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Modest Improvement of Untreated Severe Sleep-Disordered Breathing in the Middle-Aged and Elderly

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Objective It has been reported that untreated sleep-disordered breathing (SDB) deteriorates over time, however this remains contentious. The aim of the present study is to evaluate the clinical course of SDB in middle-aged and older SDB patients, and to identify how relevant factors contribute to the change in SDB severity.

Methods Baseline and follow-up polysomnographic data of 56 untreated SDB patients (mean age, 61.2±5.71) were obtained retrospectively and the mean interval was 62.4±22.0 months. Subgroup analysis was performed based on the baseline severity, and the factors associated with the course of SDB were analyzed.

Results At the baseline, 13 subjects were simple snorers, 15 had mild to moderate SDB, and 28 were severe SDB patients. While there was no significant change in apnea-hypopnea index (AHI) as a whole, subgroup analysis showed decrease of AHI in severe SDB patients (43.9±10.6 to 35.6±20.0, p=0.009). The change in supine time percent and baseline AHI were associated with the change in AHI (β=0.387, p=0.003; β=-0.272, p=0.037).

Conclusion Untreated SDB did not deteriorate over time with modest improvement in severe SDB. A proportion of severe SDB patients might expect decrease in SDB severity irrespective of changes in sleep position or body weight.

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Key Words Apnea-hypopnea index, Clinical course, Sleep position, Sleep-disordered breathing.

INTRODUCTION

Sleep-disordered breathing (SDB) is a common disorder affecting 9.0 to 15.0% of middle-aged adults,[1] and it is much more prevalent in elderly population, affecting 52.6 to 70.0% of men and 26.3 to 56.0% of women.[2,3] SDB is characterized by pharyngeal obstruction during sleep which causes recurrent cessation of breathing, and is associated with a wide range of co-morbidities, including hypertension, metabolic syndrome and cardiovascular diseases.[4-7] Long-term follow-up studies on such co-morbidities of SDB are mostly based on the assumption that the severity at the time of diagnosis does not change over time. However, previous studies reported conflicting results on the clinical course of SDB. Whether SDB progresses or not remains an important issue among clinicians and health care professionals, because the information on SDB evolution may be required to determine the long-term morbidity and mortality of individuals with SDB.

The majority of previous studies on the clinical course of SDB, either of general population[8-11] or clinical samples,[12-14] reported that untreated SDB has a tendency to deteriorate. However, there also have been considerable numbers of studies[15-17] that reported conflicting results, showing from long-term stability of the disease to improvement of SDB, especially in severe cases.

Confounding factors are assumed to be related with controversies in results of previous studies on the clinical course of SDB. Most of changes in SDB severity shown by previous stud-

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ies were significantly associated with weight change. Only two studies have reported that changes in weight did not influence the progression of SDB.[18,19] Caution also should be taken in interpreting studies on the clinical course of SDB due to variability in sleeping positions.[12,15,20] Given the role of supine position during sleep on the severity of upper airway resistance in SDB individuals,[21,22] the change in percentage of supine time between examinations is presumed to be considerably important in judging the evolution of SDB.

As such, the aim of the present study is to evaluate the clinical course of SDB in untreated middle-aged and older SDB patients, and to identify how relevant factors contribute to the change in SDB severity.

METHODS

Study design and subjects

This is a retrospective study, carried out at the sleep center of the Seoul National University Bundang Hospital. Patients who were diagnosed as SDB and did not receive treatment, were included if two overnight PSGs were conducted between 2004 and 2015. The patients went through two overnight PSGs in the process of recruitment for our previous study.[23] The interval between the two PSGs was at least 24 months, or longer. Subjects were not treated in the case of mild severity, intolerable discomfort of oral appliances or continuous positive airway pressure (CPAP) therapy, or refusal of treatment for other reasons. As we aimed to study the clinical course of SDB in middle-aged and elderly population, subjects who were under 45 years of age were excluded. Demographic and anthropometric data were obtained, such as height, weight, body mass index (BMI), waist and hip circumference and blood pressure. Information on sleepiness was obtained from the Epworth Sleepiness Scale (ESS). This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital. Informed consent was obtained from all individual participants included in the study.

Polysomnography

All subjects underwent laboratory overnight PSG (Embla™ N7000, Embla, Reykjavik, Iceland) with standard electrodes and sensors.[24] Electroencephalography electrodes were applied at O1/A2, O2/A1, C4/A1, and C3/A2. Two electrooculographies were applied at the sides of both eyes for recording vertical and horizontal eye movements. Electromyography electrodes were applied at the submentalis muscles and both anterior tibialis muscles. Strain gauges were applied at the chest and abdomen to record respiratory movements. Nasal pressure transducers were used to record airflow and pulse oximeters were applied on the index finger to measure the arterial oxygen saturation. The recordings were scored based on the standard criteria of Kales and Rechtschaffen.[25]

SBD-related variables

Apnea was defined as an episode of complete air flow cessation of at least 10 s. Hypopnea was defined as 50% or more reduction of airflow for at least 10 s, or moderate airflow reduction for at least 10 s accompanied by electroencephalographic arousal, or by oxygen desaturation (≥4%).[26] The severity of SDB was evaluated by apnea-hypopnea index (AHI), defined as the number of apnea and hypopnea events per hour. Subjects with AHI <15 were classified as simple snorers, subjects with AHI ≥15 and <30 were classified as having mild to moderate SDB, and subjects with AHI ≥30 were classified as severe SDB patients.[3,27] The change in AHI was calculated as the follow-up AHI-baseline AHI. The supine time % was calculated as [total supine time (min)/total sleep time (min)]×100. The change in supine time % was calculated as supine time % of the follow up-supine time % of the baseline.

Statistical analysis

The subjects' characteristics were expressed as mean±standard deviation (SD) for continuous variables, and as frequency or percentage for categorical variables. Differences in characteristics between the baseline and follow-up evaluations were assessed by paired t-test. One-way analysis of variance was used to compare characteristics between subgroups. Pearson's correlation analysis was performed to assess the association between the change in AHI and other variables. In order to evaluate which factor affects the change in AHI, multiple linear regression analysis was performed. Two-tailed p-values of less than 0.05 were considered to be statistically significant. All statistical analyses were conducted using the statistical software package, SPSS for Windows, version 22 (SPSS, Chicago, IL, USA).

RESULTS

A total of 56 middle aged to elderly subjects at the baseline (61.2±5.7 years) were included in this study, and 84% of them were male. The baseline demographic characteristics and polysomnographic data are summarized in Table 1. The mean AHI and BMI were 30.3±16.9 and 24.8±2.5. After a mean interval of 62.4±22.0 months (range from 26 to 110) between the baseline and follow-up PSG, we found no significant changes in AHI, supine AHI, oxygen desaturation index (ODI), BMI or minimal O_2 saturation. Supine time % (60.2±28.1 vs. 53.5±29.4) and ESS score (9.3±4.3 vs. 8.1±4.8) were significantly decreased at the follow-up evaluation. Thirteen subjects were simple snorers at baseline, but five of them were changed to

mild to moderate SDB at follow-up. Among the 15 mild to moderate SDB subjects at baseline, 4 were changed to simple snorers and 5 were changed to the severe SDB group. In the severe SDB group at baseline, 3 were changed to simple snorers, 10 were changed to the mild to moderate SDB group and 16 subjects remained in the severe SDB group.

In the subgroup analysis based on the severity of SDB in baseline, there were no difference in baseline age, proportion of male gender, weight, BMI, supine time %, ESS score, or interval between baseline and follow-up evaluation among the 3 groups (Table 2). The AHI of the severe SDB group decreased at the follow-up evaluation (43.9±10.6 vs. 35.6±20.0, p=0.009) (Figure 1) in the intra-group analysis, and the simple snorer group showed a tendency to deteriorate (p=0.079). However, supine AHI was not changed in any of the 3 groups.

The correlation analysis showed that the change in supine time % (R=0.424, p=0.001) and the baseline AHI (R=-0.323, p=0.015) (Figure 2) were significantly correlated with the change in AHI, but the follow-up duration (R=0.016, p=0.904) or baseline BMI (R=0.08, p=0.557) was not significantly correlated with changes in AHI. In addition, there was no significant association between the follow-up duration and the change in supine time % (R=-0.108, p=0.429). The result of the multiple regression analysis for the change in AHI is shown in Table 3. In the regression analysis, the change in AHI was found to be associated with the change in supine time % (β=0.387, p=0.003) and the baseline AHI (β=-0.272, p=0.037). The association with the change in BMI, baseline age, sex and the change in percentage of REM sleep were insignificant.

DISCUSSION

In the present study, 56 middle-aged and elderly SDB patients were followed-up over an average of 5.1 years, and we found that untreated SDB as a whole did not progress over time. However, the severe SDB group did improve and the mild SDB group showed a tendency to become aggravated over time in our subgroup analysis. The change in supine time %

Table 1. Comparison of demographic and polysomnographic data between baseline and follow up

	Baseline (mean±SD)	Follow up (mean±SD)	p-value
Age (yr)	61.2±5.71	66.0±5.63	<0.001
Sex (male/female)	47/9 (84%/16%)		
Follow up interval (mo)		62.4±22.0	
BMI (kg/m^2)	24.8±2.5	25.2±3.4	0.093
ESS score	9.3±4.3	8.1±4.8	0.037
AHI (events/h)	30.3±16.9	27.0±18.2	0.097
Severity			0.092
Simple snorer	13	15	
Mild to moderate	15	21	
Severe	28	20	
Supine AHI (events/h)	43.6±25.2	43.7±23.4	0.977
ODI (events/h)	22.7±15.8	21.5±18.3	0.444
Snoring (%)	31.3±21.3	25.1±20.0	0.039
Supine time (%)	60.2±28.1	53.5±29.4	0.048
Minimal SpO2 (%)	79.1±12.8	82.0±8.6	0.108
Sleep period time	442.2±46.8	449.2±37.6	0.366
Total sleep time	367.1±47.9	375.7±45.7	0.337
Sleep efficiency	81.3±62.1	80.4±49.2	0.604
Sleep latency	10.5±11.5	13.5±9.0	0.298
WASO	75.2±15.4	78.2±16.7	0.684
S1 (%)	16.0±8.6	13.9±7.8	0.086
S2 (%)	51.1±11.3	48.6±10.3	0.198
S3 (%)	2.2±4.1	4.6±6.4	0.007
REM (%)	14.2±5.7	16.6 ±7.2	0.027

Data are presented as mean±SD or frequency. BMI: body mass index, ESS: Epworth sleepiness scale, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, WASO: wake after sleep onset, S1: stage 1 sleep, S2: stage 2 sleep, S3: stage 3 sleep, REM: rapid eye movement sleep

and the baseline AHI were significantly associated with the change in AHI, but a minimal weight change did not predict SDB progression.

In contrast to the present study, many previous studies showed that SDB had a tendency to worsen over time. Large population based studies such as the Wisconsin Sleep Cohort,[11] the Sleep Heart Health Study,[8] and the Cleveland Family study[9] have demonstrated that SDB progressed over time. One other study, with 160 clinical subjects, also reported the deteriorative course of SDB.[12] The progression of SDB seen in these studies was greatly related to weight gain, and they all observed that weight gain played a critical role for longitudinal changes in the severity of SDB. Even studies that negated progressive deterioration of untreated SDB admitted that weight change affected the natural course of SDB.[16,17] Given the known relationship between body weight and severity of SDB from cross sectional studies,[27-29] it seems plausible that weight gain could exacerbate SDB over time. We found no significant association between weight change and the course of SDB, and it might be due to minimal weight changes displayed by our subjects (-0.19±2.69 kg; ranged -6.0 to 8.8 kg) during the observational period. On the other hand, several other studies have reported an in-

Table 2. Changes in clinical and polysomnographic parameters at baseline and follow up in 3 SDB severity groups

	Simple snorers, AHI <15 (N=13)	Mild to moderate SDB, 15≤ AHI <30 (N=15)	Severe SDB, AHI ≥30 (N=28)
Male, N (%)	13 (100)	11 (73.3)	23 (82.1)
Baseline age (yr)	60.4±4.6	61.1±4.6	61.6±6.8
Baseline weight (kg)	70.3±11.4	67.1±10.0	68.6±8.7
Interval (mo.)	62.2±22.0	60.6±21.1	63.4±23.1
BMI (kg/m)			
Baseline	24.8±2.7	24.0±2.3	25.3±2.4
Follow-up	26.1±5.1	24.0±2.6	25.5±2.7
p-value	0.177	0.893	0.300
AHI (event/h)			
Baseline	7.6±3.5	24.4±3.1	43.9±10.6
Follow-up	12.9±9.8	23.4±10.6	35.6±20.0
p-value	0.074	0.719	0.009
Supine AHI (event/h)			
Baseline	13.6±9.1	34.7±14.8	62.3±17.5
Follow-up	57.3±24.5	57.3±23.4	49.7±34.5
p-value	0.079	0.413	0.139
Supine time (%)			
Baseline	56.7±30.1	72.6±23.8	55.2±28.3
Follow-up	57.3±24.5	57.3±23.4	49.7±34.5
p-value	0.929	0.004	0.306
ODI (event/h)			
Baseline	4.4±2.7	17.9±6.0	33.7±13.7
Follow-up	7.6±6.7	17.4±9.6	30.1±20.8
p-value	0.080	0.844	0.193
REM (%)			
Baseline	17.5±6.3	14.4±6.1	12.6±4.6
Follow-up	14.8±8.1	19.0±6.8	16.1±6.9
p-value	0.186	0.037	0.019
ESS			
Baseline	10.3±4.4	7.3±5.4	9.9±3.4
Follow-up	10.1±4.9	5.5±3.4	8.5±4.9
p-value	0.869	0.043	0.125

Data are presented as mean±SD. SDB: sleep-disordered breathing, BMI: body mass index, AHI: apnea-hypopnea Index, ODI: oxygen desaturation index, REM: rapid eye movement sleep, ESS: Epworth sleepiness scale

significant relationship between weight change and SDB progression.[13,15,18,30] Several factors, other than fat deposition due to weight gain, have been suggested as a cause for the aggravation of SDB. These include local mechanical trauma,[30] pharyngeal nerve damage,[31] progressive loss of airway reflex,[32] pharyngeal muscle lesions[33] and ventilatory instability,[34] which all are considered to occur as a result of snoring.

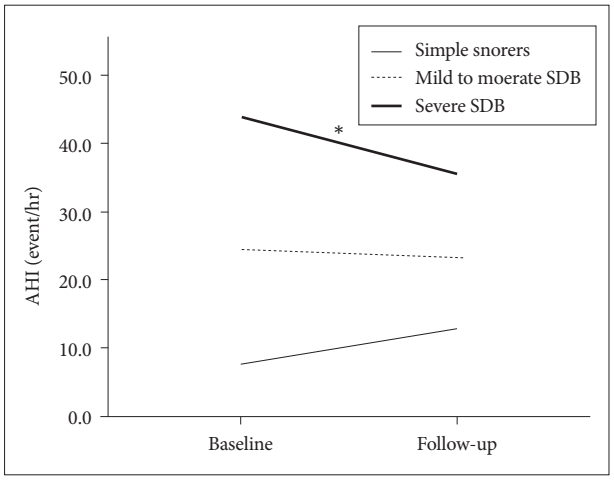

Figure 1. Changes in apnea-hypopnea index (AHI) between baseline and follow-up in 56 untreated sleep disordered breathing (SDB) patients. The AHI of severe SDB group significantly improved over time (p=0.009). *p-values less than 0.05.

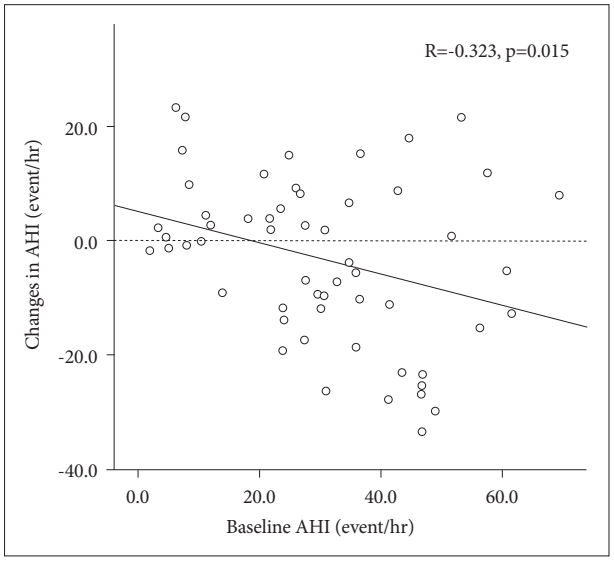

Figure 2. Correlation between the baseline apnea-hypopnea index (AHI) and the change in AHI.

In the present study, the severe SDB group improved significantly, and there was a trend of aggravation in simple snorers. This result is consistent with the majority of previous studies. Sforza et al.[19] clearly stated that they saw a negative correlation between the baseline respiratory disturbance index (RDI) and the change in RDI, and Fisher et al.[17] also reported that the improved group had significantly higher RDI at the baseline observation. It is also important to note that most studies supporting a natural worsening course of SDB studied subjects with a mild syndrome of disease at the baseline (AHI: 2.6−9.0). Considering the result of the present study and those of previous studies, it seems that mild SDB tends to worsen and severe SDB tends to improve over time. The mechanism of the progression and regression of SDB, according to baseline severity, remains uncertain. Anatomical and functional change of the upper airway, induced by chronic repetitive obstruction, could be part of the mechanism of deterioration of mild SDB patients.[35] If the increase in AHI reaches a critical point, the demand of the body to protect sleep from intolerable hypoxemia may prevent further exacerbation and preserve optimal ventilation.[36]

There is a possibility that improvement shown in the severe SDB patients in the present study was affected by the positional change between polysomnographic examinations. Supine time % was significantly decreased in the mild to moderate SDB group with the severe SDB group showing a weak tendency to decrease. It has yet to be determined that SDB patients show the change in sleeping position over time. Meanwhile, sleep position has been previously shown to either aggravate, or improve SDB. Lying in the supine position can increase the level of respiratory distress by 40 to 50%,[37,38] compared to lying in a lateral position due to the effect of gravity which narrows the pharyngeal cross-sectional area.[39,40] However, in the regression analysis of the present study, the baseline SDB severity was negatively associated with changes in

Table 3. Regression analysis of AHI changes

	Unstandardized B	Standardized β	p-value
Changes in supine time (%)	0.224	0.387	0.003
Baseline AHI (event/hr)	-0.230	-0.272	0.037
Changes in BMI (kg/m^2)	1.055	0.133	0.289
Age at baseline (yr)	-0.131	-0.052	0.672
Changes in REM (%)	-0.062	-0.034	0.794
Sex	0.335	0.009	0.943

AHI: apnea-hypopnea index, BMI: body mass index, REM: rapid eye movement sleep

SDB severity after controlling for the positional change.

There are several limitations to the current study. First, the present study included patients who visited a sleep clinic, and this might lead to selection bias reflected by a high proportion of severe and male cases. However, the result of this study could be still clinically meaningful as complications of SDB develop frequently and seriously in severe SDB. Second, the present study has a retrospective design, which limits the interpretation of this study in terms of the natural course of the illness. Third, changes in weight of the subjects were minimal to evaluate the effect of weight change on the long-term change of SDB.

In summary, untreated middle aged and elderly SDB patients did not deteriorate over a mean period of 5 years with modest improvement in severe SDB. The clinical course of SDB was associated with changes in supine time percent and the baseline SDB severity. There is a possibility that a proportion of severe SDB patients can expect improvement in SDB severity irrespective of changes in sleep position or body weight.

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