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Original Article

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Gastroesophageal Reflux Affects Sleep Quality in Snoring Obese Children

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Purpose: This study was performed to evaluate the quality of sleep in snoring obese children without obstructive sleep apnea (OSA); and to study the possible relationship between sleep interruption and gastroesophageal reflux (GER) in snoring obese children.

Methods: Study subjects included 13 snoring obese children who were referred to our sleep lab for possible sleep-disordered breathing. Patients underwent multichannel intraluminal impedance and esophageal pH monitoring with simultaneous polysomnography. Exclusion criteria included history of fundoplication, cystic fibrosis, and infants under the age of 2 years. Significant association between arousals and awakenings with previous reflux were defined by symptom-association probability using 2-minute intervals.

Results: Sleep efficiency ranged from 67-97% (median 81%). A total of 111 reflux episodes (90% acidic) were detected during sleep, but there were more episodes per hour during awake periods after sleep onset than during sleep (median 2.3 vs. 0.6, p=0.04). There were 279 total awakenings during the sleep study; 56 (20.1%) of them in 9 patients (69.2%) were preceded by reflux episodes (55 acid, 1 non-acid). In 5 patients (38.5%), awakenings were significantly associated with reflux.

Conclusion: The data suggest that acid GER causes sleep interruptions in obese children who have symptoms of snoring or restless sleep and without evidence of OSA.

Key Words: Gastroesophageal reflux, Besity, Sleep wake disorders, Child, Electric impedance, Obstructive sleep apnea

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INTRODUCTION

In the United States, obesity affects up to 17% of children. In the past decades, the prevalence has risen from 7% among children aged 6-11 years in 1980 to nearly 18% in 2012, and from 5% among adolescents aged 12-19 years to nearly 21% over the same period [1,2]. Obesity is associated with significant short and long-term morbidity, including cardiovascular disease (relative risk 1.24, 95% confidence interval [CI] 1.02-1.55) [3], type II diabetes (relative risk 5.4, 95% CI 3.4-8.5) [4], dyslipidemia (elevated low density lipoprotein cholesterol, reduced high density lipoprotein cholesterol, elevated triglyceride levels; relative risk ranging from 1.8 [95% CI 1.4-2.3] to 3.0 [95% CI 2.4-3.8]) [4], hypertension (relative risk 2.7, 95% CI 2.2-3.3) [4], and obesity-related cancer (relative risk 1.9, 95% CI 1.4-2.7; esophagus, pancreas, colorectal carcinoma, and kidney) [5]. Obesity has also been shown to be associated with sleep-disordered breathing (SDB), ranging from snoring to severe obstructive sleep apnea (OSA) [6]. SDB has been linked to increased airway resistance secondary to fatty infiltration of the pharynx and to adenotonsillar hypertrophy [7]. OSA occurs in about 36% of obese children and correlates with the severity of obesity [8]. Fragmented sleep is associated with impaired daytime function, poor academic performance, mood disorders and behavior problems [9]. The effect of obesity on the amount of nocturnal sleep and its continuity is currently unclear [10,11].

A higher prevalence of gastroesophageal reflux disease (GERD) and its complications have also been reported in obese patients [12]. The association of obesity and gastroesophageal reflux (GER) is reported with an odds ratio of 7.3 (95% CI 1.7-31.0) [13-15]. In adults, an epidemiological link between sleep disorders and GERD has been established. Among 15,699 patients evaluated for sleep disturbances, approximately 25% reported heartburn and OSA. A higher body mass index was a significant risk factor associated with heartburn [16]. Nighttime heartburn, in particular, has a significant impact on sleep quality and daytime function [17]. During sleep, there are a decreased number of reflux episodes due to inhibition of transient lower esophageal sphincter (LES) relaxation [18,19]. However, clearance of a reflux episode during sleep is slower due to reduced saliva production, the absence of resultant swallows due to saliva accumulation in the back of the throat, and subsequent swallow-induced primary peristalsis [18,19]. Additionally, esophageal sensitivity to acid perfusion is enhanced following a nocturnal sleep interruption in GERD patients compared with healthy controls [20]. Patients with more severe erosive esophagitis also have increased esophageal acid exposure during sleep compared to patients with milder esophagitis [21].

Little is known about the relationship between GERD and quality of sleep in obese children. The aims of this study were to evaluate the quality of sleep in obese children without OSA and to study the possible relationship between the quality of sleep and GER in obese children.

MATERIALS AND METHODS

Study population

We prospectively evaluated 13 obese patients who were referred to our pediatric sleep center for polysomnography (PSG) with combined esophageal pH monitoring–multichannel intraluminal impedance (EPM-MII) after being off acid suppression medications (5-7 days for proton pump inhibitors and 3 days for prokinetics). Exclusion criteria included a history of fundoplication, cystic fibrosis, and age younger than 2 years.

The study protocol was approved by the Institutional Review Board at Nationwide Children's Hospital (Columbus, OH, USA) (IRB No. 07-00385).

Polysomnography

The studies were performed in the Sleep Laboratory at Nationwide Children's Hospital with simultaneous EPM-MII (with no sedation or sleep deprivation) for 7 to 10 hours. Electrodes were applied for electroencephalograms (C4/A1, O2/A1), electro-ocu-

lograms, submental electromyograms (EMG), tibialis anterior EMGs, and electrocardiograms. Respitrace bands were placed across the thorax and abdomen to measure chest and abdominal wall movements. Nasal pressure transducer, oro-nasal thermister and end-tidal PCO_2 cannulas were used to detect airflow, and a Massimo pulse oximeter was used to continuously measure blood oxygen saturation (SaO_2). During the PSG, patients were continuously video-recorded using an infrared video camera, and continuously observed by a PSG technician who recorded events of interest. Data were recorded continuously on a Grass computerized PSG system, with all data synchronized using the smart meter. There were no restrictions to eating before testing. Changes in sleep position, meal compositions and times were recorded in a log book.

Sleep stages and arousals were scored as recommended by the American Academy of Sleep Medicine (AASM) [22,23]. Arousals were registered during sleep stages N1, N2, N3 or rapid eye movement sleep (REM) when there was an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles) that lasted at least 3 seconds, with at least 10 seconds of stable sleep preceding the change. Scoring of arousal during REM required a concurrent increase in submental EMG lasting at least 1 second. The arousal index was the number of arousals per hour of sleep.

The following definitions were used:

- Obstructive apneas: chest/abdominal wall motion with an absence or reduction of airflow by 90% for ≥2 breaths.
- Central apneas: absence of chest/abdominal wall motion and airflow for ≥2 breaths.
- Hypopneas: reductions in airflow by ≥50%, in the presence of chest/abdominal wall motion, and associated with SaO_2 desaturations (≥3%), arousals or awakenings.
- Apnea/hypopnea index (AHI): the number of apneas (central and obstructive) and hypopneas per hour of sleep.
- Desaturation: drops in oxygen saturation of ≥3% of baseline.
- Sleep efficiency: the time spent asleep (total sleep time) divided by the time period between lights off and lights on (total recording time).
- Wakened after sleep onset (WASO): the duration of waking time after initial sleep onset and before the final awakening.

The SaO_2 nadir and the percentage of sleep during which SaO_2 was less than 90%, were also tabulated.

EPM-MII

The catheter was placed so that the pH electrode was positioned above LES by 13% of the total distance between the nostrils and the LES [24]. Patients were allowed to have one meal during nighttime and meal composition was recorded in a log book. Symptoms including cough, stridor, drooling, choking, gagging, and vomiting, were registered in the impedance logger and in the log book. Symptoms were recorded by patient's caregiver, who was also oriented to push symptom's buttons on the device. Also, a parallel record was generated by a technician who followed the examination.

The following definitions were used:

- GER: a drop in impedance to ≤50% from baseline occurring in the retrograde direction in two or more of the distal-most impedance channels.
- Acid reflux episode (AGER): a GER episode (lasting ≥5 seconds) during which the pH dropped to below 4.
- Non-acid reflux episode (NAGER): a GER episode during which the pH remained ≥pH 4.
- Abnormal distal esophageal acid exposure: >7%.

Reflux episodes were characterized by their chemical content (acid/non-acid), duration of bolus contact (impedance), and chemical clearance (for acid episodes).

Statistical analysis

The relationship between a symptom and GER was evaluated by the symptom association probability (SAP). For the SAP, the study duration is divided into multiple time epochs, and the occurrence of the event (symptom, arousal and awakening) or GER episode is evaluated in each epoch. A con-

tingency table is then constructed with cells corresponding to the presence and absence of the event and reflux episode(s). The Fisher's exact test is then computed and the SAP is defined as (100×[1−p-value]). A SAP >95% is considered positive, defining a significant relationship between the event and GER. Reflux-association probability (RAP) was calculated using the same technique to identify a significant relationship between GER and preceding arousals. Symptom index was defined by the proportion of symptoms that were temporally related to GER episodes.

For respiratory events (cough), SAP calculation was performed with 5 minute windows, with the mid-point corresponding to the beginning of the reflux episode [25]. We also calculated SAP values for arousals and awakenings, using 2-minute windows, with the GER episode at the beginning of each time frame. This approach was used for total GER, NAGER, and AGER.

Numeric variables were described by median and interquartile range (IQR), unless specified otherwise, while categorical variables were described by frequency. In order to evaluate the influence of GER on sleep efficiency, patients were categorized in two groups according to sleep efficiency, using a cutoff at 85%. Although there is no established normal values for sleep efficiency for children, we chose that cutoff value because values lower than this cutoff are regarded low and associated with sleep-associated morbidity [26]. Thereafter, duration of reflux episodes, number, and relationship with arousals and awakenings were compared between the two groups using the Mann-Whitney test. Also, GER parameters during sleep time and WASO were compared with the Wilcoxon sign-rank test. For all statistical tests, a p-value <0.05 was considered significant. Statistical tests were performed with SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and baseline clinical data are shown in Table 1. Snoring was the most common indication for a PSG, and it was observed in 11/13 patients (84.6%). Sleep time during the PSG ranged from 268 to 576.5 minutes (median, 377 minutes), while WASO ranged from 14 to 191 minutes (median, 77 minutes). The median sleep efficiency was 81% (range, 67-97%), and it was lower than 85% in 8/13 patients (61.5%). Apnea hypopnea index was 0 in 9 patients (69.2%), while among those with AHI >0, the index ranged from 0.4 to 1.

The EPM-MII lasted for 12.1 to 24.5 hours, with 6/13 patients (46.2%) undergoing a complete study (more than 20 hours). The distal esophageal acid exposure ranged from 0.2 to 15.9%, with 3/6 patients having an abnormal pH study. A total of 111 GER episodes (100 acidic [90.1%], and 11 non acidic [9.9%]) were detected during sleep, while 51 episodes (48 acidic [94.1%] and 3 non acidic [5.9%]) were detected during WASO. There were significantly more episodes per hour during WASO compared to sleep time (WASO median 2.25 [0.5-4.0] vs. 0.6 [0.5-1.5], p=0.04).

Arousals

The arousal index ranged from 3 to 10 (median, 6).

Table 1. Demographic and Clinical Data of 13 Obese Patients Referred to PSG with Simultaneous EPM-MII

Variable	Data
Male sex	6 (46.2)
Age (yr)	13.4 (10.8-16.4)
Body mass index (kg/m^2)	32.9 (28.4-47.9)
Indication for PSG with EPM-MII*	
Snoring	11 (84.6)
Restless sleep	2 (15.4)
Apneas	2 (15.4)
Cough	1 (7.7)
Dyspnea	1 (7.7)
Night desaturations	1 (7.7)
Co-morbidities	
Asthma	5 (38.5)
Systemic lupus erythematosus	1 (7.7)
Traumatic brain injury	1 (7.7)

Values are presented as number (%) or median (interquartile range).
PSG: polysomnography; EPM-MII: esophageal pH monitoring–multichannel intraluminal impedance.
*More than one indication per patient.

Overall, a total of 40 arousals preceding GER episodes were detected in 9/13 patients (69.2%). Two of the 13 obese patients (15.4%) presented a positive RAP (reflux following arousal).

SAP for arousals was positive in 4/13 patients (30.8%). None of the patients presented positive SAP for arousals due to NAGER. Sleep efficiency was not significantly different in patients with a positive SAP for arousals (74.5% [67.5-83.5%] vs. 83% [74-92%], p=0.16), but 3/4 patients (75.0%) with a positive SAP for arousals presented sleep efficiency lower than 85% (p=1.0).

Awakenings

There were a total of 279 awakenings during the sleep study (median, 22 per patient; IQR, 12-26), 56 (20.1%) of those were preceded by reflux episodes (55 acid and 1 non-acid reflux) in 9/13 patients (69.2%). Among those patients, it happened in 9.1-36.4% of awakenings (median, 27.3%). A positive SAP was present in 5/13 (38.5%), 4 of whom had also a positive SAP for arousals.

The number of awakenings was higher in patients with sleep efficiency lower than 85% (25.5 [15.5-31.0] vs. 11 [11.0-22.0], p=0.04). The number of reflux episodes preceding arousals and awakenings was higher in patients with lower sleep efficiency (Table 2).

Respiratory symptoms

Desaturation was detected in 8/13 patients (61.5%), but they were significantly associated with reflux in 2 (positive SAP); a 15 year-old girl with 12 awakenings after reflux, but a negative SAP for awakenings and a 8-year-old boy with zero awakenings following a reflux episode, but a positive reflux-association probability (reflux episode causing arousal). Cough was reported in 5/13 patients (38.5%), one of whom with a positive SAP for cough (>95%).

DISCUSSION

The present study demonstrates that even in the absence of OSA, obese children may have fragmented sleep due to GER episodes. Sixty-nine percent of obese children (9/13) had awakenings that were temporally related to reflux, but only 5 had positive SAP (38.5%). The vast majority of these episodes involved AGER (55/56). Furthermore, patients with lower sleep efficiency presented more sleep time acid exposure. According to our study, non-acid reflux does not play a role in the relationship between GER and sleep quality in obese children. This is consistent with the report that obese patients have more AGER and GERD but not non-acid reflux as compared to healthy volunteers [12]. Adult studies

Table 2. Gastroesophageal Reflux (Duration and Number of Episodes) during Sleeptime and during Wakened Period after Sleep Onset (WASO)

	Sleep efficiency		p-value
	<85% (n=8)	>85% (n=5)	
AGER, sleep time (min)	67.7 (1.3-74.7)	1.1 (0-1.5)	0.05
NAGER, sleep time (min)	0 (0-0.2)	0 (0-0.5)	0.56
AGER, WASO (min)	10.2 (1.4-0.1)	0 (0-9.3)	0.07
NAGER, WASO (min)	0 (0-0.2)	0 (0-0)	0.24
AGER, sleep time (n)	8.0 (3.0-21.0)	3.0 (0-4.0)	0.06
NAGER, sleep time (n)	0 (0-1.0)	0 (0-2.0)	0.55
AGER, WASO (n)	3.5 (2.0-6.0)	0 (0-3.0)	0.14
NAGER, WASO (n)	0 (0-0.5)	0 (0-0.0)	0.24
Reflux episodes before arousals (n)	6.0 (3.5-11.0)	2.0 (0-2.0)	0.02
Reflux episodes before awakenings (n)	5.5 (2.5-10.5)	0 (0-2.0)	0.03

Values are presented as median (interquartile range).
AGER: acid gastroesophageal reflux, NAGER: non-AGER.

showed that a painful stimuli from acid reflux can be associated with arousals and brief awakenings as a protective mechanism, generating secondary peristalsis and facilitating acid clearance. According to other authors, acid reflux events might be associated with short, amnestic (i.e., patients are not able to recall them) arousals rather than a complete awakening [27].

GER-related respiratory symptoms during sleep were not associated with GER-related awakenings. Desaturations (61.6%) and cough (38.5%) were common, and temporarily correlated with reflux in 3 patients, but none of the patients had a positive SAP for arousals and awakenings. In obese patients, sleep disruption with desaturations and snoring has been correlated with OSA [28], but little is known about the role of respiratory symptoms and sleep quality in patients without OSA. It has been previously reported that while most reflux episodes related to O_2 desaturation in patients with chronic respiratory disorders are related to AGER, NAGER has also been reported to play a role [19]. EPM-MII may be important to evaluate the relationship between respiratory events and GERD because it allows assessment of NAGER. Although GER episodes were not related to subjective complaints of heartburn in our patients, pain associated with acid reflux may trigger arousals and awakenings. Poor sleep quality may also enhance esophageal sensitivity, making arousals due to pain more frequent with GER episodes because of hyperalgesia [20].

After awakening, patients presented more reflux episodes than during sleep time. This is an important piece of information, because poor sleep quality may impair appropriate control of GERD among those patients, as they present compromised sleep efficiency. A previous study has already demonstrated that increased AGER during recumbent periods is related to awakenings in adults with heartburn [29]. That happens because during sleep esophageal motility is inactive, but arousals may trigger transient LES relaxations [27]. Two patients in the present study presented significant reflux-association probability, with which we evaluated the arousals preceding reflux episodes. If OSA is present, it may also increase the incidence of reflux during sleep time due to increased negativity of intrathoracic pressure associated with increased inspiratory efforts against higher upper airway resistance precipitating reflux of gastric contents due to pressure gradient [30]. Recently, an adult study has shown that sleep dysfunction is associated with poor response to GERD treatment in patients with non-erosive disease [31].

The study has some limitations. First, the sample size was small, and limited to obese patients without OSA, a common sleep disorder in obese patients [8]. This limits our conclusions to a very specific subset of obese patients without OSA but with sleep disturbances, and it impairs multivariate analysis. On the other hand, it allows us to focus on GER events as a potential variable contributing to sleep fragmentation. Another important limitation is that we evaluated sleep efficiency with PSG, a non-ecological evaluation of the sleep [32].

Also, the sleep studies were performed and scored according to the 2007 AASM scoring rules, as they were performed before 2012. While a higher AHI might be expected using 2012 scoring for hypopneas (30% drop in nasal pressure signal) as compared to 2007 criterion (50% drop in nasal pressure signal), this difference appears to be important only at higher AHI [33]. We would expect difference to have a small effect on the low AHI reported in our study which used AHI <1.5 to rule out OSA.

Another limitation is that respiratory efforts related to arousals (RERA) were not reported in this study. We prefer to use apneas and hypopneas alone because they have the greatest association with outcomes in the pediatric literature. The utility of scoring RERAs (an option in the 2007 AASM scoring manual) is greater when using a hypopnea definition that does not include scoring based on arousals. Since we used the 2007 pediatric hypopnea definition, which is based on either desaturations or arousals, we would have missed only a small number of RERA events [34]. One study showed that RERAs were only 5% of the total number of detected events in adults with moderate OSA [35]. Furthermore, in-

ter-rater reliability has not been consistent, with 35% difference between scorers [36]. On the other hand, a direct measurement of RERAs using esophageal pressure measurement incorporated into an impedance catheter to could be an interesting approach to detect RERAs and to correlate it with GER episodes.

Our study shows that AGER is frequently associated with sleep disruptions in obese children without OSA. This suggests that pH monitoring alone (without impedance testing) would likely be sufficient to clinically investigate disrupted sleep in obese children without OSA, since non-acid reflux episodes are uncommon during sleep and are rarely associated with arousal and awakening.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014;311:806-14.
2. Bernstein A, Bilheimer LT, Makuc DM; National Center for Health Statistics. Health, United States, 2011: with special features on socioeconomic status and health. Hyattsville: U.S. Department of Health and Human Services; 2012.
3. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med 2013;159:758-69.
4. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011;365:1876-85.
5. de Mutsert R, Sun Q, Willett WC, Hu FB, van Dam RM. Overweight in early adulthood, adult weight change, and risk of type 2 diabetes, cardiovascular diseases, and certain cancers in men: a cohort study. Am J Epidemiol 2014;179:1353-65.
6. Grunstein RR, Wilcox I. Sleep-disordered breathing and obesity. Baillieres Clin Endocrinol Metab 1994;8:601-28.
7. Katz ES, D'Ambrosio CM. Pediatric obstructive sleep apnea syndrome. Clin Chest Med 2010;31:221-34.
8. Marcus CL, Curtis S, Koerner CB, Joffe A, Serwint JR, Loughlin GM. Evaluation of pulmonary function and polysomnography in obese children and adolescents. Pediatr Pulmonol 1996;21:176-83.
9. Owens JA. Neurocognitive and behavioral impact of sleep disordered breathing in children. Pediatr Pulmonol 2009;44:417-22.
10. Calamaro CJ, Park S, Mason TB, Marcus CL, Weaver TE, Pack A, et al. Shortened sleep duration does not predict obesity in adolescents. J Sleep Res 2010;19:559-66.
11. Sekine M, Yamagami T, Handa K, Saito T, Nanri S, Kawaminami K, et al. A dose-response relationship between short sleeping hours and childhood obesity: results of the Toyama Birth Cohort Study. Child Care Health Dev 2002;28:163-70.
12. Ricci G, Amella C, Forti E, Rossi A, Bersani G, Dari S, et al. 24-h pH-metry and multichannel intraluminal impedance monitoring in obese patients with and without gastroesophageal reflux disease symptoms. Obes Surg 2011;21:48-53.
13. Phatak UP, Pashankar DS. Obesity and gastrointestinal disorders. J Pediatr 2009;155:599.
14. Teitelbaum JE, Sinha P, Micale M, Yeung S, Jaeger J. Obesity is related to multiple functional abdominal diseases. J Pediatr 2009;154:444-6.
15. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet 2010;375:1737-48.
16. Fass R, Quan SF, O'Connor GT, Ervin A, Iber C. Predictors of heartburn during sleep in a large prospective cohort study. Chest 2005;127:1658-66.
17. Shaker R, Castell DO, Schoenfeld PS, Spechler SJ. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. Am J Gastroenterol 2003;98:1487-93.
18. Orr WC, Chen CL. Sleep and the gastrointestinal tract. Neurol Clin 2005;23:1007-24.
19. Thilmany C, Beck-Ripp J, Griese M. Acid and non-acid gastro-esophageal refluxes in children with chronic pulmonary diseases. Respir Med 2007;101:969-76.
20. Schey R, Dickman R, Parthasarathy S, Quan SF, Wendel C, Merchant J, et al. Sleep deprivation is hyperalgesic in patients with gastroesophageal reflux disease. Gastroenterology 2007;133:1787-95.
21. Adachi K, Fujishiro H, Katsube T, Yuki M, Ono M, Kawamura A, et al. Predominant nocturnal acid reflux in patients with Los Angeles grade C and D reflux esophagitis. J Gastroenterol Hepatol 2001;16:1191-6.
22. Grigg-Damberger M, Gozal D, Marcus CL, Quan SF, Rosen CL, Chervin RD, et al. The visual scoring of sleep and arousal in infants and children. J Clin Sleep Med 2007;3:201-40.
23. Iber C; American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated

events: rules, terminology and technical specifications. Westchester: American Academy of Sleep Medicine; 2007.
24. Strobel CT, Byrne WJ, Ament ME, Euler AR. Correlation of esophageal lengths in children with height: application to the Tuttle test without prior esophageal manometry. J Pediatr 1979;94:81-4.
25. Weusten BL, Roelofs JM, Akkermans LM, Van Berge-Henegouwen GP, Smout AJ. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 1994;107:1741-5.
26. Javaheri S, Storfer-Isser A, Rosen CL, Redline S. Sleep quality and elevated blood pressure in adolescents. Circulation 2008;118:1034-40.
27. Fass R. Effect of gastroesophageal reflux disease on sleep. J Gastroenterol Hepatol 2010;25 Suppl 1:S41-4.
28. Narang I, Mathew JL. Childhood obesity and obstructive sleep apnea. J Nutr Metab 2012;2012:134202.
29. Allen L, Poh CH, Gasiorowska A, Malagon I, Navarro-Rodriguez T, Cui H, et al. Increased oesophageal acid exposure at the beginning of the recumbent period is primarily a recumbent-awake phenomenon. Aliment Pharmacol Ther 2010;32:787-94.
30. Kim SE, Kim N, Oh S, Kim HM, Park MI, Lee DH, et al. Predictive factors of response to proton pump inhibitors in korean patients with gastroesophageal reflux disease. J Neurogastroenterol Motil 2015;21: 69-77.
31. Penzel T, Becker HF, Brandenburg U, Labunski T, Pankow W, Peter JH. Arousal in patients with gastro-oesophageal reflux and sleep apnoea. Eur Respir J 1999;14:1266-70.
32. de la Vega R, Miró J. The assessment of sleep in pediatric chronic pain sufferers. Sleep Med Rev 2013;17: 185-92.
33. Nixon GM, Hyde M, Biggs SN, Walter LM, Horne RS, Davey MJ. The impact of recent changes to the respiratory scoring rules in pediatrics. J Clin Sleep Med 2014;10:1217-21.
34. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597-619.
35. Cracowski C, Pépin JL, Wuyam B, Lévy P. Characterization of obstructive nonapneic respiratory events in moderate sleep apnea syndrome. Am J Respir Crit Care Med 2001;164:944-8.
36. Ayappa I, Norman RG, Krieger AC, Rosen A, O'malley RL, Rapoport DM. Non-Invasive detection of respiratory effort-related arousals (REras) by a nasal cannula/pressure transducer system. Sleep 2000;23:763-71.