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Scientific Research

Significant Association of Nightly Nasal Continuous Positive Airway Pressure Using Time with Weight Change in Japanese Patients with Obstructive Sleep Apnea-Hypopnea Syndrome

Tsuguo Nishijima[1,2*], Sayaka Ishitoya[2], Tomomi Mikasa[2], Tetsuya Kizawa[1,2], Keisuke Hosokawa[1,2,3], Susumu Takahashi[1,2,3], Hiroshi Kagami[2], Akira Suwabe[3], Shigeru Sakurai[1]

[1]Division of Behavioral Sleep Medicine, School of Medicine, Iwate Medical University, Morioka, Japan
[2]Department of Respirology, Hachinohe Red Cross Hospital, Aomori, Japan
[3]Department of Laboratory Medicine, School of Medicine, Iwate Medical University, Morioka, Japan
Email: [*]tsuguo@ck9.so-net.ne.jp

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Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is one of the representative sleep disorders believed to be associated with metabolic syndrome. Nasal continuous positive airway pressure (nCPAP) ventilation is the first choice therapy for OSAS, which has been reported to cause an improvement in body fat mass, hepatocellular damage and hypertension. Study Objectives: We evaluated whether the changes in the body weight observed in patients with OSAS may have potential associations with the sleep time during which the patients are under nCPAP. Method: A total of 194 patients (148 obese and 46 non-obese) in whom nCPAP use was present for more than 70% of the nights were enrolled in this study. Using the electronic records of the night use time for CPAP devices, we examined whether the habitual sleep time during nCPAP is associated with changes in body weight. Results: In the non-obese OSAS group, the patients with night time use of nCPAP devices for 6 to 7 hours showed the greatest and the most sustained decrease in body weight. In the obese patients with OSAS, on the other hand, a U-shaped relationship has been demonstrated between a percent weight gain over 9 years and a minimal weight gain in patients with habitual sleep for 5 to 6 hours. Conclusions: These results suggest that changes in body weight in patients with OSAS are associated with habitual sleep time.

[*]Corresponding author.

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Keywords

Bodyweight, Obesity, CPAP, OSAS, Sleep Time during CPAP

1. Introduction

Obesity is one of the strongest risk factors for obstructive sleep apnea syndrome (OSAS) [1]. People of Asian origin, such as the Japanese, are likely to develop OSAS even with mild degrees of obesity, suggesting that, in addition to obesity, cranio-facial morphology is also an important contributor for the development of OSAHS [2]. Nasal continuous positive airway pressure (nCPAP) is considered to be the first-line therapy for OSAS as it is able to reduce the obstructive apneas and hypopneas during sleep. Over the last several decades, a large body of literature has accumulated indicating that nCPAP has favorable effects not only for daytime sleepiness, but also for hypertension [3]-[5], cardiovascular disease [6] [7] and glucose metabolism [8] [9].

A number of previous studies have shown that habitual sleep duration may be an important determinant of body weight with short sleep duration being an independent risk factor for obesity. Using data from the Nurses Health Study, Patel *et al*. [10] have reported that, compared to the subjects with a sleep duration of 7 hours per night, those with habitual short sleep duration (<5 hours per night) have a mean weight gain of 15 kg over 16-year period. Several other reports have also emphasized the public health relevance of short sleep duration and, in particular, its association with type 2 diabetes mellitus [8] [11] and hypertension [12] [13]. Interestingly, long sleep duration (>9 hours per night) has also been associated with a number of adverse health consequences including early mortality [14]-[17]. Despite the burgeoning evidence on the implications of short and long sleep duration, the implications of habitual sleep time in OSAS patients on nCPAP therapy has not previously characterized, particularly with regard to changes in body weight.

These findings suggest probable interactions among sleep time, sleep quality and changes in body weight. Therefore, we need to pay attention to obesity in OSAS patients not only as a cause but also as an outcome of OSAS. However, any reports are not available on relations between the use time for nCPAP devices and the changes in body weight. The present study focused on obesity and analyzed the relationships among the night wearing time for nCPAP devices, the time of sleep (estimated from daily recorded time) and the changes in body weight.

2. Materials and Methods

2.1. Subjects

This study involved 206 patients satisfying all of the following requirements: 1) OSAS diagnosed by overnight polysomnography (PSG) at the Sleep and Respiratory Disorders Clinic of Hachinohe Red Cross Hospital between January 20, 2001 and June 28, 2009; and 2) initiation of nCPAP therapy in accordance with the indications for CPAP therapy under the national health insurance system in Japan. A total of 194 patients (148 obese and 46 non-obese) in whom nCPAP use was present for more than 70% of the nights were selected for analysis in accordance with criteria described later. Patients at risk for changes in body weight or those with confounding medical conditions such as chronic obstructive pulmonary disease (COPD), diabetes mellitus (diabetes mellitus diagnosed based on International Diagnostic Criteria had been excluded) and malignancy were excluded from analysis. Consent to participate in the study was obtained in writing from all subjects. All diagnostic and therapeutic tests were conducted within the framework of routine clinical management. The study was approved by the Ethics Committee of Hachinohe Red Cross Hospital. This study was approved by the Ethics Review Boards of Hachinohe Red Cross Hospital, and written informed consent was obtained from all subjects.

2.2. Daytime Sleepiness Evaluation

The attending physician at the outpatient clinic of our hospital took a detailed disease history from each subject during the first visit and conducted a physical examination. Sleepiness was evaluated using the Epworth Sleepiness Scale (ESS).

2.3. Polysomnography Test

PSG was conducted with a Allis Sleepware v. 2.7.43 (Philips Respironics) program. All sleep studies were carried out in a special room of the Iwate Medical University Hospital equipped with an air conditioner. PSG was started at 8 pm. and ended at 6 am. the following morning. As far as possible, PSG was carried out under equal conditions in accordance with the American Academy of Sleep Medicine (AASM) Manual [18]. PSG at about 3 months after the start of nCPAP treatment was carried out under settings identical to the pre-treatment PSG except for use of the nCPAP device.

2.4. nCPAP Introduction and Titration

The nCAPA was prescribed with the REM star Auto M series (Philips Respironics, MA, USA) for OSAS patients whose AHI was 20 events/h or more, in accordance with the criteria for coverage by the national health insurance system of Japan. The auto-CPAP mode was adopted for pressure setting during the first 2 weeks of nCPAP. The optimum pressure level was estimated from the records of the on-board memory to modify the fixed pressure and to continue treatment under equal conditions.

2.5. Estimation of Habitual Sleep Duration

Each patient was surveyed to ascertain: a) average sleep latency, which was defined as the time to sleep onset after the application of nCPAP; b) the time from waking in the morning until removal of nCPAP. Habitual sleep duration was then determined by subtracting the total time awake from the average nightly use of nCPAP (hereinafter called “average usage”).

2.6. Percent Change in Body Weight (%Δkg)

The body weight of each patient at the first examination (baseline body weight) was subtracted from the body weight recorded at the end of August 2009 and was then divided by the baseline body weight, to yield the percent change in body weight (%Δkg). After the 13th month of initiating nCPAP, the %Δkg for each 6-month period was determined and associations with average nighttime nCPAP use and the duration of nCPAP use examined.

2.7. Statistical Analysis

The subjects were grouped according to sleep time (at intervals of one hour), to detect any possible relationship between sleep time and %Δkg. StatView5.0 (Abacus Concepts) was employed for statistical analysis. One factor ANOVA was used for comparison with the control group. $P < 0.05$ was regarded statistically significant.

3. Results

3.1. Selection of Patients for Analysis

All patients diagnosed as having OSAS were divided into two groups based on body mass index (BMI) at baseline on Japanese Diagnostic Criteria: the non-obese group (BMI < 25 kg/m^2, n = 51) and the obese group (BMI ≥ 25 kg/m^2, n = 155). Each group was further subdivided into two groups according to the percentage of days of nCPAP (%DDU) which was determined by the following equation: (days of device usage/total therapy days) ×100. In the non-obese group, 46 patients were in the %DDU ≥ 70% group and 5 patients were in the %DDU < 70% group. In the obese group, 148 patients were in the %DDU ≥ 70% group and 7 patients were in the %DDU < 70% group. To eliminate the influence of the frequency of device usage, %DDU ≥ 70% was defined as acceptable usage and changes in body weight were examined in these patients only (**Table 1**).

3.2. Duration of nCPAP Use and Change in Body Weight (%Δkg)

In the non-obese group, no significant associations were noted between Δkg and total therapy days. (**Figure 1(a)**) Specifically, BMI remained within the range of ±2 SD in all patients regardless of the nCPAP usage period. In the obese group, however, BMI decreased significantly within 1.5 years after of the initiation of nCPAP therapy but showed no significant change during the subsequent follow-up (**Figure 1(b)**).

Table 1. Characteristic of the subjects and PSG data.

	Obese with OSAS group	Non-obese with OSAS group	P-value
N	148	46	NS
Age (year)	56.7 ± 1.0	62.8 ± 1.6	NS
BMI (kg/m^2)	29.2 ± 4.2	22.5 ± 1.3	<0.0001
ESS	12.7 ± 0.3	11.5 ± 1.8	NS
TST(min)	333.5 ± 13.5	317.0 ± 14.7	NS
%Stage N1 (%)	45.5 ± 2.9	36.7 ± 3.1	<0.05
%Stage N2 (%)	38.5 ± 2.5	45.7 ± 2.8	NS
%Stage N3 (%)	1.0 ± 0.3	0.9 ± 0.5	NS
%Stage R (%)	14.7 ± 1.1	16.4 ± 1.2	NS
AHI (events/hr)	51.5 ± 2.7	37.7 ± 2.4	<0.0001
Arousal index (events/hr)	44.5 ± 3.1	31.8 ± 15.8	<0.005

Data are shown as mean ± S.D., NS = Not significant; OSAS = Obstructive sleep apnea hypopnea syndrome; ESS = Epworth sleepiness scale; TST = Total sleep time; REM = Rapid eye movement; SpO_2 = Oxygen saturation of peripheral artery; AHI = Apnea hypopnea index.

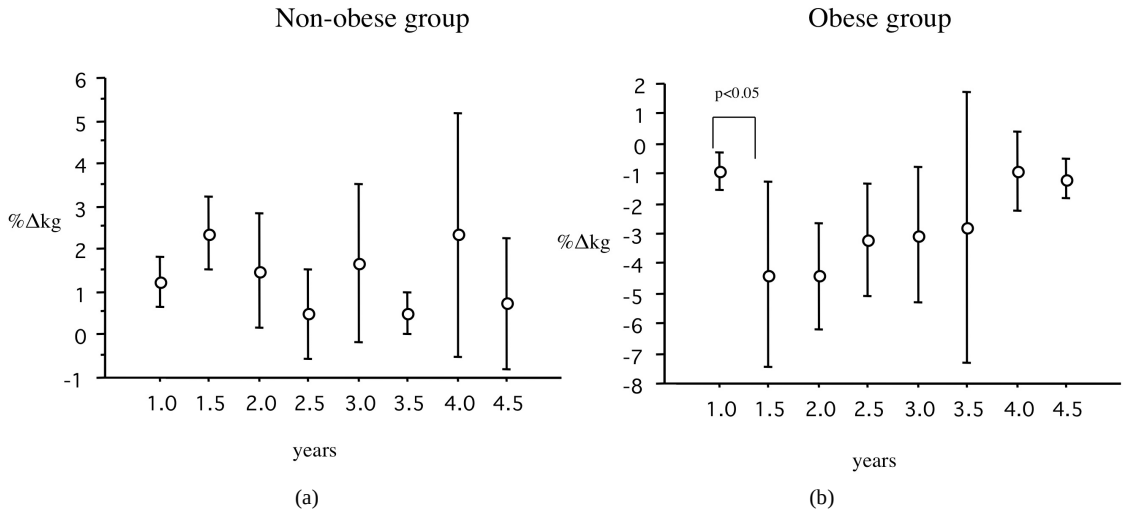

Figure 1. %Δkg: The percent change in body weight, the non-obese group (BMI < 25 kg/m^2) obese group (BMI ⩾ 25 kg/m^2).

3.3. Hours of nCPAP Use and Change in Body Weight (%Δkg)

In the non-obese group, percent change in body weight was 9.3 ± 1.6%Δkg for patients with a sleep time on nCPAP (ST-CPAP) of less than 4 hours (ST-CPAP < 4 hr). Weight change as a function of sleep time on nCPAP was as follows: a) 7.2 ± 2.9%Δkg with nCPAP sleep time of 4 - 5 hours; b) 0.7 ± 1.2%Δkg with nCPAP sleep time of 5 - 6 hours; c) 0.3 ± 1.2%Δkg with nCPAP sleep time of 6 - 7 hours; d) 1.2 ± 1.0%Δkg with nCPAP sleep time of 7 - 8 hours and e) 3.2 ± 1.7%Δkg with nCPAP sleep time of greater than 8 hours. As compared to the %Δkg in the ST-CPAP < 4 hr group, the percent changes in body weight were significantly smaller in the 5 hr ≤ ST-CPAP < 6 hr group ($p < 0.005$), the 6 hr ≤ ST-CPAP < 7 hr group ($p < 0.005$), the 7 hr ≤ ST-CPAP < 8 hr group ($p < 0.0001$) and the 8 hr ≤ ST-CPAP group ($p < 0.05$). As compared to %Δkg in the 4 hr ≤ ST-CPAP < 5 hr group, percent changes in body weight were significantly smaller in the 5 hr ≤ ST-CPAP < 6 hr group, the 6 hr ≤ ST-CPAP < 7 hr group and the 7 hr ≤ ST-CPAP < 8 hr group (each $p < 0.05$). There was no significant difference in %Δkg between any two of the 5 hr ≤ ST-CPAP < 6 hr, 6 hr ≤ ST-CPAP < 7 hr and 7 hr ≤ ST-CPAP < 8 hr groups.

Significant weight loss was noted when sleep time on nCPAP was in the following ranges: 5 hr ≤ ST-CPAP < 6 hr, 6 hr ≤ ST-CPAP < 7 hr and 7 hr ≤ ST-CPAP < 8 hr. Percent change in body weight (%Δkg) was the largest

when the range was 6 hr ≤ ST-CPAP < 7 hr. %Δkg was smallest when the range was ST-CPAP < 4 hr. %Δkg did not differ significantly between the ST-CPAP < 4 hr group and the 4hr ≤ ST-CPAP < 5 hr group or the 8hr ≤ ST-CPAP group (**Figure 2(a)**).

In the obese group, %Δkg was the greatest (5.6 ± 1.1%Δkg) when ST-CPAP was over 8 hr (8 hr ≤ ST-CPAP) and weight gain was also noted when ST-CPAP was less than 4 hr (3.3 ± 1.81%Δkg). As compared to the %Δkg in the ST-CPAP < 4 hr group, %Δkg was significantly smaller in the 4 hr ≤ ST-CPAP < 5 hr group (−3.3 ± 1.7%Δkg, $p < 0.05$), the 5 hr ≤ ST-CPAP < 6 hr group (4.1 ± 1.1%Δkg, $p > 0.05$) and the 6 hr ≤ ST-CPAP < 7 hr group (−2.5 ± 0.8%Δkg, $p < 0.05$), and tended to be smaller in the 7 hr ≤ ST-CPAP < 8 hr group though the difference was not statistically significant (−0.8 ± 1.1%Δkg, $p > 0.05$). In both the obese and the non-obese group, %Δkg was distributed along the U-shaped curve with the maximum percent reduction (lower end) located at 5 hr ≤ ST-CPAP < 6 hr (**Figure 2(b)**).

4. Discussion

In the study by Peppard *et al*. [19], a 10% weight gain during 4 years increased the apnea/hypopnea index (AHI; an indicator of the severity of OSAS) by 32% while a 10% weight loss reduced AHI by 26%. Also they reported that a 10% weight gain caused a 6-fold increase in the probability of an AHI increase over 15 events/hr. Weight loss is therefore a valid means of treating OSAS. It is estimated that body weight needs to be reduced by 20% to reduce AHI by 50%. Interestingly, in the Wisconsin sleep cohort, Peppard *et al*. reported that a 10% - 20% weight loss was achieved only by 3% of the cohort. These results indicate that treatment of OSAS solely on weight loss is difficult in clinical practice. Thus, while associated with a myriad of beneficial effects, weight loss is perhaps not practical as a sole means for managing patients with OSAS. In this study there was the significant

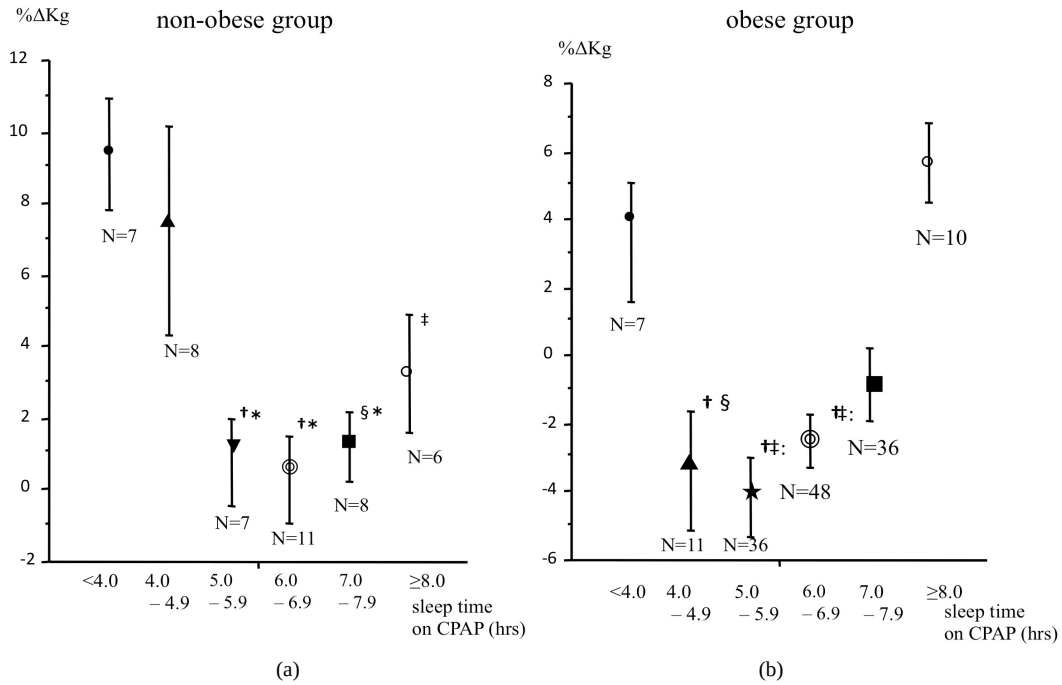

Figure 2. Hours of CPAP use and change in body weight. (a): Significance of differences in percent change in body weight relative to the group with sleep time less than 4 hours (‡: $p < 0.05$, †: $p < 0.005$, §: $p < 0.001$). Comparison of each group with the 4.0 ≤ Sleep time < 5.0 group (*: $p < 0.05$). (b): Significance of differences in body weight changes relative to the group with sleep time less than 4 hours (†: $p < 0.05$). Significance of differences in body weight changes relative to the group with sleep time less than 8 hours(§: $p < 0.05$, ‡: $p < 0.01$). %Δkg: The percent change in body weight. Sleep time on nCPAP (ST-CPAP) = C − (A+B): Each patient was interviewed as to the time from nCPAP application until falling asleep on a representative day during the therapy (A) and the time from waking in the morning until removal of the nCPAP device (B). A + B was subtracted from average device usage time (C, hereinafter simply called "average usage") to yield the sleep time on nCPAP per day (hereinafter called "sleep time").

difference in weight loss in non-obese OSAS patients by securing a sufficient sleep time, but only a slight weight loss was recognized in obese OSAS patients.

According to a number of recent reports [20] [21], habitual sleep time is shorter in obese than in non-obese individuals, and insufficient sleep may well promote obesity. It is also known that obese individuals are more likely to have daytime sleepiness regardless of the presence/absence of OSAS [22]. These findings suggest that there are probably interactions among sleep time, sleep quality and changes in body weight. Therefore, it is certainly possible that in OSAS patients, obesity is not only a cause but also as an outcome of the disease. It is well established that visceral fat accumulation is significantly correlated with OSAS severity, as assessed by the AHI [23]. There are also data showing that nCPAP therapy may significantly reduce the amount of visceral fat without changing body weight [24], suggesting a bi-directional association between OSAS and obesity

To data, however, very few reports have focused on the impact of sleep quality on body weight changes in patients with OSAHS treated with nCPAP therapy. In the present study, we examined the absolute and percent changes in body weight as a function both of the sleep time and the night wearing time for nCPAP devices, which were obtained by interviewing OSAS patients. The impact of habitual sleep duration is becoming clear. Kojima *et al*. [25] conducted a follow-up of 5322 inhabitants of Gifu Prefecture in Japan for a mean period of 11.9 years and analyzed the death rate in relation to sleep patterns (including sleep time). In their study, the risk for death was significantly higher in males reporting sleep time to be over 8 hours or less than 7 hours as compared to those whose reported sleep time was 7 - 8 hours, while no such tendency was noted in females. A 16-year follow-up survey of 68,183 female nurses in the USA had also shown that mean body weight was 1.14 kg greater in those subjects whose sleep time was below 5 hours than in those with sleep time below 7 hours, 0.71 kg greater in the group with a sleep time of 6 hours than in that with a sleep time of 7 hours, and differed little among the groups with sleep times of 8, 9 and 7 hours. The percentages of females recording a 15 kg or more weight gain during the 16-year period were 1.28 and 1.11 times higher in the group with sleep time below 5 hours than in those with sleep times of 7 hours and 6 hours, respectively, while the percentage did not differ among the groups with sleep times of 7, 8 or 9 hours. Based on these results, the investigators suggested that insufficient sleep is associated with weight gain and obesity [10]. The results in our present study are considered to strongly support their observation. However in this study do not check quality of sleep by formal polysomnogrphy. Our study intends for OSAS of the good control of nCPAP. Sleep time and quality of the sleep may participate in a weight loss.

There is also reportedly a higher risk for heart diseases if sleep time per night is less than 7.5 hours [26]. Within the framework of a cohort study (Coronary Artery Risk Development in Young Adults: CARDIA), Knutson *et al*. [27] evaluated sleep time and quality using data collected with an Actigraph during a 5-year period from 578 individuals who were 33 - 45 years of age at the start of the study. They additionally compared blood pressure at 5 years after the start of the study with the baseline blood pressure. The percentage of individuals who developed hypertension was higher in the group in whom the sleep time had been relatively short for 5 years or longer, thus indicating that shortening of sleep time raised the risk for hypertension. The percentage of individuals who developed hypertension was 37% higher in the group with a sleep time of 5 hours than in that with a sleep time of 6 hours.

Our study results suggest that an OSAS-associated reduction in sleep quality can have potential effects on body weight. If high compliance with nCPAP is ensured for patients with OSAS, we may also expect favorable effects on hypertension and a reduction in the total death rate from OSAS [28]. Burazeri *et al*. [29] showed that death rate (particularly from cardiovascular events) was high in the long sleep group (over 8 hours). In the present study, it was shown that even if the quality of daily sleep is improved by nCPAP therapy, insufficient sleep or excessively long sleep can cause weight gain or suppress the effect of nCPAP therapy in preventing weight gain, possibly leading to exacerbation of obesity. This finding is quite akin to the aforementioned findings of the general population survey conducted by Burazeri *et al*.

And no association was noted between the duration of nCPAP use and absolute percent change in body weight (%Δkg) in our study. Instead, sleep time on nCPAP appeared to be associated with changes in body weight. These results suggest that in the non-obese group, weight loss may be unlikely if sleep time is less than 5 hours. The results suggest that in obese patients with OSAS, absolute and percent weight gain are smallest when sleep time is over 5 hours but is less than 6 hours and that sleep of less than 4 hours or over 8 hours may lead to weight gain.

Exacerbation of obesity can contribute to raising the death rate from OSAS via its impact on health-related

complications. In the present study, %Δkg was larger in obese patients with OSAHS receiving nCPAP therapy that had relatively long sleep times. Thus, if a long-term prospective survey of individuals grouped by sleep time is performed, it might allow the interactions among sleep time, obesity and cardiovascular events to be elucidated.

Our study did not involve direct evaluation of habitual sleep duration. However, because analysis of data in the present study was confined to those patients in whom nCPAP usage was frequent, it was possible to objectively judge from the available data that these patients were receiving nCPAP consistently. Furthermore, it was possible for us to confirm by overnight polysomnography that the quality of sleep improved following the start of nCPAP therapy. We may therefore say that objectivity was also assured to some degree in the present study regarding the assessment of sleep quality and time.

When dealing with OSAHS, it is not practical to simply implement measures aimed at resolving obesity as the therapy of first choice. Instead, nCPAP therapy, capable of rapidly resolving apnea-hypopnea events (a fundamental feature of OSAHS), may be viewed as indispensable in the treatment of OSAHS. However, inappropriate application of nCPAP therapy disregarding the quality of sleep or its irrational extension may lead to an intractable disease course. To facilitate control of obesity and early weaning from nCPAP therapy, it seems essential to provide appropriate guidance to individual patients based on objective data demonstrating patient adherence to this therapy.

5. Limitations of This Study

Because the sample size in this study was too small to strengthen our conclusion, it is necessary to conduct a large-scale multi-institutional joint study. In addition, it is necessary to evaluate parallel changes in an AHI score and in a body weight before and after an intervention by nCPAP. An evaluation including life styles of the patients such as a meal or an exercise also needs to be performed in the future.

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