J Gastroenterol 2004; 39:815–820
DOI 10.1007/s00535-004-1416-8

Journal of Gastroenterology

Review

The relationship between gastroesophageal reflux disease and obstructive sleep apnea

Pal Demeter[1] and Akos Pap[2]

[1]Department of Gastroenterology, St. Margaret's Hospital, Becsi str. 132, Budapest 1032, Hungary
[2]Department of Gastroenterology, MAV Hospital, Budapest, Hungary

There has been an accumulating body of research concerning the extraesophageal complications of gastroesophageal reflux disease over the past decade. Given the cardiological, pulmonological, laryngeal, and dental aspects of such complications, an interdisciplinary approach is required. The most recognized manifestations are noncardiac chest pain, bronchial asthma, chronic bronchitis, chronic cough, and posterior laryngitis, as well as the acidic damage of dental enamel. This article focuses on the potential relationship between reflux disease and obstructive sleep apnea, which has been raised only more recently. Because of the decrease of primary peristalsis and the reduced production of saliva, as well as the diminished acid and volume clearance of the esophagus, sleeping can be considered as a risk factor of the reflux event by itself. Moreover, it should also be taken into account that the transdiphragmatic pressure increases in parallel with the growing intrathoracic pressure generated during obstructive apnea episodes. This has a non-negligible effect on the phrenoesophageal ligament, which is connected to the lower esophageal sphincter. Repetition of the pressure changes results in insufficiency of the cardia. While this pressure change produces a considerable suction effect, further reducing the clearing mechanism of the gastric volume, lower esophageal sphincter insufficiency can directly lead to reflux disease. The challenge for gastroenterologists is to gain further insight into this relationship and to play a more active role in the complex therapy of the disease, as well as to develop a new diagnostic approach towards the severe forms of gastroesophageal reflux disease.

Key words: gastroesophageal reflux disease, sleep apnea

Received: November 28, 2003 / Accepted: June 14, 2004
Reprint requests to: P. Demeter

Introduction

It is well known that gastroesophageal reflux disease (GERD), besides its classical symptoms, is associated with extraesophageal symptoms and complications as well (Table 1).[1–4] The most common ones are respiratory symptoms, noncardiac chest pain, and posterior laryngitis. Recurrent otitis media and dental erosion are relatively less common. Apart from the various respiratory disorders, such as chronic cough, bronchial asthma, and chronic bronchitis, the question has been raised that there could be a connection between obstructive sleep apnea (OSA) and GERD as well.

In everyday clinical practice, GERD is often diagnosed on the basis of serious respiratory disorders in the absence of typical upper-gastrointestinal complaints. It is also a common experience that the patients complain of waking up during the night less or more frequently with an unfamiliar sensation of panic, a choking fit, or an acidic burning sensation. The development of reflux disease can often be identified underlying these events. But there can be a reverse situations as well: in the background of severe—therapeutically refractory—GERD, we have to consider the presence of OSA.

Gastroesophageal reflux disease

GERD is a complex motility disorder which is usually accompanied by typical symptoms (retrosternal burning sensation or/and pain, regurgitation of the gastric contents, sour taste in the mouth, etc.) and—in a number of cases—by further complications such as erosive esophagitis of more severe damage of the esophagus (stricture, Barrett metaplasia, adenocarcinoma). The nonerosive form of the disease (nonerosive reflux disease; NERD) represents about 60% of the cases, while the erosive form (erosive reflux disease; ERD) and

Table 1. Summary of extra-esophageal complications of GERD according to speciality

Speciality	Symptom/Complication
Cardiology	Noncardiac chest pain (NCCP) "Linked" angina
Pulmonology	Bronchial asthma Chronic cough Pulmonary fibrosis
Otorhino-laryngology	Posterior laryngitis Reflux pharyngitis Chronic sinusitis
Odontology	Dental erosion (early caries)
General Medicine	Halitosis Xerostomia Furred tongue
Psychiatry	Sleep disorders Sexual disorders Anxiety
Pediatrics	Recurrent pneumonia Apparent life-threatening event (ALTE) Apnea (sudden infant death—SIDS) Otitis media (children's deafness)

complicated erosive cases comprise 35% and 5%, respectively.[5] Proper diagnosis—besides the correct anamnesis—can be ensured with upper panendoscopy, esophageal pH-metry, and esophageal manometry.

Obstructive sleep apnea (OSA)

Sleep-related breathing disorders include conditions which are characterized by consciously or unconsciously experienced periods of hypopnea, apnea, or coughing fits, with interrupted sleep, resulting in daytime somnolence. If apnea/hypopnea periods occur more than ten times an hour, then the daytime symptoms emerge and we have a "sleep-awake" disease group, those with so-called sleep apnea-hypopnea syndrome. Within this category, OSA is manifested in repetitive apnea periods and is associated with obesity, snoring, and hypersomnia. These periods develop mainly as a result of anatomical (wide neck, obesity, retrognathia) or other factors that significantly reduce the diameter of, or close, the pharynx, with a decrease of muscular tension. This leads to increased upper respiratory resistance, which causes the passing air flow through the upper airway to become turbulent, generating the snoring phenomenon. If the stricture is so severe that it leads to obstruction, apnea occurs. During an obstructive apnea event, an inefficient, powerful but desynchronized respiratory effort takes place. In such cases, the diaphragm, which secures the main muscle work of srespiration, and the auxiliary respiratory muscles become completely desynchronized. This augments the already negative intrathoracic pressure further towards the negative direction to the point when arousal occurs, due to the muscle work or the extreme pressure gradient and hypoxemia. The arousal restores the normal muscular tension that allows free inspiration, with unblocked admission of air into the lower respiratory tract. This cycle may arise 300–400 times a night for an OSA patient, which leads to the fragmentation of sleep and explains the serious daytime somnolence. By contrast, reduced respiratory regulation by the central nervous system or inert or periodical breathing due to muscular weakness causes central apnea, in which respiratory work is not observed at all during the period of apnea. In a mixed type of the disorder, interruption is experienced regarding both the airflow and the respiratory movements, but this is followed by intensive movement of the diaphragm in the second half of the apnea period.[6,7]

From these findings it emerges that, when examining the potential linkages between GERD and sleep-related breathing disorders, the most interesting question is the possible relationship between reflux disease and OSA.

GERD and sleeping—anatomy and physiology

The esophagus is a 20 to 25-cm-long hollow tube, with sphincter-like functions, and it is secured with two high-pressure zones, one on each end. The part between these two ends is the so-called tubular esophagus. The functioning of the upper esophageal sphincter (UES)

ensures swallowing, and it also prevents the aspiration and the swallowing of air. The mucosa of the epiglottis contains special receptors which play a role in aspiration prevention as well. These receptors mediate aspiration preventive reflex responses, including swallowing, cessation of breathing, airway constriction or closure, and coughing. These reflexes can also be activated via regurgitation of the gastric contents.[8] The lower esophageal sphincter (LES) prevents the reflux of the gastric contents into the esophagus, while it also secures the passage of the swallowed food into the stomach when it is relaxed. The difference between the abdominal and the thoracic pressure, the compressive effect of the gastric bubble, the converged mucosal folds, and the transverse muscular fibers of the diaphragm (right crural diaphragm, His angle, musculomucosal valve) contribute to the blocking function of the LES. The motor response of the esophagus to reflux events is peristalsis. Primary peristalsis is the most frequent response, which acts against the reflux through the stimulation of swallowing. This is the first reaction in 90% of the events. Secondary peristalsis is a rare but important phenomenon, which is carried out through distension of the esophagus. It is mainly important during sleep, when swallowing is impaired.[9] The esophagus clears away the regurgitated contents through its motor activity (volume clearance). The produced bicarbonate and saliva play a role in neutralizing the regurgitated acidic fluid (acid clearance). In addition, gravitational force also counteracts regurgitation.

Two pathomechanisms have been described concerning reflux-induced respiratory symptoms:

(1) Nocturnal acid reflux → microaspiration → exudative mucosal reaction
(2) Acid reflux → esophagus → vagus nerve → bronchoconstriction

The diameter of the respiratory tract decreases in both mechanisms, and this may worsen symptoms or cause them.

Compared with wakefulness, sleep could be regarded as an unstable respiratory period with obstructive and central hypopneas and apneas. These periods may be found even in healthy people as a result of decreased activity of the respiratory drive during sleep. Respiration is not a static process. Both under healthy and pathological conditions it influences the esophagus, which is located in the intrathoracic area. This fact can be explained partly by positional factors and partly by mechanical events. During inspiration, a pressure-difference develops between the alveoli and the outer space: decompression is generated under inspiration, while compression occurs under expiration. Inspiration with a closed glottis (Müller manuever) causes the intrapulmonary and consequently the intrathoracic pressure to fall below the atmospheric level by around 10 cm H_2O. On the other hand, exhalation with a closed glottis (Valsalva maneuver) results in an increase of the intrathoracic pressure significantly above the atmospheric level due to the work of the diaphragm and the abdominal and auxiliary respiratory muscles. Such powerful pressure changes can be observed during defecation or sneezing. The position of the body—lying on the back, or on one side, standing, or sitting—modifies the pressure conditions. In some respiratory diseases, the subatmospheric intrathoracic pressure rises with the volume increase produced by the increased resistance of the respiratory tract. This, in itself, predisposes to reflux of the gastric contents, especially in the relaxed state of the smooth muscle when the body is in the supine position, when the diameter of the cartilaginous respiratory tract tissue is narrowed in relation to the lower position of the esophagus, which consists of softer connective tissue.[10]

The relationship between GERD and OSA: an overview of the literature

There is controversy around this issue, somewhat similar to the decade-long polemic on the relationship between OSA and hypertension, which concluded with the confirmation of a causal effect produced by OSA.[11,12]

On the basis of physiological studies analyzing the effect of sleep on gastroesophageal physiology, a claim arose that sleep itself could be connected to gastroesophageal reflux events. On the other hand, the European Community Respiratory Health Survey,[13] published in 2003, noted that the GERD that develops during sleep is an important determinant of respiratory imbalance, because it may play a role as an aggravating or causal factor in relation to nocturnal asthma, chronic cough, recurrent bronchitis, and respiratory disorders during sleep. The physiological antireflux mechanisms—swallowing rate, salivation, the pressure of the upper and lower esophageal sphincters, gastric emptying—are reduced, and the "heartburn-signal" is depressed during sleep.[14,15] Esophageal pH-metry and polysomnography performed in parallel during sleep have revealed that acid production decreases considerably compared with that in the state of wakefulness. There is no difference between the rapid eye movement (REM) and the non-REM sleep phases in this respect, although acid production shows a significant reduction in the deeper sleeping phases. In contrast, acid production is raised in healthy people during awakening.[16] It was also shown, by Kahrilas and co-workers,[15] that the LES pressure decreased with the deepness of sleep even for healthy volunteers.

A further factor to be considered regarding the OSA-GERD relationship is that the diaphragm is connected to the LES through the phrenoesophageal ligament (PEL).[17] During sleep apnea, the respiratory work of the diaphragm increases greatly. This increased burden affects the cardia through the frequent changes in the position of the PEL. This leads partly to the loss of cardia muscle tone (cardia insufficiency). Indeed, it is a well-known finding that OSA patients often experience a burning sensation in their esophagus as well as acid regurgitation into the pharynx. The occurrence of impaired swallowing has been documented in relation to this.[18,19] Nevertheless, the observation that both GERD and OSA patients are corpulent seems to have hindered the identification of the relationship between reflux disease and OSA. In fact, the two most common risk factors for GERD are obesity and alcohol abuse, both of which increase the intraabdominal pressure and decrease esophageal clearance.

Teramoto et al.[20] found that reflux complaints were more prevalent among elderly patients with OSA than in non-OSA patients of a similar age and body mass index (BMI). Their conclusion was that OSA is a statistically relevant factor concerning the presence of GERD. In a study investigating samples of young populations in three countries, Gislason et al.[21] reported a rather challenging finding. According to their article, 4.6% of the young population complained of known symptoms of GERD, which tended to be associated with obesity. At the same time, the manifestations of certain forms of respiratory disorders during sleep, as well as nocturnal asthma, were more frequent in this group compared with the rest of the population. They inferred that the presence of nocturnal GERD could be related to asthma as well as to the obstructive respiratory disorders occurring during sleep. The suggested explanation was that the pressure gradient between the esophagus and the stomach increases due to the augmented intrathoracic pressure, which sucks up the gastric contents into the esophagus. This, in turn, produces a further pharyngeal spasm in patients with sleep-related breathing disorders, while it can also lead to bronchoconstriction or coughing in asthmatic patients, by causing microaspiration. Earlier studies conducted by the same team, using epidemiological methods, showed that, in a young patient population, nocturnal GERD prevailed as an independent risk factor for snoring, daytime somnolence, and other sleep complaints, such as symptoms of insomnia, restless sleep, and early awakening.[22,23] Turning to more direct measurements, Ing et al.[24] found that significantly more reflux events were identified for OSA patients compared to controls during one-channel esophageal pH-metry. However, these reflux events typically did not display a temporal coincidence with the respiratory events in the two-channel pH-metry performed by Penzel and co-workers.[25] While the coincidence of the reflux and apnea events remains an issue to be resolved, the number of reflux events was reduced with nasal continuous positive airway pressure (nCPAP) treatment for both OSA and reflux patients.[26,27] This would imply that OSA is a causal factor regarding GERD. At the same time, the apnea-hypopnea index remained unchanged, while the frequency of the patients' arousal was suppressed with histamine receptor 2-blocker treatment (nizatidine). It is worthwhile to note, in this respect, that studies focusing on patients with aperistaltic esophagus imply that arousal from sleep is generated by high reflux under pH4 and the reflux of gastric contents for longer than 5 min.[28] Research by Suganuma et al.[29] also seems to point to a more complex causal relationship, as they showed that GERD itself could cause sleep disorders as well. Indeed, Senior and co-workers[30] treated patients with a confirmed OSA-GERD condition with 20 mg omeprazole two times a day, and they observed a significant improvement concerning OSA in 30% of the patients (the apnea index improved).

In our own study we investigated ten OSA patients. The simultaneous presence of the OSA-GERD combination was identified in eight patients (80%). These patients were also treated with 20 mg omeprazole two times a day, with an average follow-up time of 2.7 months. Combining this treatment with dietary advice, we observed that daytime somnolence—which is a leading symptom of OSA—appreciably decreased. Even though the ultimate therapeutic solution is nCPAP treatment in such patients, it appears that the complementary treatment of GERD is important as well.[31] This view seems to be shared by Foresman,[32] who notes that patients suffering from OSA and GERD simultaneously present a therapeutic challenge. As an illustration of this challenge, Wolf and Furman[33] presented a case of a patient with long-term, severe GERD, who was treated with a high dose of omeprazole and antacids. Eventually OSA was identified in the background of this condition, which came to light due to the patient's complaint of daytime somnolence. The nCPAP therapy brought about a significant improvement regarding GERD and the other symptoms as well.[33] However, nCPAP could decrease gastroesophageal reflux in patients without OSA by increasing the intraesophageal pressure.[34] Therefore, the improvement in GERD brought about by nCPAP may not be caused by the effect of a positive airway pressure on OSA.

In their overview of some more recent research, Field and Flemons[35] commented that the data are rather insufficient to clarify the relationship between GERD and OSA, and well-planned, randomized studies would be needed in the future.[35] In a recent article, Unal and co-

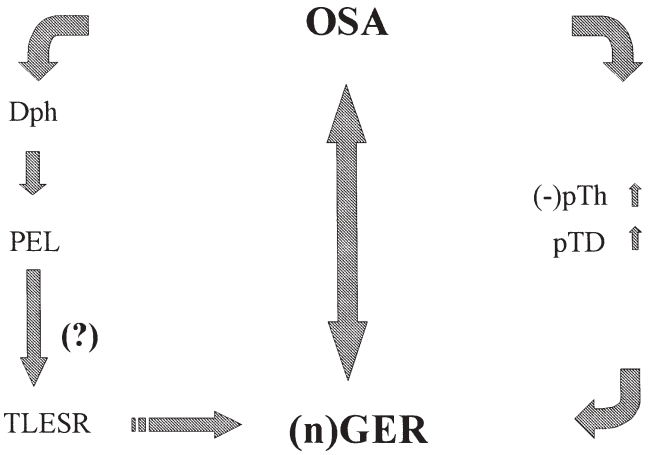

Fig. 1. The authors' suggestions for presumed points connecting obstructive sleep apnea and gastroesophageal reflux disease. *OSA*, obstructive sleep apnea; *(n)GER* (nocturnal) gastroesophageal reflux; *Dph*, diaphragm; *PEL*, Phrenoesophageal ligament; *TLESR*, transient low esophageal sphincter relaxation; *(−)pTh*, negative intrathoracic pressure; *pTD*, transdiaphragmatic gradient of pressure

workers[36] also explored an interesting research avenue. They reported that seropositivity for *Helicobacter pylori* was significantly higher in an OSA group of patients than in healthy controls.

Conclusion

In the light of the above reviewed lines of evidence, there is a strong reason to believe that GERD and OSA potentially exhibit a two-way, mutually reinforcing relationship. This is particularly supported by the observation that treating either of the two conditions improves the other one as well. During the obstructive apnea period, the significant changes in transdiaphragmatic pressure facilitate the migration of the gastric contents toward the esophagus. On the other hand, the same repetitive pressure changes engender an irreversible destructuring of the phrenoesophageal ligament. This leads to LES insufficiency as an ultimate reason for the development of GERD. The large and repeated changes of the pressure gradient also, presumably, play a role in maintaining the duration of the refluxate clearance (Fig. 1). It is also a plausible hypothesis that GERD contributes to the development of arousal from sleep, and consequently contributes to the changes in some cognitive functions, as is evidenced by reduced daytime vigilance.

In addition, arousal from sleep could cause repetitive changes in the tone of the LES that would eventually result in daytime insufficiency in its work as well. Apart from this, the presence of a high pressure gradient in the lying position may facilitate a migrant reflux up to the pharyngeal region, which could eventually result in microaspiration, triggering asthmatic or coughing attacks. At the same time, the further narrowing of the pharyngeal region of the upper respiratory tract could lead to several forms of sleep-disordered breathing, such as OSA or snoring.

As a result of the depressed muscle control of the respiratory drive during sleep, there is considerable muscle tone relaxation in the pharyngeal region. Given that numerous receptors are located in the pharynx, the high reflux of either acid or gastric contents, added to this muscle relaxation, could lead to choking as a result of a delayed awakening from sleep. Taking all these factors together, we are facing two multifactorial conditions which have a distinct impact on each other, especially in certain anatomical situations, such as retrognathia or maxillo-facial abnormalities. The coexistence of the two conditions plays an important role in the therapeutic considerations.

References

1. De Vault KR. Extraesophageal symptoms of GERD. Cleve Clin J Med 2003;70:S20–32.
2. Kirk AJ. Reflux dyspareunia. Thorax 1986;41:215–6.
3. Scarinci IC, McDonald-Haile J, Bradley LA, Richter JE. Altered pain perception and psychosocial features among women with gastrointestinal disorders and history of abuse: a preliminary model. Am J Med 1994;97:108–18.
4. Quigley E. Non-erosive reflux disease: part of the spectrum of gastro-esophageal reflux disease, a component of functional dyspepsia, or both? Eur J Gastroenterol Hepatol 2001;13:S13–8.
5. Richter JE. Extraesophageal presentations of gastroesophageal reflux disease: an overview. Am J Gastroenterol 2000;95:S1–3.
6. Olson EJ, Moore WR, Morgenthaler TI, Gay PC, Staats BA. Obstructive sleep apnea-hypopnea syndrome. Mayo Clin Proc 2003;78:1545–52.
7. Kuna ST, Remmers JE. Pathogenesis and mechanism of sleep apnea. In: Fletchner EC, editor. Abnormalities of respiration during sleep. 1st ed. London: Grune and Stratton; 1986. p. 147–9.
8. Thach BT. Maturation and transformation of reflexes that protect the laryngeal airway from liquid aspiration from fetal to adult life. Am J Med 2001;111:S69–77.
9. Holloway RH. Esophageal body motor response to reflux events: secondary peristalsis. Am J Med 2000;108:S20–6.
10. Khoury RM, Camacho-Lobato L, Katz PO, Mohiuddin MA, Castell DO. Influence of spontaneous sleep positions on nightime recumbent reflux in patients with gastroesophageal reflux disease. Am J Gastroenterol 1999;94:2069–73.
11. Davies RJO, Várdi VK, Clarke M, Stradling JR. Identification of sleep disruption and sleep disordered breathing from the systolic blood pressure profile. Thorax 1993;48:242–7.
12. Davies RJO, Crosby J, Várdi VK, Clarke M, Stradling JR. Non-invasive beat to beat arterial blood pressure during non-REM sleep in obstructive sleep apnoea and snoring. Thorax 1994;49:335–9.
13. Knox J, Jarvis D, Walter EH. ECRHS II Steering Committee. The European Community Respiratory Health Survey II. Eur Respir J 2003;21:556.

14. Parischa Jay P. Effect of sleep on gastroesophageal physiology and airway protective mechanism. Am J Med 2003;115:114–8.
15. Kahrilas PJ, Dodds WJ, Dent J. Effect of sleep, spontaneous gastroesophageal reflux, and a meal on upper esophageal sphincter pressure in normal human volunteers. Gastroenterology 1987; 92:466–71.
16. Stacher G, Presslich B, Starker H. Gastric acid secretion and sleep stages during natural sleep. Gastroenterology 1975;68:1449–55.
17. Stiennon OA. The anatomic basis for the lower esophageal contraction ring. Plication theory and its applications. Am J Roentgenol Radium Ther Nucl Med 1963;90:811–22.
18. Teramoto S, Sudo E, Ohga E. Impaired swallowing reflex of patients with obstructive sleep apnea syndrome. Chest 1999;116: 17–21.
19. Teramoto S, Kume H, Ouchi Y. Nocturnal gastroesophageal reflux: symptom of obstructive sleep apnea syndrome in association with impaired swallowing. Chest 2002;122:2266–7.
20. Teramoto S, Ohga E, Matsui H, Matsuse T, Ouchi Y. Obstructive sleep apnea syndrome may be a significant cause of gastroesophageal reflux disease in older people. J Am Geriatr Soc 1999;47: 1273–4.
21. Gislason T, Janson C, Vermieire P, Plaschke P, Bjornsson E, Gislason D, et al. Respiratory symptoms and gastroesophageal reflux: a population based study of young adults in three European countries. Chest 2002;120:158–63.
22. Janson C, Gislason T, De Backer W. Prevalence of sleep disturbances among young adults in three European countries. Sleep 1995;18:589–97.
23. Janson C, De Backer W, Gislason T. Increased prevalence of sleep disturbances and daytime sleepiness in subjets with bronchial asthma. Eur Resp J 1996;9:2132–8.
24. Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastroesophageal reflux. Am J Med 2000;108:S120–5.
25. Penzel T, Becker HF, Branderburg U, Labunski T, Pankow W, Peter JH. Arousal in patients with gastro-esophageal reflux and sleep apnoea. Eur Respir J 1999;14:1266–70.
26. Green BT, Broughton WA, O'Connor JB. Marked improvement in nocturnal gastroesophageal reflux in large cohort of patients with obstructive sleep apnea treated with continuous positive airway pressure. Arch Intern Med 2003;13:41–5.
27. Kerr P, Shoenut JP, Millar T, Buckle P, Kryger MH. Nasal CPAP reduces gastroesophageal reflux in obstructive sleep apnea syndrome. Chest 1992;101:1539–44.
28. Shoenut JP, Yamashiro Y, Orr WC, Kerr P, Micflikier AB, Kryger MH. Effect of severe GER on sleep stage in patients with aperistaltic esophagus. Dig Dis Sci 1996;41:372–6.
29. Suganuma N, Shigedo Y, Adachi H, Watanabe T, Kumano-Go T, Terashima K, et al. Association of gastroesophageal reflux disease with weight gain and apnea, and their disturbance on sleep. Psychiatry Clin Neurosci 2001;55:255–6.
30. Senior BA, Khan M, Schwimmer C, Rosenthal L, Benninger M. Gastroesophageal reflux and obstructive sleep apnea. Laryngoscope 2001;111:2144–6.
31. Demeter P, Várdi Visy K, Sike R, Tóth GT, Magyar P. The relationship of obstructive sleep apnea and gastroesophageal reflux disease. Z Gastroenterol 2003;41:16.
32. Foresman BH. Sleep-related gastroesophageal reflux. J Am Osteopath Assoc 2000;100:S7–10.
33. Wolf S, Furman Y. Sleep apnea and gastroesophageal reflux disease. Ann Intern Med 2002;136:490–1.
34. Kerr P, Shoenut JP, Steens RD, Millar T, Micflikier AB, Kryger MH. Nasal continuous airway pressure: a new treatment for nocturnal gastroesophageal reflux? J Clin Gastroenterol 1993;17:276–80.
35. Field KS, Flemons WW. Is the relationship between obstructive sleep apnea and gastroesophageal reflux clinically important? Chest 2002;121:1730–3.
36. UNal M, Ozturk L, Ozturk C, Kabal A. The seroprevalence of *Helicobacter pylori* infection in patients with obstructive sleep apnoea: a preliminary study. Clin Otolaryngol 2003;28: 100–2.