Nasal CPAP Improves the Quality of Life and Lessens the Depressive Symptoms in Patients with Obstructive Sleep Apnea Syndrome

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Abstract

Objective **To assess changes in response to nasal continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea syndrome (OSAS) concerning excessive daytime sleepiness (EDS), depressive state, and quality of life (QOL).**

Patients and Methods **We assessed for EDS using the Epworth sleepiness scale (ESS), for mood using The Zung self-depression scale (SDS), and for QOL using Short-Form 36 (SF-36) in 132 patients with obstructive sleep apnea syndrome (OSAS) and control subjects. Patients had severe OSAS (apnea-hypopnea index, 59.4±23.8/h) and were more hypersomnolent and depressed, and had poorer QOL than 38 age- and gender-matched controls.**

Results **Before treatment most QOL domains in the SF-36 were significantly associated with patients' SDS scores. With nasal CPAP, ESS and SDS scores were respectively decreased from 9.7±4.5 to 4.0±2.4 ($p<0.0001$) and from 49.2±10.4 to 45.1±9.6 ($p<0.0005$). Total SF-36 score and scores for seven of eight domains were increased significantly with treatment. Thus, nasal CPAP lessens EDS and depression, and improves QOL, in patients with severe OSAS. Further, magnitudes of changes in total SF-36 scores and in five of eight domains correlated significantly with magnitude of change in SDS score upon nasal CPAP treatment. No relationship was evident between treatment-associated score changes in SF-36 domains and ESS score change.**

Conclusion **Although patients with severe OSAS have poorer QOL than control subjects, nasal CPAP appears to improve QOL by alleviating depression.**
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Key words: obstructive sleep apnea syndrome, nasal continuous positive airway pressure, excessive daytime sleepiness, Epworth sleepiness scale, self-rating depression scale, quality of life

Introduction

Obstructive sleep apnea syndrome (OSAS) is a disorder in which patients repeatedly stop breathing during sleep, causing pathophysiologic changes that affect the neuropsychological and cardiovascular systems (1). These repeated episodes of apnea disrupt sleep continuity, cause multiple electroencephalographic arousals, and adversely impact sleep architecture (2). Patients with OSAS therefore may develop a number of problems related to neuropsychological functions. Several reports have demonstrated relationships between OSAS and neuropsychological and functional deficits (3–12), including excessive daytime sleepiness (EDS) (3–6), depression (7–9), and decreased quality of life (QOL) (10–12). Recently we reported that patients with severe OSAS have poor QOL and show depressive symptoms that appear to impair QOL to a far greater extent than does EDS (13).

Nasal continuous positive airway pressure (CPAP) has been the first-line treatment for OSAS for many years (14, 15). Several studies have shown that nasal CPAP decreases EDS (16–18), while improving neuropsychological function (19–21) and QOL (22–24). In a randomized, controlled trial, Jenkinson et al (18) demonstrated the beneficial effects of nasal CPAP on EDS and QOL in patients with OSAS. Millman et al (21) reported that 11 OSAS patients with depression who were treated with nasal CPAP showed significant improvement in depression scale scores. Considering the QOL improvement of patients with OSAS, 29 patients with OSAS were studied prospectively during treatment with

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nasal CPAP by D'Ambrosio et al (22), who assessed QOL effects using the Medical Outcome Study Short Form (SF) 36 (25). All SF-36 domains were improved after 8 weeks of treatment with nasal CPAP. Bennett et al (24) similarly demonstrated that 4 weeks of nasal CPAP treatment improved QOL as measured by the SF-36, and found that this improvement was correlated with sleep fragmentation severity. However, the correlation observed was not robust, and associations between improvements of EDS, neuropsychological deficits, and QOL are not fully understood with respect to CPAP treatment in patients with OSAS. We recently demonstrated a significant correlation between QOL compromise and depression before treatment in patients with severe OSAS (13). We presently set out to assess the effects of nasal CPAP on EDS, neuropsychological functions, and QOL, with special attention to how changes were related to one another.

Subjects and Methods

One-hundred-thirty-two consecutive patients who were diagnosed with OSAS by polysomnography (PSG) and were candidates for nasal CPAP treatment were included in this study. Our entry criteria were an apnea-hypopnea index (AHI) of greater than 20/h accompanied by EDS. These criteria are those by which the Japanese national health insurance program authorizes use of nasal CPAP. No patients had chronic lung disease, and none were receiving bronchodilator therapy. All patients gave informed consent for this study which was approved by the Human Research Committee of Nihon University School of Medicine. PSG consisted of a continuous recording of an electroencephalogram (EEG), electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), airflow at the nose and mouth (thermister), movements of the chest and abdomen (inductance plethysmography), and oxyhemoglobin saturation (SaO_2) by pulse oximetry. Analysis and interpretation of PSG data followed standard techniques (26). Apnea was defined as cessation of airflow at the nose and mouth lasting at least 10 seconds. Hypopnea was defined as a decrease in airflow, and in rib cage excursions exceeding 50%, associated with an oxygen saturation at least 4% below the preceding baseline value (27). The AHI was calculated as the number of apneic and hypopnea events per hour of sleep. Mean and minimum SaO_2 also were calculated from the PSG data.

Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS), a well-validated eight-item self-completion questionnaire (28). Patients were asked to score the likelihood of falling asleep in eight different situations with different levels of stimulation, resulting in a final score of 0 (least sleepy) to 24 (most sleepy).

QOL was assessed using SF-36 questionnaires (25). In a preparatory longitudinal cohort study of several health-status measures, the SF-36 showed the best reliability, validity and sensitivity for patients with OSAS (29). The SF-36 is a 36-item questionnaire that measures physical functioning (PF), role limitations imposed by physical problems (RP), bodily pain (BP), general health perceptions (GHP), vitality (VT), social functioning (SF), role limitations imposed by emotional problems (RE), and mental health (MH). Raw scores for each subscale were transformed to percentage scores (0% to 100%), according to a recommended formula (25): percentage score=[(raw subscale score – lowest possible score)/possible score range] ×100. In all instances, a higher score indicated a better health status.

We used Zung's self-rated depression scale (SDS) (30) to assess depressive state. This inventory has 20 items concerning various symptoms of clinically significant depression. Each item has a four-point range, and the items are balanced for yes/no tendencies. We chose this instrument for several reasons. As a self-report measure with an established degree of subject acceptability, it was practical for repeated use. Of particular relevance, the SDS has been used widely in various patient groups and in healthy persons, providing considerable validation data as well as a large number of comparison groups to aid in interpretation of results. SDS scores reported here were obtained, as outlined by Zung (31), by multiplying raw scores (potentially ranging from 20 to 80) by 1.25 to yield results between 25 and 100.

For comparison, 38 age- and gender-matched controls were also assessed using the ESS, the SF-36 for QOL, and the SDS. Controls were selected from among persons undergoing a routine annual health checkup at our hospital who had no symptoms suggestive of OSAS such as loud snoring, EDS, or respiratory abnormalities during sleep. However, PSG was not performed on controls.

Nasal CPAP for OSAS patients was titrated to completely abolish snoring and apnea, and to maintain an SaO_2 above 90% during sleep. Nasal CPAP titration studies showed that the AHI, the arousal index, the mean SaO_2 and the lowest SaO_2 were 4.2±3.1/h, 12.1±8.2/h, 96±2%, 90±5%, respectively. The patients were instructed to use nasal CPAP at the titrated pressure during sleep every night for more than 4 hours. After 8 weeks of nasal CPAP treatment, the adherence to treatment based on patients' self-reports was checked, and the ESS, SF-36, and SDS were readministered.

Results are presented as the mean±standard deviation (SD). Group differences were assessed with unpaired t- tests and the changes after treatment were assessed with paired t-tests. We also determined the Pearson linear correlation between certain variables. A p value below 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics of patients and normal controls are shown in Table 1. The mean age of patients was 48.8± 11.9 years. While age did not significantly differ between patients and controls, patients were more obese (in terms of body mass index or BMI) than controls. The patients were considered to have severe OSAS, and they were more hyper-

Table 1. Baseline Characteristics of Subjects

	Patients	Controls	p
Number of participants	132	38	
Male/female, number	124/8	35/3	
Age, years	48.8±11.9	45.8±11.2	NS
BMI, kg/m^2	28.3±4.3	23.5±3.2	<0.0001
ESS score	9.7±4.5	5.0±2.1	<0.001
SDS score	49.2±10.4	43.2±7.5	<0.001
AHI, per h	59.4±23.8		
Arousal index, per hour	47.2±19.6		
Mean SaO_2, %	90.9±4.9		
Lowest SaO_2, %	68.0±11.1		

Data are presented mean±SD. BMI: body mass index, ESS: Epworth sleepiness scale, SDS: self-rating depression scale, AHI: apnea-hypopnea index.

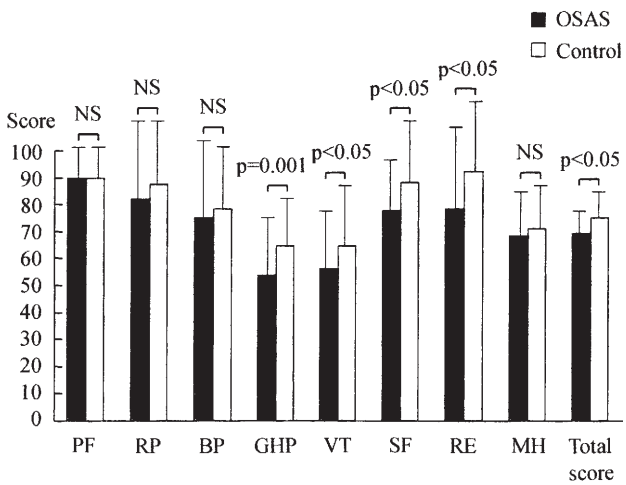

Figure 1. Comparisons of untreated patients with controls for total SF-36 and individual domains. SF-36: Short Form 36, OSAS: obstructive sleep apnea syndrome, PF: physical functioning, RP: role limitations imposed by physical problems, BP: bodily pain, GHP: general health perceptions, VT: vitality, SF: social functioning, RE: role limitations imposed by emotional problems, MH: mental health, NS: not significant.

somnolent and showed more depressive tendencies than normal controls.

In the SF-36 pretreatment, patient scores for the GHP, VT, SF, and RE domains as well as the total score were significantly lower than scores of controls, while RF, RP, BP, and MH did not differ significantly between these groups (Fig. 1). Six of eight domains (PF, BP, GHP, VT, SF, and RE) and total score on the patients' baseline SF-36 correlated negatively with SDS (Table 2). ESS did not correlate with any SF-36 domains (Table 3), although it did correlate with mean SaO_2. As for the relationship between SF-36 domains and severity of OSAS, only RP correlated significantly with AHI ($r=-0.225$, $p<0.01$) while GHP correlated with mean SaO_2 ($r=0.185$, $p<0.05$).

Table 2. Correlations between SDS Score and SF-36 before Treatment

Variable	Regression coefficient	p value
PF	–0.352	0.0001
RP	–0.145	0.1246
BP	–0.286	0.0020
GHP	–0.533	<0.0001
VT	–0.535	<0.0001
SF	–0.335	0.0003
RE	–0.405	<0.0001
MH	–0.615	<0.0001
Total SF-36	–0.632	<0.0001

SDS: self-rating depression scale, SF-36: Short Form 36, PF: physical functioning, RP: role limitations imposed by physical problems, BP: bodily pain, GHP: general health perceptions, VT: vitality, SF: social functioning, RE: role limitations imposed by emotional problems, MH: mental health.

Table 3. Correlations between ESS and SF-36 before Treatment

Variables	Regression coefficient	p value
PF	–0.141	0.1093
RP	–0.143	0.1042
BP	–0.109	0.2164
GHP	–0.146	0.0970
VT	–0.155	0.0765
SF	–0.126	0.1514
RE	–0.104	0.2365
MH	–0.011	0.8990
Total SF-36	–0.149	0.0889

ESS: Epworth sleepiness scale, SF-36: Short Form 36, PF: physical functioning, RP: role limitations imposed by physical problems, BP: bodily pain, GHP: general health perceptions, VT: vitality, SF: social functioning, RE: role limitations imposed by emotional problems, MH: mental health.

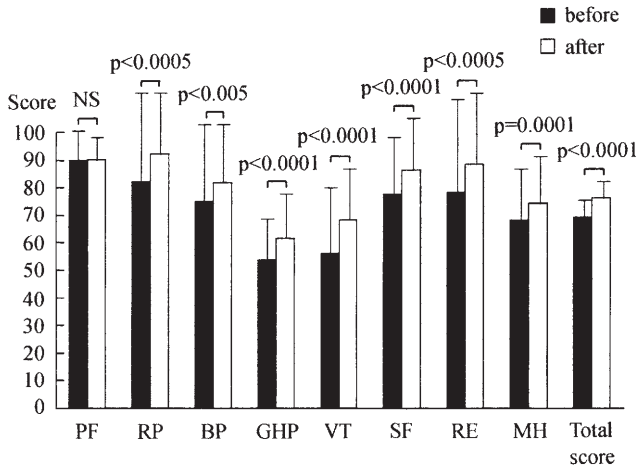

Figure 2. Patient SF-36 and domains scores before and after 8 weeks of nasal CPAP treatment. SF-36: Short Form 36, CPAP: continuous positive airway pressure, PF: physical functioning, RP: role limitations imposed by physical problems, BP: bodily pain, GHP: general health perceptions, VT: vitality, SF: social functioning, RE: role limitations imposed by emotional problems, MH: mental health, NS: not significant.

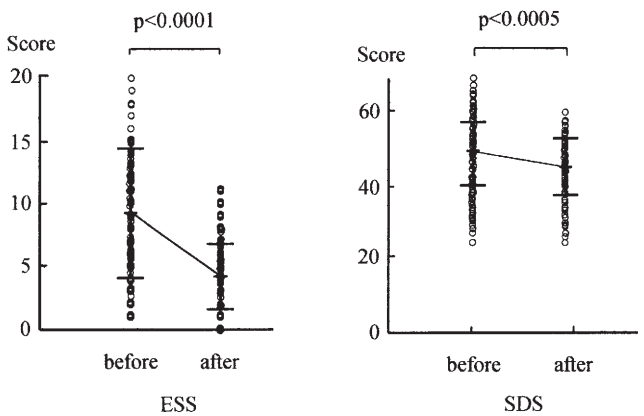

Figure 3. Patient ESS and SDS score before and after 8 weeks of nasal CPAP treatment. ESS: Epworth Sleepiness Scale, SDS: Self-rating Depression Scale, CPAP: continuous positive airway pressure.

The effects of nasal CPAP treatment on QOL are shown in Fig. 2. The total SF-36 score and all domain scores except for PF had improved significantly after 8 weeks of nasal CPAP treatment. Other variables also showed changes: ESS was significantly reduced after treatment from 9.7±4.5 to 4.0±2.4, and the SDS score also had decreased significantly from 49.2±10.4 to 45.1±9.6, as shown in Fig. 3. The magnitude of improvement (changes after treatment; ΔQOL) in five of eight SF-36 domains (PF, GHP, VT, SF, and MH) total SF-36 score were correlated significantly with magnitude of improvement in SDS (changes after treatment; ΔSDS, Table 4). No significant relationship was noted between ΔQOL and the magnitude of improvement in ESS (changes after treatment; ΔESS).

Table 4. Correlations between ΔSDS and ΔSF-36 after Treatment

Change	Regression coefficient	p value
ΔPF	0.227	0.0119
ΔRP	0.049	0.6170
ΔBP	0.037	0.7096
ΔGHP	0.211	0.0316
ΔVT	0.249	0.0104
ΔSF	0.203	0.0374
ΔRE	0.178	0.0699
ΔMH	0.296	0.0021
ΔTotal SF-36	0.318	0.0010

ΔSDS: change after treatment in Self-rating Depression Scale, ΔSF-36: change after treatment in Short Form 36, ΔPF: change after treatment in physical functioning, ΔRP: change after treatment in role limitations imposed by physical problems, ΔBP: change after treatment in bodily pain, ΔGHP: change after treatment in general health perceptions, ΔVT: change after treatment in vitality, ΔSF: change after treatment in social functioning, ΔRE: change after treatment in role limitations imposed by emotional problems, ΔMH: change after treatment in mental health.

Discussion

We previously showed that patients with severe OSAS have poorer QOL, which is associated with depression rather than with EDS (13). In the present study, which included more than twice as many subjects as the previous one, these results did not differ basically from the previous findings, although we had found significant differences in RP and MH between patients and controls in the previous report. The total SF-36 score and all SF-36 domains except for RP showed significant negative correlations with SDS, supporting the suggestion of the smaller study that QOL might be determined largely by the depressive status in patients with severe OSAS.

Eight weeks of nasal CPAP treatment significantly improved EDS, SDS, and most SF-36 domains in the present study; these results were consistent with previous reports that nasal CPAP treatment decreased EDS (16–18) and improved neuropsychological functions (19–21) and QOL (20–24). Recently, Hida et al (32) showed that nasal CPAP treatment for 3–6 months improved the QOL using SF-36 in Japanese patients with OSAS and obesity-hypoventilation syndrome (OHS). Their results were relatively consistent with the present results. Interestingly, they found that the improvement of some domains of SF-36 had a significant correlation with the improvement in the ESS score. In contrast, the present study did not show any correlation between ΔSF-36 and Δ ESS, but found a relationship with ΔSDS. This discrepancy

may be due to the differences of patient characteristics. Their subjects were more hypersomnolent and included the most severe type of OSAS and OHS.

A randomized controlled study using subtherapeutic CPAP as the control condition demonstrated that effective CPAP treatment for 8 weeks improved EDS, both subjectively and objectively, and also improved QOL as evaluated by the SF-36 (18). However, no comment was made concerning an association between improvements of EDS and QOL. Bennett et al (24) reported a significant association between all sleep fragmentation indices and health status improvement after nasal CPAP, although relationships between pretreatment health status and sleep fragmentation were weak. They also found a significant association between EDS (evaluated by ESS) and some SF-36 domains, concluding that improvement of health status with nasal CPAP is correlated with decreases in sleep fragmentation severity and EDS, although this correlation still was not strong. We found that 8 weeks of nasal CPAP treatment improved EDS, QOL, and depressive status, with improvement of QOL being associated with SDS rather than ESS improvement. As shown by our pretreatment findings, most QOL domains correlated strongly with the SDS but not the ESS. In posttreatment results, improvement of QOL was also correlated with improvement of SDS, again supporting the hypothesis that QOL in patients with severe OSAS depends on the depressive status. However, the reason that ΔSDS was significantly correlated with five domains (ΔPF, ΔGHP, ΔVT, ΔSF and ΔMH) and not with ΔRP, ΔBP or ΔRE is unclear. Generally, GHP, VT and MH seem to be related to mood or depression. Therefore, ΔSDS may correlate with the improvement of mental components such as GHP, VT, and MH.

Although nasal CPAP has previously been demonstrated to improve mood or alleviate depression (19–21), the mechanisms underlying this improvement are unknown. Repetitive arousals or oxygen desaturation in brain tissue during sleep presumably contributes to the development of depression. When nasal CPAP is titrated properly, apnea and hypopnea in patients with OSAS are abolished completely, and arousals and oxygen desaturation disappear during CPAP. Whether arousals or episodes of desaturation during sleep are responsible for mood disturbance or depression are uncertain. Since SDS before and after treatment did not correlate significantly with measures of OSAS severity (AHI, mean SaO_2, and lowest SaO_2), or with sleep disturbance (arousal index and sleep architecture), we could not find a factor accountable for depression in patients with severe OSAS.

Although the present study showed significant differences in EDS, mood, and QOL between controls and patients with OSAS before treatment, controls were not matched in BMI to patients, and did not undergo PSG. However, controls were selected from among persons undergoing a routine annual health check-up who had no abnormal symptom. Therefore, we considered controls as "purely normal".

The present study was not placebo controlled. After skepticism was expressed concerning the effectiveness of nasal CPAP because of a lack of randomized controlled trials (33), several randomized placebo-controlled studies were reported (17, 18, 34, 35). Most of these demonstrated the clinical effectiveness of nasal CPAP in terms of EDS (17, 18), QOL (34), and cardiovascular complications (35). Henke et al (34) compared the effectiveness of therapeutic and subtherapeutic (placebo) CPAP for improving neuropsychological functions in patients with OSAS, finding no intergroup differences in changes in routine clinical test results during a period when one group received effective CPAP and the other received ineffective CPAP. These data suggest the feasibility and importance of using ineffective CPAP as a placebo control in studies evaluating effects of treatment. However, a placebo-controlled trial is not easy to carry out as a relatively large-scale study, and most placebo-controlled trials examining the effectiveness of nasal CPAP in improving QOL have been performed in relatively small numbers of OSAS patients (17, 18, 34). When Sin et al (36) recently demonstrated clinical effectiveness of nasal CPAP in terms of QOL as measured by the SF-36 in over 300 OSAS patients, they did not include placebo-treated controls.

Finally, we confirmed that QOL in patients with severe OSAS depended on depressive status, while improvement of QOL with CPAP was associated with improvement of depression. Such improvement of QOL and amelioration of depression by treatment are important for patients, and are distinct from other common physician goals such as improved survival outcomes.

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