and environmental factors may play important role in nocturnal asthma symptoms. However, more studies are needed to elucidate the efficiency of the asthma treatment aiming to target this nocturnal increase in inflammation. Moreover, many conditions have the potential to contribute to nocturnal asthma and should be further investigated. Beside optimal medical management for asthma, current evidence supports the use of continuous positive airway pressure to control nocturnal asthma symptoms if OSA coexists. Similarly, proton-pump inhibitor in patients with comorbid GERD has been shown to improve nocturnal asthma and possibly PEFR and/or FEV_1. The treatment for allergic rhinitis, including chronic rhinosinusitis, is also necessary.

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