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Original Article

The Influence of Gastroesophageal Reflux Disease on Daytime Sleepiness and Depressive Symptom in Patients With Obstructive Sleep Apnea

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Background/Aims
As there is insufficient evidence for a relationship between gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA), we investigated whether OSA diagnosed by polysomnography (PSG) is related to GERD.

Methods
A total of 402 subjects was evaluated. Overnight PSG was performed and a few questionnaires on GERD, anxiety, depression, and daytime sleepiness were administered. An apnea-hypopnea index < 5 was the classification criterion for subjects without OSA. Subjects with heartburn or acid regurgitation at least once a week were classified as having GERD.

Results
Among the 402 subjects, 318 had OSA and 84 did not. The prevalence of GERD was 12.9% among patients with OSA and 10.7% among those without (P = 0.590). The prevalence of GERD did not correlate with OSA severity (P = 0.474). Patients with OSA with GERD had higher Stanford Sleepiness Scale (P = 0.004), Epworth Sleepiness Scale (P = 0.001), and depression (P < 0.001) scores than patients with OSA without GERD. Subjects with nocturnal gastroesophageal reflux symptoms had a higher body mass index, waist-to-height ratio, and waist circumference-to-height index than those without symptoms. Multiple logistic regression showed that higher Epworth Sleepiness Scale and depression scores were independent factors associated with GERD in patients with OSA.

Conclusions
The prevalence of GERD in patients with OSA was 12.9%. The prevalence of GERD did not correlate with OSA severity. Daytime sleepiness and depression seem to be associated with GERD in patients with OSA, while nocturnal reflux symptoms seem to be related to obesity in OSA.

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Key Words
Depression; Gastroesophageal reflux; Obesity; Polysomnography; Sleep apnea, obstructive

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Introduction

The prevalence of gastroesophageal reflux disease (GERD) has been gradually increasing in the Eastern world. The prevalence of symptom-based GERD was reported at 5.2-8.5% from 2005 to 2010 in Eastern Asia.[1] During sleep, esophageal and gastric motility is decreased, and the time for esophageal mucosa exposure to gastric acid is increased. This may exacerbate the symptoms of gastroesophageal reflux, which causes awakening and thus interrupts sleep. GERD and obstructive sleep apnea (OSA) which is one of the most common sleep disorders, are thought to affect each other, but the relationship has never been clearly demonstrated. There is some evidence for a link between GERD and OSA.[2] Omeprazole therapy for GERD has been shown to reduce the occurrence of apnea attacks.[3] The use of proton pump inhibitors can improve the quality of life associated with sleep disturbance.[4] In the case-control study, it has been suggested that OSA may increase the risk of Barrett's esophagus through obesity and GERD.[5] The known risk factors for OSA are advanced age, male sex, and obesity.[6] Furthermore, some risk factors are common for both disorders. Obesity, for example, is a major risk factor for OSA and GERD. Organization for Economic Cooperation and Development statistics show that obesity rates range from 4.2% (Japan) to 40.0% (USA) of the total adult population when a body mass index (BMI) of 30 kg/m^2 or more is used as the defining criterion for obesity.[7] Over the years, the prevalence of overweight and obesity has also increased in Korea.

While weight loss has been shown to result in improvements in OSA parameters,[8] it is unclear whether it is strongly associated with both diseases because of similar risk factors, or whether there might be a causal relationship between both OSA and GERD. Furthermore, it is not clear whether OSA severity has any causal relationship with reflux symptoms. The aim of this study is thus to investigate the prevalence of GERD in patients with OSA diagnosed by overnight polysomnography (PSG). In addition, we assessed the risk factors for GERD in patient with OSA.

Materials and Methods

Subjects

We consecutively enrolled 424 subjects who were suspected of having OSA and underwent full overnight PSG at the sleep clinic of St. Paul's Hospital, the Catholic University of Korea, between September 2009 and September 2015. Twenty-two subjects who did not complete the questionnaire were excluded. The subjects completed several questionnaires on reflux symptoms, anxiety and depression, and daytime sleepiness. Finally, 402 subjects were included in this study. The study, summarized in Figure 1, was approved by the institutional review board of our hospital (IRB No. PC14RISI0037).

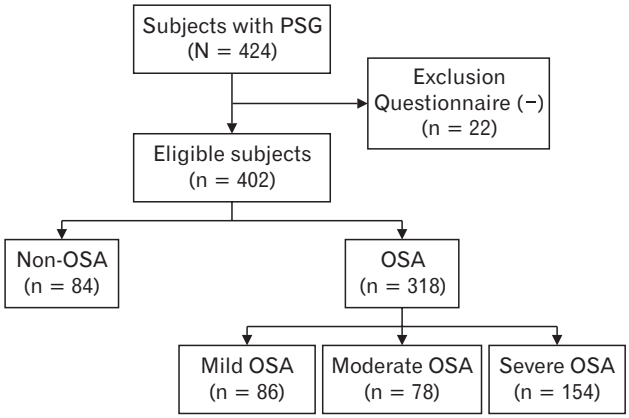

Figure 1. Flow chart of the study. PSG, overnight polysomnography; OSA, obstructive sleep apnea.

Polysomnography

PSG (Somnostar Pro 7-3a; Somnostar/Cardinal Health, Dublin, OH, USA) was conducted overnight. Apnea was defined as a reduction in airflow of more than 90.0% lasting at least 10 seconds. Hypopnea was defined as a decrease in airflow of more than 50.0% for at least 10 seconds and a decrease in arterial oxygen saturation of more than 4.0% or arousal.[9] The apnea-hypopnea index (AHI) was defined as the sum of apneas and hypopneas per hour. OSA severity was defined as mild for an AHI $\geq$ 5 and $<$ 15, moderate for an AHI $\geq$ 15 and $\leq$ 30, and severe for an AHI $>$ 30/hour. Total sleep time was defined as the total amount of recorded sleep during the PSG. The sleep period time was defined as the elapsed time from sleep onset to the end of the last epoch of sleep. Sleep efficiency was defined as the percentage of time spent asleep while in bed. Sleep is broken down into 5 phases: wake, N1, N2, N3, and R. Stages N1 to N3 are considered non-rapid eye movement sleep, each progressively going deeper. Stage R is referred to as rapid eye movement sleep.

Questionnaires

Reflux questionnaire

The reflux questionnaire was based on a questionnaire that our

group has previously used.[10-14] The subjects were asked questions about the occurrence of typical reflux symptoms such as heartburn and acid regurgitation and answered as follows: 0, none; 1, less than once a month; 2, approximately once a month; 3, approximately once a week; 4, more than twice a week; and 5, every day. Subjects with heartburn or acid regurgitation at least once a week were designated as having GERD. Subjects were asked about the presence of nocturnal reflux symptoms if they had woken up while sleeping due to reflux symptoms.[14]

Anxiety and depression score

As the questionnaire on anxiety and depression, we used the Korean version of the Hospital Anxiety and Depression Scale, which has been validated.[15,16] Scores of 8 or higher were defined as abnormal states of anxiety and depression.

Other questionnaires

Two questionnaires were used to identify daytime sleepiness. The Stanford Sleepiness Scale (SSS) was used to assess weekly awakening, classified into 1 to 7 points according to the degree of alertness.[17] The Epworth Sleepiness Scale (ESS) was used to assess weekly sleep overload in 8 situations where sleep occurs in everyday life. If a patient's total score on the ESS was higher than 10, he/she was classified as having persistent drowsiness.[18,19]

Obesity-related Parameters

We used the BMI, the waist-to-height ratio (WHR), and the waist circumference-to-height index (WHI, waist circumference/height^2 in cm/m^2) as tools to detect obesity. The WHR has been shown to be superior to the BMI and waist circumference for identifying cardiometabolic risk factors in both men and women,[20] while

Table 1. Demographics of the Study Subjects

Variables	OSA (n = 318)	Non-OSA (n = 84)	Total (N = 402)	*P*-value
Age (yr)	50.9 ± 12.6	45.7 ± 17.8	49.8 ± 14.0	0.016[a]
Sex				< 0.001[a]
Men	237 (74.5)	34 (40.5)	271 (67.4)	
Women	81 (25.5)	50 (59.5)	131 (32.6)	
Hypertension	105 (33.0)	19 (22.6)	124 (30.9)	0.066
DM	43 (13.5)	11 (13.1)	54 (13.4)	0.919
Alcohol	195 (61.5)	40 (47.6)	235 (58.6)	0.022[a]
Smoking				< 0.001[a]
Never	161 (50.6)	66 (78.6)	227 (56.5)	
Current	62 (19.5)	6 (7.1)	68 (16.9)	
Ex-smoker	95 (29.9)	12 (14.3)	107 (26.6)	
Aspirin	53 (16.7)	9 (10.7)	62 (15.5)	0.176
NSAIDs	22 (6.9)	7 (1.8)	29 (7.2)	0.661
Anti-anxiety drug	20 (6.3)	8 (9.5)	28 (7.0)	0.304
PPI	29 (9.2)	8 (9.5)	37 (9.2)	0.916
GERD	41 (12.9)	9 (10.7)	50 (12.4)	0.591
BMI (kg/m^2)	27.2 ± 4.3	23.3 ± 3.3	26.4 ± 4.4	< 0.001[a]
WHR	0.57 ± 0.06	0.52 ± 0.06	0.56 ± 0.07	< 0.001[a]
WHI (cm/m^2)	34.36 ± 4.68	32.03 ± 4.82	33.87 ± 4.80	< 0.001[a]
SSS score	2.55 ± 1.07	2.63 ± 0.92	2.56 ± 1.04	0.238
ESS score	9.49 ± 4.07	8.62 ± 3.98	9.31 ± 4.06	0.067
HADS				
Anxiety score	4.69 ± 3.75	6.43 ± 3.87	5.06 ± 3.84	< 0.001[a]
Depression score	5.99 ± 3.65	7.58 ± 4.29	6.32 ± 3.84	0.002[a]
AHI (events/hr)	35.45 ± 25.28	2.09 ± 1.44	28.48 ± 26.27	< 0.001[a]

[a]$P < 0.05$: statistical significance.
OSA, obstructive sleep apnea; DM, diabetes mellitus; PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; BMI, body mass index; WHR, waist-to-height ratio; WHI, waist circumference-to-height index; SSS, Stanford Sleepiness Scale; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; AHI, apnea-hypopnea index.
Data are presented as mean ± SD or n (%).

the WHI is a new index of abdominal obesity based on height in addition to waist circumference.[21]

Statistical Methods

The patient's categorical data are presented as mean ± standard deviation. Categorical variables were evaluated with chi-square tests or Fisher's exact test. Continuous variables were evaluated using *t* tests. Differences between GERD and controls were assessed using chi-square and *t* tests. Both univariate and multivariate analyses were performed to identify risk factors for GERD, with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). The level of statistical significance was $P < 0.05$ for all analyses.

Table 2. Clinical Characteristics of the Subjects According to Gastroesophageal Reflux Disease

Variables	OSA (N = 318)		*P*-value
	GERD (+) (n = 41)	GERD (−) (n = 277)	
Age (yr)	52.1 ± 11.2	50.7 ± 12.8	0.518
Sex			0.831
Men	30 (73.2)	207 (74.7)	
Women	11 (26.8)	70 (25.3)	
Hypertension	13 (31.71)	92 (33.2)	0.848
DM	8 (19.51)	35 (12.6)	0.229
Alcohol	22 (53.0)	173 (62.5)	0.365
Smoking			0.703
Never	22 (53.7)	139 (50.2)	
Current	9 (22.0)	53 (19.1)	
Ex-smoker	10 (24.4)	85 (30.7)	
Aspirin	4 (9.8)	49 (17.8)	0.200
NSAIDs	2 (4.9)	20 (6.3)	0.751
Anti-anxiety drug	3 (7.3)	17 (6.2)	0.732
PPI	9 (22.0)	20 (7.3)	0.006[a]
BMI (kg/m^2)	28.1 ± 4.4	27.0 ± 4.3	0.117
WHR	0.58 ± 0.07	0.57 ± 0.06	0.128
WHI (cm/m^2)	35.52 ± 5.12	34.19 ± 4.60	0.102
SSS score	3.00 ± 1.22	2.48 ± 1.03	0.004[a]
ESS score	11.71 ± 4.91	9.16 ± 3.83	0.001[a]
HADS			
Anxiety score	5.20 ± 4.00	4.62 ± 3.72	0.454
Depression score	8.05 ± 3.75	5.68 ± 3.54	< 0.001[a]

[a]$P < 0.05$: statistical significance.
OSA, obstructive sleep apnea; GERD, gastroesophageal reflux disease; DM, diabetes mellitus; PPI, proton pump inhibitor; BMI, body mass index; WHR, waist-to-height ratio; WHI, waist circumference-to-height index; SSS, Stanford Sleepiness Scale; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale.
Data are presented as mean ± SD or n (%).

Results

Baseline Characteristics

Among the 402 subjects who all underwent PSG, 318 (79.1%) had OSA. Of these patients, 74.5% were men (n = 237) and 25.5% (n = 81) were women. Table 1 shows the clinical characteristics according to the presence of OSA. Fifty subjects (12.4%) had reflux symptoms at least once a week. Forty-one patients with OSA (12.9%) and 9 patients in the non-OSA group (10.7%) had reflux symptoms, with the difference not being statistically significant ($P = 0.591$). Table 2 shows the clinical characteristics of the OSA according to the presence of GERD. Subjects with OSA with GERD had higher scores on the SSS than subjects with OSA without GERD (3.0 ± 1.2 vs 2.5 ± 1.0, $P = 0.004$). ESS scores were also much higher in patients with GERD than in patients without GERD (11.7 ± 4.9 vs 9.2 ± 3.8, $P = 0.001$). Depression scores were higher in patients with GERD than in patients without GERD (8.1 ± 3.8 vs 5.7 ± 3.5, $P < 0.001$). The prevalence of GERD did not correlate with OSA severity ($P = 0.608$) (Fig. 2).

Obesity-related Parameters in Gastroesophageal Reflux Disease With Obstructive Sleep Apnea

Patients with GERD had a higher BMI, WHI, and WHR than patients without GERD, there was no statistically significant difference. However, if the patient was classified based only on the nocturnal reflux symptoms regardless of GERD definition or other GERD symptoms, patients with OSA with nocturnal symptoms had a higher BMI, WHI, and WHR than patients with OSA

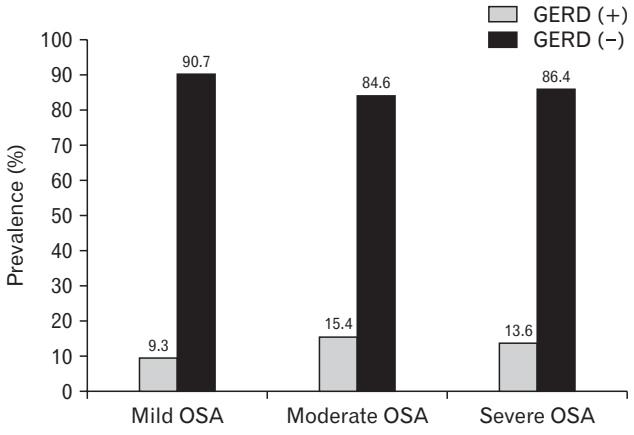

Figure 2. The prevalence of gastroesophageal reflux disease (GERD) according to obstructive sleep apnea (OSA) severity.

Table 3. Obesity-related Parameters According to the Presence of Nocturnal Reflux Symptoms in Patients With Obstructive Sleep Apnea

Variables	Nocturnal reflux symptoms[a]		Total (N = 318)	*P*-value
	(+) (n = 52)	(−) (n = 266)		
GERD	18 (34.6)	23 (8.7)	41 (12.9)	< 0.001[b]
BMI (kg/m^2)	28.2 ± 4.1	26.9 ± 4.3	27.2 ± 4.3	0.031[b]
WHR	0.59 ± 0.06	0.57 ± 0.06	0.57 ± 0.06	0.008[b]
WHI	35.48 ± 4.77	34.14 ± 4.65	34.36 ± 4.68	0.047[b]

[a]Nocturnal reflux symptoms was classified based only on the nocturnal reflux symptoms regardless of gastroesophageal reflux disease (GERD) definition or other GERD symptoms.
[b]$P < 0.05$: statistical significance.
BMI, body mass index; WHR, waist-to-height ratio; WHI, waist circumference-to-height index.
Data are presented as n (%) or mean ± SD.

Table 4. Risk Factors for Gastroesophageal Reflux Disease Among Obstructive Sleep Apnea Based on Logistic Regression Analyses

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
SSS score	1.47 (1.12-1.92)	0.005[a]	1.29 (0.95-1.75)	0.100
ESS score	1.15 (1.07-1.25)	< 0.001[a]	1.12 (1.03-1.22)	0.008[a]
Depression score	1.18 (1.08-1.29)	< 0.001[a]	1.16 (1.06-1.27)	0.001[a]

[a]$P < 0.05$: statistical significance.
SSS, Stanford Sleepiness Scale; ESS, Epworth Sleepiness Scale.

without nocturnal symptoms (Table 3).

Risk Factors for Gastroesophageal Reflux Disease in Patients With Obstructive Sleep Apnea

High scores of SSS, ESS, and depression were statistically significant risk factors for GERD in OSA by univariate logistic regression. Multivariate logistic regression then identified high ESS and depression scores as risk factors for GERD in OSA (Table 4).

Polysomnography Findings According to Gastroesophageal Reflux Disease Symptoms

There was no statistically significant difference compared to patients without GERD in study groups (Table 5).

Table 5. Polysomnographic Findings of the Study Groups According to the Presence of Gastroesophageal Reflux Disease

Variables	OSA (N = 318)		*P*-value
	GERD (+) (n = 41)	GERD (−) (n = 277)	
Minimum oxygen saturation (%)	77.7 ± 10.5	79.2 ± 8.6	0.567
Sleep period time (min)	396.1 ± 52.4	405.9 ± 57.7	0.429
Total sleep time (min)	333.3 ± 77.0	339.4 ± 65.6	0.826
Sleep efficiency (%)	81.1 ± 16.2	81.9 ± 13.4	0.814
N1 (%)	35.6 ± 18.9	33.9 ± 16.0	0.650
N2 (%)	44.6 ± 13.1	45.1 ± 12.5	0.947
N3 (%)	5.0 ± 6.8	5.2 ± 8.3	0.788
Arousal index	24.9 ± 28.0	21.3 ± 23.2	0.707
AHI (events/hr)	40.8 ± 30.6	34.7 ± 24.4	0.376

OSA, obstructive sleep apnea; GERD, gastroesophageal reflux disease; AHI, apnea-hypopnea index.
Data are presented as mean ± SD.

Discussion

This study revealed that the prevalence of GERD in patients with OSA was 12.9%. The prevalence of GERD did not correlate with OSA severity. We also found that daytime sleepiness and depression seem to be associated with GERD and nocturnal reflux symptom may be related to obesity in patients with OSA.

A study conducted in the USA showed that the severity of OSA does not correlate with the percentage of patients with GERD.[22] Another study has also failed to demonstrate that more severe OSA is associated with worse GERD,[23] with the authors suggesting that both diseases are common entities that share similar risk factors but are not causally linked. Contrary to these studies, a study in a Korean sample recently found that reflux esophagitis was associated with more severe OSA.[24] In 216 patients who underwent endoscopy and PSG, OSA parameters including AHI were found to be worse in the reflux esophagitis than in the no esophagitis group. In our study, about 75.0% of the subjects who underwent full overnight PSG had OSA, and 12.5% had of these GERD, similar to another study conducted in Korea, where 9.0% of patients who underwent PSG were found to have GERD.[25] A recent study with 1104 patients conducted in Turkey reported that 38.9 % had GERD (once a week of heartburn and/or regurgitation) in the OSA group, showing a higher prevalence of GERD with OSA compared with our study. However, non-OSAS group also had a prevalence of 32.0 %, which is not much different from the OSA group. Similar to our results, this study suggested that the prevalence of GERD between OSA and non-OSAS was not different

regardless of the different prevalence of GERD in the population.[26] One explanation for this difference might be differences in BMI: the low prevalence of GERD in our study might be related to the fact that our patient population was less obese than usual samples in other countries (mean BMI: 27.2 kg/m^2). Even though the prevalence of GERD is increasing in Asia, it is still higher in Western countries. In the above-mentioned study conducted in the USA, for example, GERD was found in 22.0% of 1023 subjects.[22]

In this study, obesity-related parameters including BMI, WHR, and WHI did not differ between in OSA patient with and without GERD. However, the obesity-related parameters were found to be higher in patients with nocturnal reflux symptoms. This suggests that obesity may be associated with nocturnal reflux symptoms. WHI, a new index of abdominal obesity, could be a more accurate risk factor for GERD than the BMI, since GERD seems to be more associated with abdominal obesity than with overall body fat. Another study also suggested that abdominal obesity could be an independent risk factor for reflux esophagitis.[27] In addition, visceral fat may increase the risk of reflux esophagitis through inflammatory cytokines.[28] Abdominal obesity rather than BMI could thus be a better tool for detecting GERD in Korea, where not many people are severely obese.

The scores of the SSS and ESS, the parameters used to evaluate daytime sleepiness in the current study, were higher in subjects with OSA with GERD than in subjects with OSA without GERD. In addition to the deterioration of sleep quality due to OSA, nocturnal reflux symptoms due to GERD might lead to daytime sleepiness. GERD has also been suggested to be associated with anxiety and depression.[29] The link between psychological distress, such as anxiety and depression, and GERD is complicated. Gastroesophageal reflux symptoms and psychological distress can affect each other. In other words, gastroesophageal reflux symptoms can aggravate psychological distress, but psychological distress can also provoke them. Furthermore, quality of life in GERD may be more related to anxiety and depression than to symptom severity.[12] Depression scores were significantly higher in the GERD group than in the non-GERD group, indicating a relation between depression and GERD. In a population-based study, the prevalence of GERD was significantly higher in patients with major depressive disorder, and a multivariate logistic regression analysis showed that major depressive disorders were significantly associated with GERD.[30] Sleep dysfunction, anxiety, and depression have all been associated with GERD, especially in non-erosive reflux disease (NERD).[31,32] In fact, anxiety and depression may play an important role in the occurrence of GERD, and especially in NERD.[33] A Taiwanese study also suggested that GERD increases the risks of depression, anxiety, and sleep disorders.[34] The evidence of the linkage between depression and OSA is however inconclusive. Some authors have reported that patients with OSA do not show a clinically significant degree of depression or have levels of depressive symptoms no higher than healthy controls.[35] Other authors have however found that OSA is associated with clinically significant depression.[36] Depression may also play an important role in non-adherence, with a recent meta-analysis finding that depression is associated with poor compliance to medications across a range of chronic conditions.[37] One postal survey of 178 established continuous positive airway pressure (CPAP) users found an association between depression scores and non-compliance to therapy.[38] In a recent study of 240 CPAP-naïve patients with OSA, depression was independently associated with poorer adherence during home-based auto-titrating continuous positive airway pressure therapy.[39] Poor adherence to CPAP therapy remains the greatest obstacle to the treatment of OSA. In patients with OSA with GERD, a high depression score can be a risk factor for non-compliance with CPAP adherence. Treatment of GERD in patients with OSA may thus be a potential target for clinicians to enhance adherence to CPAP therapy.

The strengths of the present study are as follows. First, we determined the prevalence of GERD in patients with OSA. Second, we tried to find out if there is a difference in the prevalence of GERD according to the severity of OSA patients. Third, it was suggested that there would be a relationship between nocturnal reflux symptoms and obesity related parameters. Finally, it was revealed that GERD and depression might be related in patients with OSA patients.

The current study has several limitations. Firstly, this was a retrospective analysis, and the results might have been affected by the biases and limitations of such studies. Secondly, the number of patients with GERD among the subjects who underwent PSG was small, which obviously limits the interpretation of the results. Thirdly, because we did not conduct endoscopy, we could not compare patients with GERD to other subgroups such as those with ERD and NERD. However, as endoscopy is not required for a GERD diagnosis, we used validated questionnaires to diagnose GERD and performed PSG for the OSA diagnosis. Finally, some of these persons who might be classified as non-GERD had real GERD. In this study, we could not to clarify the causative relationship between OSA and GERD. A prospective study is required on a large scale to verify the cause-and-effect relationship. Finally, some OSA patients with nocturnal reflux symptoms did not fulfill the definition of GERD of this study and these persons who were

classified as non-GERD might have possibility of real GERD.

Taken together, the present study does not show a relationship between the severity of OSA and the presence of GERD in a sample of patients. The presence of GERD and the severity of OSA did not correlate either. However, OSA and GERD seem to be linked indirectly, as we found 2 parameters of daytime sleepiness to be associated with GERD. Nocturnal gastroesophageal reflux symptoms seem to be related to obesity in OSA.

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Conflicts of interest: None.

Author contributions: Hyeon Hui Kang collected patients, analyzed the data, drafted the manuscript, tables, and figures, and approved the final version to be published; Chul-Hyun Lim analyzed the data, revised the manuscript, tables, and figures, and approved the final version; Jung Hwan Oh designed the study, analyzed the data, revised the draft, and approved the final version; Min-Jae Cho helped to analyze data, and approved the final version; and Sang Haak Lee collected patients and approved the final version.

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