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Obstructive Sleep Apnea in Obese Noninsulin-Dependent Diabetic Patients: Effect of Continuous Positive Airway Pressure Treatment on Insulin Responsiveness*

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ABSTRACT

Patients with noninsulin-dependent diabetes mellitus (NIDDM) are often obese and frequently complain of tiredness. These features are also characteristically seen in patients with obstructive sleep apnea (OSA). Therefore, it was the aim of this study to assess the prevalence of OSA among a group of obese NIDDM patients who have some clinical features of OSA. The effect of reversal of OSA by nasal continuous positive airway pressure (CPAP) treatment on insulin responsiveness was also investigated.

From a population of 179 NIDDM patients with a body mass index (BMI) greater than 35 kg/m^2, we performed ambulatory sleep monitoring on 31 (15 males and 16 females) who admitted to either heavy snoring or excessive sleepiness. Results were reviewed by a sleep physician blinded to the clinical status of the patients, and 22 (70%) were found to have moderate or severe OSA, with mean oxygen desaturation indexes of 10.3 ± 5.3 and 30.7 ± 13.2 episodes/h, respectively.

A subgroup of 10 patients (seven males and three females) with a mean BMI of 42.7 ± 4.3 kg/m^2 was treated with nightly CPAP for 4 months. These subjects all had significant OSA, with frequent obstructive apneas (mean, 47 ± 31.6 episodes/h) and oxygen desaturation (mean minimum O_2 saturation, 74 ± 9.5%), as determined by polysomnography. One patient was excluded from analysis because of infrequent use of CPAP. Insulin responsiveness in terms of glucose disposal measured by hyperinsulinemic euglycemic clamps improved from 11.4 ± 6.2 to 15.1 ± 4.6 μmol/kg·min ($P < 0.05$) during CPAP treatment.

These results indicate that OSA occurs commonly in obese NIDDM patients with excessive sleepiness or heavy snoring. Treatment of their OSA may improve insulin responsiveness. (*J Clin Endocrinol Metab* **79:** 1681–1685, 1994)

PATIENTS with noninsulin-dependent diabetes mellitus (NIDDM) are often obese, hypertensive, and have symptoms of fatigue and lethargy. These are also clinical features typically seen in patients with obstructive sleep apnea (OSA), a disorder characterized by heavy snoring and repetitive closure of the upper airway during sleep (1). Indeed, sleep disturbance in diabetes has been studied by several groups, but the findings are not conclusive (2–4). As obesity aggravates both NIDDM and OSA, it is reasonable to expect that their coexistence will be more common in obese patients. Moreover, hyperinsulinemia as a result of insulin resistance appears to occur in OSA (5–7), and this may be related to increased catecholamine secretion (8, 9). Thus, it is possible that treatment of OSA will ameliorate insulin resistance.

The first aim of this study was to evaluate the coexistence of OSA with NIDDM in markedly obese diabetic patients who have symptoms suggestive of OSA. The second aim was to investigate whether treatment of OSA with nasal continuous positive airway pressure (CPAP) (10, 11) in these patients can improve insulin responsiveness.

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Subjects and Methods

The 31 subjects for ambulatory sleep studies were selected from patients attending the Diabetes Center of Royal Prince Alfred Hospital over a 2-yr period who fulfilled the following criteria: 1) NIDDM, 2) body mass index (BMI) greater than 35 kg/m^2, and 3) admitted to either being a heavy snorer or being excessively sleepy during the day. This history of heavy snoring and/or hypersomnolence was confirmed by a questionnaire administered by another person on a separate occasion.

All of the patients shown by ambulatory sleep studies to have evidence of moderate or severe OSA were asked to participate in the study examining the effects of CPAP treatment on insulin responsiveness. Ten patients agreed, and they underwent nocturnal polysomnography. Three of these patients were receiving insulin treatment, six were taking oral hypoglycemic agents, and one was treated with diet alone.

The study was approved by the ethics review committee of our institution, and all patients gave informed consent.

Ambulatory sleep studies

Ambulatory sleep studies were performed using a portable digital recording device that monitors snoring sounds, oxygen saturation, heart rate, and body position (MESAM, Madaus Electronics Sleep Apnea Monitor, Madaus Medizin Elektronik, Freiburg, Germany) (12). Computer-based analysis of data yields a number of parameters, including oxygen desaturation index (episodes per h), lowest oxygen saturation (percentage), oxygen saturation less than 90% (percent time), and loud

snoring (percent time). Patients were connected to the MESAM in the afternoon, and recording was programmed to commence automatically at home at a specified time, usually around 2200 h, and to continue until the following morning. Data were down-loaded onto an IBM-compatible personal computer, and subsequently presented in 10-min epochs, which were hand scored by an experienced sleep physician, who was blinded to the clinical status of the patients. The patients were classified into 1) severe, 2) moderate, or 3) no significant OSA, based on the number of obstructive respiratory events and the degree and frequency of O_2 desaturation.

Sleep studies

Polysomnograms were performed between 2100–0700 h. Sleep state was recorded with two channels of electroencephalogram (C1/A3 and C2/A4), two channels of electrooculogram, and one channel of submental electromyogram (EMG). Breathing variables included chest wall and abdominal motion (Respitrace, Ambulatory Monitoring, Ardsley, NY), nasal airflow by measuring pressure change in nasal prongs (Grass volumetric, Grass Instrument Co., Quincey, MA), and arterial oxyhemoglobin saturation (Ohmeda Biox 3700e, Louisville, CO). An electrocardiogram was recorded continuously. All variables were recorded continuously on a 16-channel electroencephalograph (Grass Instruments). Calculated respiratory variables were apnea/hypopnea index (the number of apneas and hypopneas per h of sleep), apnea duration, and minimal arterial oxygen (O_2) saturation during apneas. Apnea was defined as cessation of air flow for at least 10 s with O_2 desaturation undefined, or cessation of air flow for less than 10 s (but at least one respiratory cycle) if associated with an O_2 desaturation of more than 4%. Hypopnea was defined as a reduction in amplitude of air flow or thoraco-abdominal wall movement greater than 50% of the baseline measurement for more than 10 s (O_2 desaturation need not occur) or the same reduction with an accompanying O_2 desaturation of at least 4% (no time limit). These respiratory events were defined as obstructive if they occurred in association with continued diaphragm EMG activity and thoraco-abdominal wall movement. Central events were defined as those accompanied by the absence of diaphragm EMG activity and thoraco-abdominal wall movement. Sleep recordings were scored in 30-s epochs and staged according to the criteria of Rechtschaffen and Kales (13).

A further sleep study was subsequently performed to determine the CPAP pressure required to abolish snoring, apneas, and O_2 desaturation. During the 4 months of CPAP treatment, the CPAP pressure was adjusted according to symptomatic response and the results of ambulatory sleep monitoring, performed after 1 and 4 months of treatment. Patients were reviewed by a sleep physician at least twice during the study period. All diabetic treatment was kept constant throughout.

Insulin responsiveness studies

Insulin responsiveness was measured by a hyperinsulinemic euglycemic clamp (14) before and after 4 months of CPAP treatment. This was performed after a 10-h overnight fast, and all diabetic medications were omitted on the morning of the clamp. A retrograde cannula was inserted into the right arm for blood sampling, and a warming blanket was used to arterialize the blood. A second cannula was inserted into the left arm for the insulin and glucose infusions. Insulin (1.2 μmol/kg) was given iv as a bolus and then continued as an infusion (0.82 μmol/kg BW·h). A high insulin infusion rate was selected to ensure adequate hyperinsulinemia to adequately suppress hepatic glucose output in these very insulin-resistant patients. The variable rate of glucose infusion, calculated according to a predetermined algorithm, was commenced when the blood glucose level fell to 5 mmol/L to clamp it within the range of 4.5–5.5 mmol/L, and this continued for a period of at least 60 min. An insulin responsiveness index (M value; micromoles per kg/min) was calculated from the mean glucose infusion rate during the 30- to 60-min period of the clamp (except in patient JH, in whom the 15- to 45-min period was used because of technical problems in the measurement of blood glucose levels in the subsequent time points in one of the clamps). Glucose values during the study were determined by a Yellow Springs Autoanalyzer (Yellow Springs Instrument Co., Yellow Springs, OH). Insulin levels were measured by RIA and were confirmed not to be different between the two clamps (3.79 ± 1.45 *vs.* 3.66 ± 1.35 nmol/L). Fasting levels of insulin-like growth factor-I (IGF-I), GH, and cortisol were also measured before each clamp by RIA.

Data analysis

Results are expressed as the mean ± SD. One-way analysis of variance with *post-hoc* Duncan's multiple range test was used to compare results of the three groups of patients with severe, moderate, or no significant OSA. A paired *t* test was used to compare insulin responsiveness before and after CPAP treatment. $P < 0.05$ was considered significant.

Results

Over the 2-yr recruitment period, a total of 179 patients with BMI greater than 35 kg/m^2 attended the Diabetes Center for clinical management. Among these, 31 patients (16 females and 15 males) admitted that they were heavy snorers or had daytime hypersomnolence. All agreed to participate in the ambulatory sleep-monitoring study. Their mean age was 50.3 ± 9.1 yr, and their mean BMI was 41.6 ± 4.7 kg/m^2. The 10 patients (7 males and 3 females) who were recruited for the CPAP-insulin responsiveness studies had a mean age of 50.8 ± 9.6 yr and a mean BMI of 42.7 ± 4.3 kg/m^2.

Ambulatory sleep studies

From the results of the MESAM monitor and without knowledge of their clinical status, 9 patients were classified by the sleep physician as having severe OSA, 13 as having moderate OSA, and the remaining 9 as having no significant OSA. The age, hemoglobin-A_{1c} (HbA_{1c}), BMI, blood pressure, and respiratory parameters of the different groups are shown in Table 1. There were no significant difference in their age, HbA_{1c}, BMI, or blood pressure. However, the severe OSA group clearly had more frequent and more severe O_2 desaturation (Table 1). Of the 15 male patients studied, 14 were graded to have moderate or severe OSA, whereas only 8 of the 16 females were similarly affected. All of the women with moderate or severe OSA were postmenopausal, whereas

TABLE 1. The clinical and respiratory parameters of patients studied by ambulatory sleep monitoring

	OSA		
	Severe (n = 9)	Moderate (n = 13)	Nil (n = 9)
Age (yr)	51.2 ± 10.9	52.4 ± 6.9	46.4 ± 8.7
BMI (kg/m^2)	41.6 ± 4.8	42.4 ± 4.5	40.6 ± 4.7
HbA_{1c} (%)	7.5 ± 1.0	9.1 ± 1.6	8.4 ± 2.1
Systolic BP (mm Hg)	143 ± 15	138 ± 17	138 ± 24
Diastolic BP (mm Hg)	90 ± 6	87 ± 12	85 ± 8
O_2 desaturation Index (episodes/h)	30.7 ± 13.2[a]	10.3 ± 5.3[a]	4.8 ± 2.6
Lowest O_2 Saturation (%)	72.6 ± 7.5[a]	85.0 ± 6.2	88.2 ± 1.6
O_2 saturation <90% (% time)	15.7 ± 21.0[b]	2.5 ± 4.2[b]	0.2 ± 0.3
Loud snoring (% time)	31.4 ± 15.8[a]	24.2 ± 10.0	12.1 ± 7.4

BP, Blood pressure.
[a] $P < 0.01$ *vs.* group with no OSA.
[b] $P < 0.03$ *vs.* group with no OSA.

5 of the 8 with no OSA were premenopausal. None of the women was taking progestogen treatment.

CPAP-insulin responsiveness studies

On nocturnal polysomnography, the 10 recruited patients had a mean apnea/hypopnea index of 47 ± 31.6 and a mean minimum O_2 saturation of 74 ± 9.5%.

One patient (P) was excluded from the analysis because of extremely infrequent reported CPAP use and clear evidence of persisting repetitive oxygen desaturations on his MESAM study on CPAP. For the remaining nine patients, treated with CPAP at a mean pressure of 16 ± 3 cm H_2O, the respiratory parameters measured by ambulatory sleep studies clearly improved during therapy (Table 2).

The results of insulin responsiveness before and after CPAP treatment for individual patients are shown in Fig. 1. Seven of the 10 patients showed an improvement in insulin responsiveness. When all 10 patients were included, there was a 28% increase in the mean insulin responsiveness after CPAP treatment, which approached statistical significance ($P < 0.06$). When one patient (P) was excluded because of clear evidence of ineffective CPAP treatment, the change in insulin responsiveness in terms of glucose disposal was statistically significant (mean M value, 11.4 ± 6.2 *vs.* 15.1 ± 4.6 μmol/kg·min; $P < 0.05$). There was no relationship found between the degree of improvement in insulin responsiveness and the severity of OSA.

There was no significant change in BMI during the study period (42.7 ± 4.3 *vs.* 42.8 ± 4.3 kg/m^2) to account for the observed improvement in insulin responsiveness. Over the treatment period, there was no change in the fasting insulin level (0.33 ± 0.12 *vs.* 0.30 ± 0.11 nmol/L), fasting blood glucose level (10.5 ± 3.3 *vs.* 11.7 ± 2.8 mmol/L), HbA_{1c} (8.9 ± 1.5% *vs.* 8.9 ± 1.2%; normal range, 3.5–6.0%), systolic blood pressure (136 ± 20 *vs.* 144 ± 11 mm Hg), diastolic blood pressure (87 ± 7 *vs.* 84 ± 8 mm Hg), or fasting levels of IGF-1 (13.9 ± 4.8 *vs.* 13.6 ± 3.8 nmol/L; normal range, 6.6–30.0 nmol/L), GH (0.33 ± 0.3 *vs.* 0.28 ± 0.2 μg/L; normal range, 0–5 μg/L), or cortisol (469.5 ± 238.2 *vs.* 339 ± 115.9 nmol/L; normal range, 160–600 μg/L).

TABLE 2. Respiratory parameters measured by ambulatory sleep monitoring before and on CPAP treatment

	Before CPAP	On CPAP treatment
O_2 desaturation Index (episodes/h)	20.2 ± 17.2	3.0 ± 2.1[a]
Lowest O_2 Saturation (%)	80.6 ± 9.1	89.8 ± 2.7[a]
O_2 saturation < 90% (% time)	12.2 ± 22.9	0.35 ± 0.5
Loud snoring (% time)	23.7 ± 13.8	4.8 ± 5.2[b]

[a] $P < 0.02$ *vs.* baseline.
[b] $P < 0.01$ *vs.* baseline.

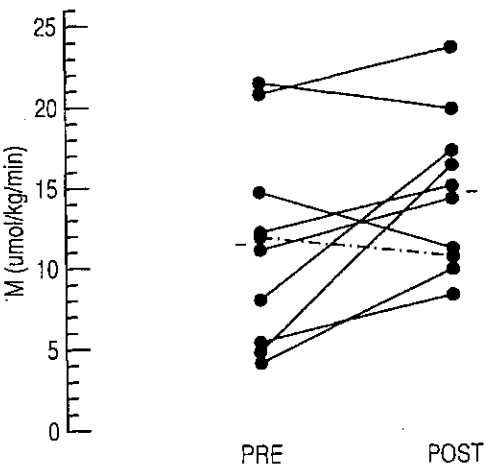

FIG. 1. Individual data, showing insulin responsiveness (M) before (pre) and after (post) the period on CPAP treatment. *Horizontal lines* indicate the mean M values before and after CPAP. The *dotted line* represents the result for patient (P), who was using CPAP treatment infrequently.

Discussion

The picture of a NIDDM patient with poor metabolic control, obesity, lethargy, hypertension, and cardiac abnormalities is a common clinical scenario and therapeutic problem. Apart from hyperglycemia, all of these features are also manifested in typical OSA patients. The recognition of OSA in diabetic patients is important because its treatment not only leads to relief of hypersomnolence, but may also reduce cardiovascular disease, which is an important source of morbidity in diabetes.

Relatively few studies have examined the relationship between OSA and diabetes, and the findings are somewhat conflicting. Mondini *et al.* (2) found a relationship between neuropathy and sleep-related breathing abnormalities in type I insulin-dependent diabetic patients. However, Catterall *et al.* (4) studied sleep patterns in diabetic patients and found no abnormalities. Katsumata *et al.* (3) reported a high prevalence of OSA in a Japanese diabetic population. Based on glucose tolerance test results of 34 patients with OSA, they found a diabetic pattern in 13 patients and a further 12 patients with impaired glucose tolerance.

As obesity aggravates both OSA and NIDDM, the coexistence of these two conditions is more likely to occur in the severely obese; therefore, our efforts were concentrated in this group of people. Another reason to investigate obese patients with diabetes is that their management poses a special problem. Due to their insulin resistance, even a high dosage of insulin often fails to achieve normoglycemia, whereas at the same time, overinsulinization in the presence of poor dietary habits leads to undesirable weight gain, further accentuating the insulin resistance. In these patients, reduction of insulin resistance is a worthwhile goal, and therapeutic maneuvers, such as exercise, weight loss, and a low fat diet, can make a contribution. OSA is known to be associated with hyperinsulinemia, and this may be related to underlying insulin resistance mediated by increased catecholamine secretion (8, 9). Thus, potentially, successful treatment of OSA will reduce insulin resistance in this group of difficult to manage diabetic patients.

In the cohort of obese NIDDM patients with symptoms suggestive of OSA that we studied, there were certainly many patients with coexisting NIDDM and OSA. Seventy-

one percent of these patients were classified as having moderate or severe OSA on the basis of ambulatory sleep monitoring. As we did not study those patients with BMI greater than 35 kg/m^2 without symptomatic heavy snoring or hypersomnolence, we cannot be certain of the prevalence of OSA if diabetic patients were selected on the basis of weight alone. However, even in the unlikely event that OSA was not present in any of the 148 patients who we did not study, the prevalence of moderate and severe OSA in NIDDM patients with BMI greater than 35 kg/m^2 would still be 12%. Larger studies are required to determine the true prevalence of OSA in obese diabetic patients and whether the prevalence is higher than that in similarly obese, but nondiabetic, individuals. A recent epidemiological study of men and women, 30–60 yr old, found that the prevalence of sleep-disordered breathing was 9% for women and 24% for men, based on polysomnography (15). In this study (15), obesity was strongly associated with the presence of sleep-disordered breathing. However, there are scant data specifically examining the prevalence of OSA in people within the range of body weight we studied. In a recent report, 29 asymptomatic women with BMI greater than 30 kg/m^2 were studied by MESAM, and 20% were found to have OSA of severity similar to that in our moderate and severe groups (16). It is clear from our data that OSA is common in severely obese NIDDM patients, at least in those with symptoms suggestive of OSA, and its presence should be considered in their overall clinical management. There is now good evidence that central obesity is also an independent determinant for the presence of OSA, and measurement of the waist/hip ratio may further improve the identification of individuals at risk (17). Our male and postmenopausal female patients showed a much higher predilection to OSA, and these are also risk factors that should be borne in mind.

Apart from symptomatic relief, treatment of OSA has been shown to alleviate hypertension (18, 19), cardiac failure (20), and neuroendocrine abnormalities (21). Preliminary studies found that oxygen desaturation is associated with high circulating insulin levels, raising the possibility that OSA may cause insulin resistance and hyperinsulinemia (5–7). Our finding that CPAP treatment improved insulin responsiveness by 28% supports this concept. Facchini *et al.* (22), in a study looking at the effect of 8 weeks of CPAP treatment, did not show any improvement of overnight glucose tolerance in obese patients with OSA. In fact, they found that plasma glucose and insulin levels increased after CPAP treatment. However, they only studied four patients and did not use the more precise technique of glucose clamping to quantify insulin responsiveness.

The precise mechanism of the beneficial effect of CPAP treatment on insulin responsiveness is not clear. Due to the nature of CPAP treatment, it was not possible to include a placebo arm in the protocol to control for the effects of closer supervision of patients. Previous studies have shown a reduction of catecholamine levels after treatment of OSA with CPAP therapy (23). In 5 of the 10 patients studied, we measured fasting epinephrine and norepinephrine levels before and after CPAP treatment and found no clear trend (data not shown), but more detailed studies are required to evaluate fully the role of catecholamines in mediating the improvement in insulin responsiveness. Similarly, the serum cortisol level was not changed by CPAP treatment. A previous study (21) showed that a rise in IGF-I occurs after CPAP treatment, but the current data do not show evidence of a change in IGF-I or GH levels to suggest that they had an influence on insulin responsiveness. However, our cohort of patients was fewer in number and consisted of severely obese, diabetic patients.

It is disappointing that the rise in insulin responsiveness was not associated with an improvement in metabolic control. A reason for this may be that the increase in insulin responsiveness is relatively modest, especially in the context of severe insulin resistance in these severely obese patients. We may also be at the plateau part of the dose-response curve between glycemia and insulin resistance, where improvement in one would not necessarily be paralleled by improvement in the other. Studies of patients with a milder degree of obesity and insulin resistance would be of interest to clarify this point. It is also possible that 4 months of CPAP treatment are not enough to induce the maximum benefit, and some of the patients may not have complied fully with the CPAP treatment. Recently, it has been reported that objectively measured CPAP use by patients with OSA is often less than self-estimated use (24). Moreover, many patients use CPAP irregularly. Using ambulatory sleep monitoring before and during CPAP treatment, we were able to demonstrate the effectiveness of CPAP treatment in reversing airway obstruction in all but 1 patient (P). However, we were not able to obtain quantitative data on the extent of CPAP usage to determine whether this correlated with changes in insulin responsiveness. Despite attempts to ensure good compliance in our patients, it is likely that this was less than perfect, and this may explain the lack of improvement in 3 of the 10 patients. Future studies using CPAP devices that provide objective monitoring of CPAP use will be of great interest.

In conclusion, we have demonstrated that OSA and NIDDM often coexist in markedly obese patients with symptoms of somnolence and heavy snoring. Awareness of this phenomenon is important in their overall management, as the coexistent OSA is often sufficiently severe to warrant treatment in its own right. Moreover, relief of OSA may be of benefit in reducing morbidity from cardiovascular disease, which is a major concern in these diabetic patients. Treatment of OSA is also associated with improvement in insulin responsiveness.

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