ORIGINAL ARTICLE

CPAP for the Metabolic Syndrome in Patients with Obstructive Sleep Apnea

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ABSTRACT

BACKGROUND

Obstructive sleep apnea is associated with an increased prevalence of the metabolic syndrome and its components. It is unclear whether treatment of obstructive sleep apnea syndrome with continuous positive airway pressure (CPAP) would modify these outcomes.

METHODS

In our double-blind, placebo-controlled trial, we randomly assigned patients with obstructive sleep apnea syndrome to undergo 3 months of therapeutic CPAP followed by 3 months of sham CPAP, or vice versa, with a washout period of 1 month in between. Before and after each intervention, we obtained measurements of anthropometric variables, blood pressure, fasting blood glucose levels, insulin resistance (with the use of homeostasis model assessment), fasting blood lipid profile, glycated hemoglobin levels, carotid intima–media thickness, and visceral fat. The metabolic syndrome was defined according to National Cholesterol Education Program Adult Treatment Panel III criteria, with Asian cutoff values for abdominal obesity.

RESULTS

A total of 86 patients completed the study, 75 (87%) of whom had the metabolic syndrome. CPAP treatment (vs. sham CPAP) was associated with significant mean decreases in systolic blood pressure (3.9 mm Hg; 95% confidence interval [CI], 1.4 to 6.4; P=0.001), diastolic blood pressure (2.5 mm Hg; 95% CI, 0.9 to 4.1; P<0.001), serum total cholesterol (13.3 mg per deciliter; 95% CI, 5.3 to 21.3; P=0.005), non–high-density lipoprotein cholesterol (13.3 mg per deciliter; 95% CI, 4.8 to 21.8; P=0.009), low-density lipoprotein cholesterol (9.6 mg per deciliter; 95% CI, 2.5 to 16.7; P=0.008), triglycerides (18.7 mg per deciliter; 95% CI, 4.3 to 41.6; P=0.02), and glycated hemoglobin (0.2%; 95% CI, 0.1 to 0.4; P=0.003). The frequency of the metabolic syndrome was reduced after CPAP therapy (reversal found in 11 of 86 patients [13%] undergoing CPAP therapy vs. 1 of 86 [1%] undergoing sham CPAP). Accelerated hypertension developed 1 patient receiving CPAP therapy first, intolerance to CPAP developed in 2 others, and another patient declined to continue sham CPAP.

CONCLUSIONS

In patients with moderate-to-severe obstructive sleep apnea syndrome, 3 months of CPAP therapy lowers blood pressure and partially reverses metabolic abnormalities. (Funded by Pfizer; ClinicalTrials.gov number, NCT00694616.)

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Obstructive sleep apnea is a highly prevalent but underrecognized clinical problem. The Wisconsin Sleep Cohort Study[1] estimated a prevalence of 24% among men and 9% among women in that state. In an urban setting in northern India, the prevalence of obstructive sleep apnea and the obstructive sleep apnea syndrome is reported to be 13.7% and 3.8%, respectively.[2] The metabolic syndrome, a cluster of cardiovascular risk factors, is associated with obstructive sleep apnea.[3] Its prevalence varies from 74 to 85% among patients with obstructive sleep apnea and from 37 to 41% among patients with nonobstructive sleep apnea.[4,5] Obstructive sleep apnea has been shown to be an independent risk factor for hypertension[6] and insulin resistance.[7]

Continuous positive airway pressure (CPAP) is the first-line treatment for symptomatic obstructive sleep apnea. However, the effect of CPAP on the metabolic syndrome is unclear. Most studies have shown a decrease in blood pressure with the use of CPAP,[8-10] with a few exceptions.[11] Studies of the effect of CPAP on insulin resistance[8,12,13] and the lipid profile[8,14-16] have reported disparate results. Two studies[8,17] have assessed the effect of CPAP on the metabolic syndrome in patients with obstructive sleep apnea, with divergent results. Most studies of CPAP to treat components of the metabolic syndrome have had small study populations, a short duration of intervention, and no control group or washout period.[8,11-13,17] To assess the effect of CPAP therapy on the metabolic syndrome and its components, we designed a double-blind, placebo-controlled, randomized, crossover trial with 3 months of CPAP and 3 months of sham CPAP and a 1-month washout period between interventions.

METHODS

PATIENTS

We recruited patients, 30 to 65 years of age, from the Sleep Laboratory of the Department of Medicine at the All India Institute of Medical Sciences hospital in New Delhi, India. Inclusion criteria were no previous or current CPAP therapy, obstructive sleep apnea that was of moderate or greater severity, and excessive daytime somnolence. Exclusion criteria were previous or current treatment for hypertension, diabetes mellitus, or dyslipidemia or any evidence of end-organ damage due to these conditions. (Detailed inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Patients were randomly assigned to undergo either CPAP or sham CPAP for 3 months, followed by a washout period of 1 month and then crossover to the other intervention for 3 months. The sham CPAP modifications consisted of a flow-restricting Teflon connector and a mask containing tiny escape holes in it. These modifications were indistinguishable to the untrained eye. Thus, the investigators and patients were unaware of the intervention assignments.

CONDUCT OF THE STUDY

The study was conducted in accordance with the protocol (available at NEJM.org and in brief form in Table S4 in the Supplementary Appendix). The protocol was approved by the local ethics committee. Written informed consent was obtained from each participant. The study was supported by Pfizer through an investigator-initiated research grant, but Pfizer had no role in the study design, data analysis, writing of the manuscript, or decision to submit the manuscript for publication. The authors vouch for the completeness and veracity of the reported work as well as the fidelity of the reported work to the protocol.

RANDOMIZATION

The randomization sequence was generated by a statistician not otherwise involved in the study, by means of a computer-generated random-number table. An unrestricted randomization scheme was followed. The randomization numbers were contained in serially numbered, sealed, opaque envelopes kept by office staff who were not involved in outcome measurements.

THE METABOLIC SYNDROME

The metabolic syndrome was defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria,[18] with the cutoff value for defining abdominal obesity of 90 cm for men and 80 cm for women, as recommended by the World Health Organization guidelines for South Asians.[19] Individual criteria were each given a score, which were summed; a sum of 3 or greater was considered to indicate the presence of the metabolic syndrome.

ASSESSMENTS

Assessments were repeated at the beginning and end of each of the two 3-month intervention periods.

Sleep

All participants underwent overnight polysomnography, as described previously,[20] and the data were scored manually according to the recommendations of the American Academy of Sleep Medicine.[21] Obstructive sleep apnea was defined as an apnea–hypopnea index (AHI) score of 5 or more events per hour, with the severity described as mild for an AHI score of 5 to less than 15, moderate for an AHI score of 15 to 30, and severe for an AHI score of more than 30.[21] Obstructive sleep apnea syndrome was defined as the presence of obstructive sleep apnea with excessive daytime somnolence. Excessive daytime somnolence was assessed with the use of the Epworth Sleepiness Scale,[22] with a score of more than 10 suggestive of excessive daytime somnolence.

Anthropometric Variables

Body weight, neck length, and waist, hip, and neck circumferences were measured (Table S2 in the Supplementary Appendix). Percent of predicted neck circumference was calculated according to the Davies and Stradling formula[23] as (1000 × neck circumference in centimeters) ÷ (0.55 × height in centimeters + 310).

Blood Pressure

Blood pressure was measured, with the use of a periodically calibrated mercury sphygmomanometer, to the nearest 2 mm Hg in patients in the sitting position after at least 5 minutes of rest. The mean of three measurements was recorded.

Laboratory Tests

We estimated the fasting blood glucose level by using the glucose oxidase method, the fasting plasma insulin level by using an enzyme-linked immunosorbent assay, and the glycated hemoglobin level. Triglyceride, high-density lipoprotein (HDL) cholesterol, and total cholesterol levels were measured by means of an immunocolorimetric assay, and the low-density lipoprotein (LDL) cholesterol level was calculated with the use of the Friedewald equation.[24] Insulin resistance was calculated by means of the homeostasis model assessment method.[25]

Imaging

We measured abdominal fat content by using a single cross-sectional computed tomographic (CT) scan at the level of the umbilicus, according to standard methods.[26] Carotid intima–media thickness (CIMT) was assessed with the use of conventional two-dimensional ultrasonography[27] (Table S3 and Fig. S1 and S2 in the Supplementary Appendix).

STATISTICAL ANALYSIS

For the primary outcome, we estimated that we would need to enroll 72 patients to detect a reduction in the frequency of the metabolic syndrome of 15% with CPAP as compared with sham CPAP, with statistical power (1 minus the β value) of 80%, allowing for a type I (α) error of 0.05. Allowing for a loss to follow-up of 20%, 90 patients were required to undergo randomization.

Statistical analysis was performed with the use of a statistical software package (Stata 11.0 for Windows, Stata). Continuous variables were summarized as means ±SD or medians (and interquartile ranges), and categorical variables as proportions. Comparisons between groups were done by means of an independent t-test if the data were normally distributed and a Mann–Whitney U test if not. The chi-square test was used to analyze categorical variables. The treatment effects of CPAP and sham CPAP were compared with the use of a paired t-test if the data were normally distributed and the Wilcoxon signed-rank test if not. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Predefined subgroup analysis was conducted on data from patients who actually underwent CPAP therapy for an average of 5 or more hours per night. Post hoc subgroup analyses were performed according to the baseline body-mass index (BMI) and metabolic values. Effects of order of intervention and time period were assessed by means of analysis of variance for a 2-by-2 crossover study.

RESULTS

STUDY PARTICIPANTS

Ninety patients were randomly assigned to an intervention, with 46 patients to undergo CPAP first

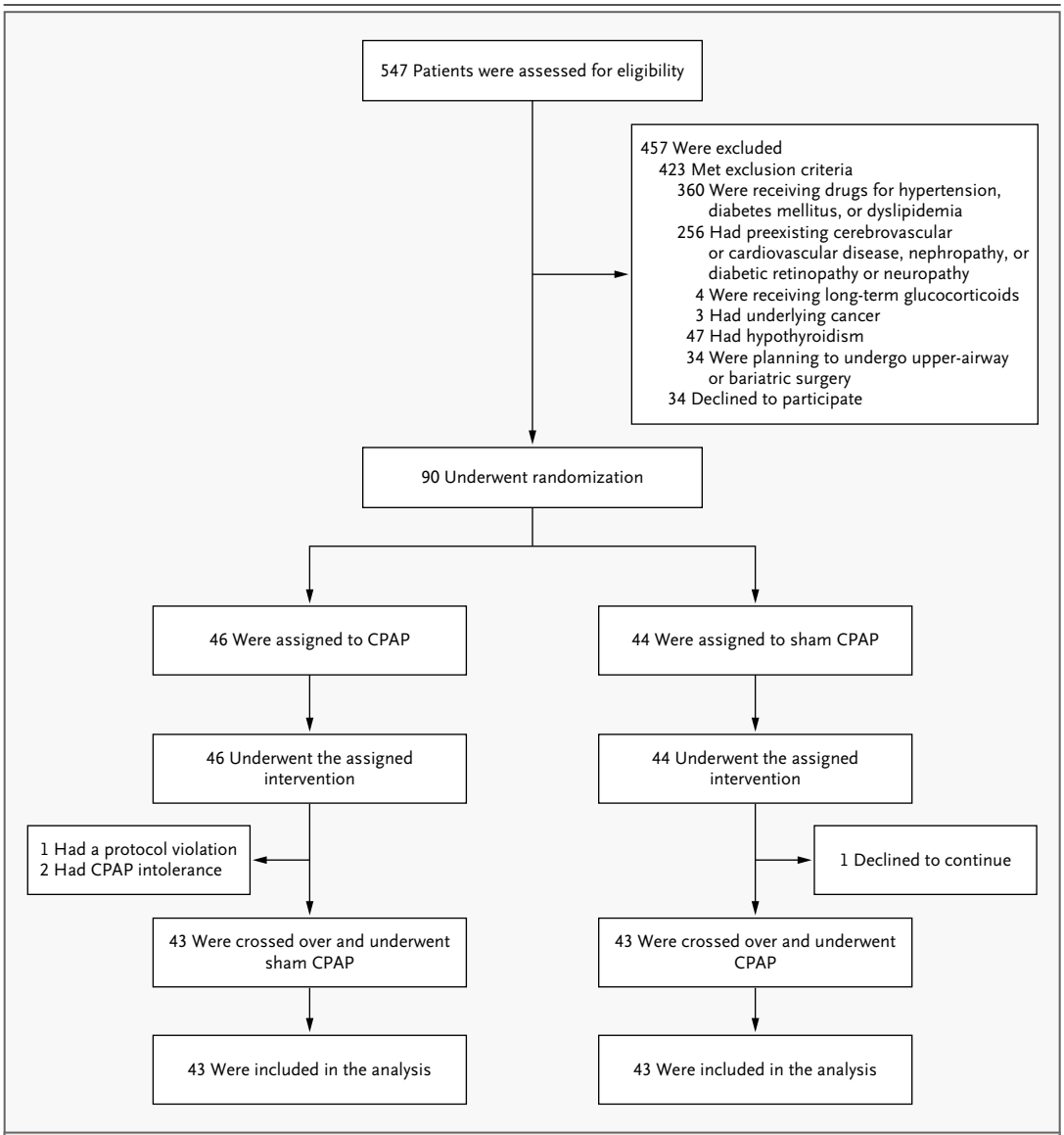

Figure 1. Screening, Enrollment, and Follow-up of the Study Patients.
Some patients were excluded for more than one reason.

and 44 to undergo sham CPAP first (Fig. 1). Three patients in the CPAP-first group and one in the sham-first group discontinued the study. Therefore, 86 patients completed the study.

At baseline, the CPAP-first group had significantly higher total cholesterol, triglyceride, and glycated hemoglobin levels than the sham-first group (Table 1). There were no significant differences in polysomnographic variables between the two groups, however (Table 2). Seventy-five of the 86 patients (87%) had the metabolic syndrome at the time of recruitment (38 in CPAP-first group and 37 in sham-first group).

EFFECT OF INTERVENTION ON THE METABOLIC SYNDROME

Seventy-one of 86 patients (83%) had the metabolic syndrome at the start of CPAP therapy, as compared with 70 of 86 patients (81%) at the start of sham CPAP. The frequency of the metabolic syndrome decreased after CPAP therapy as compared with sham CPAP (Table 3). After CPAP therapy,

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	CPAP First (N=43)	Sham CPAP First (N=43)	P Value
Age — yr	45±8	45±8	0.83
Male sex — no. (%)	36 (84)	41 (95)	0.08
BMI†	33.8±4.7	31.8±5.2	0.06
Waist circumference — cm	115.2±12.1	112.0±12.1	0.24
Percent of predicted neck circumference — %	101.2±9.5	100.4±7.7	0.31
Systolic blood pressure — mm Hg	133.2±9.9	131.1±8.4	0.19
Diastolic blood pressure — mm Hg	89.1±8.1	87.8±7.6	0.60
Hypertension — no. (%)	20 (47)	20 (47)	1.00
Fasting blood glucose — mg/dl	107.2±15.4	105.9±13.0	0.82
Diabetes mellitus — no. (%)	21 (49)	24 (56)	0.52
Fasting insulin — IU/liter			0.24
Median	13.0	12.1	
Interquartile range	9.0–19.5	7.6–15.4	
Insulin resistance			0.15
Median	3.6	3.1	
Interquartile range	2.3–5.0	2.0–4.0	
Glycated hemoglobin — %	6.0±0.6	5.6±0.5	0.01
Triglycerides — mg/dl	197.3±93.1	156.2±62.0	0.02
Cholesterol — mg/dl			
Total	211.7±36.1	191.1±39.3	0.01
HDL	44.0±5.9	41.8±6.4	0.08
LDL	128.2±29.2	117.1±31.0	0.09
Dyslipidemia — no. (%)	36 (84)	38 (88)	0.53

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. To convert values for glucose to millimoles per liter, multiply by 0.055. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

14 of the 71 patients with the metabolic syndrome (20%) no longer fulfilled the criteria for the syndrome, while symptoms of the syndrome developed in 3 of the 15 patients (20%) without the metabolic syndrome at the start. Of the 70 patients with the metabolic syndrome at the start of sham CPAP, at the end of the intervention period, 5 (7%) no longer fulfilled the criteria, while symptoms developed in 4 of the remaining 16 (25%). The metabolic syndrome score decreased from 3.27±0.93 before CPAP to 2.94±0.89 after CPAP (mean difference, 0.33; 95% confidence interval [CI], 0.14 to 0.51; P=0.001) as compared with a change from 3.34±0.97 before sham CPAP to 3.21±0.88 after sham CPAP (mean difference, 0.13; 95% CI, 0.07 to 0.32; P=0.20). Of the 14 patients whose metabolic syndrome resolved after CPAP therapy, the specific criterion or criteria that resolved was blood pressure in 5 patients, fasting blood glucose in 2, triglycerides in 2, HDL cholesterol in 3, triglycerides and HDL cholesterol in 1, and triglycerides, HDL cholesterol, and fasting blood glucose in 1. None of the patients showed improvement in abdominal circumference.

EFFECT ON COMPONENTS OF THE METABOLIC SYNDROME AND ANTHROPOMETRIC VARIABLES

There was a significant reduction in systolic and diastolic blood pressure, glycated hemoglobin, triglycerides, and LDL, non-HDL, and total cholesterol after CPAP therapy as compared with sham therapy, as well as a significant increase in the HDL to total cholesterol ratio (Table 3). Concomitantly, there were significant decreases in BMI

Table 2. Polysomnographic Variables in the Study Population.*

Variable	CPAP First (N=43)	Sham CPAP First (N=43)	P Value
ESS score	14.8±3.7	14.1±3.5	0.33
AHI score — events/hr	47.9±19.6	47.8±17.3	0.99
Arousal index score — events/hr	29.5±4.0	27.8±3.4	0.74
Total sleep time — min	442.1±10.2	435.4±7.3	0.59
Sleep stage — % of total sleep time			
N1	63.7±11.9	67.9±10.6	0.09
N2			0.15
Median	13.6	11.7	
Interquartile range	9.8–21.1	8.0–14.7	
N3			0.47
Median	3.2	2.3	
Interquartile range	0.6–6.5	0.7–4.8	
REM			0.93
Median	15.5	15.0	
Interquartile range	8.1–23.1	9.2–18.8	
Oxygen saturation — %			
Minimum			0.68
Median	69.7	69.7	
Interquartile range	60.0–76.2	59.1–80.2	
Baseline minus minimum			0.99
Median	24.8	24.7	
Interquartile range	20.5–32.7	15.1–34.5	
Oxygen saturation <90% — % of total sleep time	28.7±23.5	29.7±24.6	0.84

* Plus–minus values are means ±SD. Scores on the Epworth Sleepiness Scale (ESS) range from 0 to 24, with a score of more than 10 suggestive of excessive daytime somnolence. AHI denotes apnea–hypopnea index, and REM rapid eye movement.

and visceral and subcutaneous fat (Table 4). Post hoc subgroup analyses and correlations between change in BMI and metabolic variables are presented in Tables S5 through S7 in the Supplementary Appendix.

ADHERENCE

Adherence was higher with CPAP than with sham CPAP (Table S10 in the Supplementary Appendix). The adherence to sham CPAP depended on whether it was given first or second (4.8±1.4 vs. 4.1±1.1 hours per night, P=0.02).

We conducted an analysis of the predefined subgroup of patients whose mean adherence with CPAP was 5 or more hours per night (n=51). Among the 51 patients, the mean reductions in systolic and diastolic blood pressure were 5.6 and 3.3 mm Hg, respectively, as compared with 3.9 and 2.5 mm Hg, respectively, in the whole study population. This subgroup, as compared with the whole study population, had significantly greater mean reductions in several other variables as well — glycated hemoglobin (0.25 vs. 0.21%), CIMT (0.034 vs. 0.014 mm), triglycerides (26 vs. 19 mg per deciliter [0.29 vs. 0.21 mmol per liter]), HDL cholesterol (4.16 vs. 0.04 mg per deciliter [0.11 vs. 0.00 mmol per liter]), LDL cholesterol (15 vs. 10 mg per deciliter [0.39 vs. 0.26 mmol per liter]), and total cholesterol (21 vs. 13 mg per deciliter [0.54 vs. 0.34 mmol per liter]). The changes in HDL cholesterol and CIMT with CPAP were not significant in the whole study population.

ORDER AND PERIOD EFFECTS

There was no significant effect of order of the intervention on any outcome variable. A signifi-

Table 3. Effects of CPAP versus Sham CPAP on Components of the Metabolic Syndrome.*

Variable	Treatment Effect		Difference or Odds Ratio (95% CI)	P Value†
	CPAP (N=86)	Sham CPAP (N=86)		
Abdominal circumference — cm	−0.53±2.42	0.20±3.49	−0.73 (−2.15 to 0.68)	0.32
Systolic blood pressure — mm Hg	−3.07±8.02	0.79±7.22	−3.86 (−6.37 to −1.35)	0.001
Diastolic blood pressure — mm Hg	−2.81±6.07	−0.33±5.25	−2.49 (−4.13 to −0.85)	<0.001
Fasting blood glucose — mg/dl	−1.78±11.37	−0.43±9.40	−1.35 (−4.43 to 1.74)	0.10
Fasting insulin — mU/liter	1.75±11.48	3.33±14.54	−1.59 (−5.60 to 2.42)	0.35
Insulin resistance	0.42±3.10	0.81±3.67	−0.39 (−1.40 to 0.62)	0.23
Glycated hemoglobin — %	−0.03±0.42	0.19±0.49	−0.21 (−0.36 to −0.07)	0.003
Triglycerides — mg/dl	−18.86±71.43	−0.21±80.75	−18.65 (−41.57 to 4.27)	0.02
Cholesterol — mg/dl				
Total	−9.36±31.46	3.90±21.95	−13.26 (−21.25 to −5.28)	0.005
HDL	−0.05±12.85	−0.08±12.28	0.04 (−3.82 to 3.89)	0.75
LDL	−5.72±26.56	3.83±20.44	−9.55 (−16.65 to −2.46)	0.008
Non-HDL	−9.32±32.94	3.98±22.74	−13.30 (−21.79 to −4.82)	0.009
HDL:total cholesterol	0.01±0.07	−0.01±0.07	0.02 (−0.01 to 0.04)	0.01
LDL:total cholesterol	0.00±0.08	0.01±0.07	−0.01 (−0.03 to 0.01)	0.58
Reversal of the metabolic syndrome — no. (%)	11 (13)	1 (1)	12 (9 to 99)	0.003

* Plus–minus values are means ±SD. Treatment effect was calculated by subtracting the value after the 3-month intervention period from the value before the period, except for reversal of the metabolic syndrome, for which percentages of patients with reversal of the syndrome are shown. Difference was calculated for all variables except the metabolic syndrome, by subtracting the sham CPAP effect from the CPAP effect; the value for reversal of the metabolic syndrome is the odds ratio. To convert values for glucose to millimoles per liter, multiply by 0.055. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

† P values were calculated with the use of the Wilcoxon signed-rank test, except for reversal of the metabolic syndrome, for which Fisher's exact test was used.

cant effect of time period was seen only for HDL cholesterol (Table S8 in the Supplementary Appendix).

ADVERSE AND SERIOUS ADVERSE EVENTS

In one patient in the CPAP-first group, accelerated hypertension developed during CPAP therapy; this patient was administered antihypertensive drugs, the use of which constituted a protocol violation. Another two patients in the CPAP-first group had intolerance to CPAP therapy and discontinued it within the first month. A patient in the sham-first group discontinued the sham CPAP therapy. These four patients were excluded from the analysis. Other adverse events reported included skin irritation (in 51% of all patients), nasal bridge discomfort (in 44%), nasal congestion (in 28%), headache (in 26%) and mask leaks (in 30%) (Table S11 in the Supplementary Appendix). Patients undergoing sham CPAP reported no improvement in daytime somnolence.

DISCUSSION

Both obstructive sleep apnea and the metabolic syndrome are important cardiovascular risk factors and they may act synergistically. CPAP is the first-line treatment for moderately severe obstructive sleep apnea and may be useful for treating the metabolic syndrome or metabolic abnormalities associated with obstructive sleep apnea.

We specifically chose patients who had moderately severe, or even more severe, obstructive sleep apnea syndrome with the metabolic syndrome or some of its components. These patients were selected because they have a high risk of death or complications from the obstructive sleep apnea syndrome. To eliminate confounding ef-

Table 4. Effect of CPAP versus Sham CPAP on Anthropometric Variables.*

Variable	Treatment Effect		Difference (95% CI)	P Value†
	CPAP (N=86)	Sham CPAP (N=86)		
ESS score	−5.3±4.4	−0.6±2.0	−4.7 (−5.6 to −3.8)	<0.001
Weight (kg)	−0.37±2.45	0.33±2.20	−0.70 (−1.40 to −0.03)	0.03
BMI	−0.10±0.86	0.18±0.74	−0.29 (−0.51 to −0.06)	<0.001
Waist-to-hip ratio	−0.001±0.027	0.130±1.207	−0.131 (−0.389 to 0.127)	0.49
Percent of predicted neck circumference (%)	−0.72±2.47	0.02±3.16	−0.74 (−1.52 to 0.05)	0.07
Subcutaneous fat (cm^2)	−0.55±2.56	0.34±2.67	−0.89 (−1.67 to −0.12)	<0.001
Visceral fat (cm^2)	−1.05±2.63	0.01±2.18	−1.06 (−1.80 to −0.32)	0.01
Ratio of visceral fat to subcutaneous fat	−2.36±12.20	−0.48±8.27	−1.88 (−5.13 to 1.37)	0.49
CIMT (mm)	0.000±0.102	0.014±0.075	−0.014 (−0.040 to 0.001)	0.07

* Plus–minus values are means ±SD. Treatment effect was calculated by subtracting the value after the 3-month intervention period from the value before the period. Difference was calculated by subtracting the sham CPAP effect from the CPAP effect. CIMT denotes carotid intima–media thickness, and ESS Epworth Sleepiness Scale.
† P values were calculated with the use of the Wilcoxon signed-rank test.

fects, only patients with the obstructive sleep apnea syndrome who had not previously undergone CPAP or any other therapy for components of the metabolic syndrome were recruited. Despite adequate blinding and randomization, patients in the two intervention groups differed at baseline with regard to key characteristics such as total cholesterol, triglyceride, and glycated hemoglobin values. However, since this was a crossover trial, these differences should have had minimal effects on the results.

In 20% of the patients with the metabolic syndrome who underwent CPAP therapy, the metabolic syndrome resolved within 3 months, which is a clinically significant improvement. However, the reversal of the metabolic syndrome was usually due to a significant reduction in only one of the components, with no particular component driving this effect. A randomized crossover trial by Coughlin and colleagues[8] of a previously studied population did not show a significant reduction in the prevalence of the metabolic syndrome after 6 weeks of CPAP therapy, whereas an uncontrolled trial[17] showed a significant decline in the prevalence of the metabolic syndrome after 6 months.

In agreement with most prior studies, we have demonstrated a significant reduction in blood pressure with the use of CPAP.[10,11] The mechanism for development of hypertension in patients with obstructive sleep apnea may be related to sleep fragmentation and nocturnal hypoxemia resulting in sympathetic overdrive. This hypothesis is further strengthened by the evidence of significantly better response of blood pressure to CPAP treatment in more compliant patients and the lack of improvement in patients having obstructive sleep apnea without excessive daytime somnolence.[28]

There was also a significant improvement with CPAP in the ratio of HDL to total cholesterol and levels of total cholesterol, triglycerides, and LDL and non-HDL cholesterol. A significant increase in HDL cholesterol was seen only in more compliant patients, a finding similar to results from uncontrolled studies that have shown a beneficial effect of CPAP on lipid abnormalities.[13,16,17,29] However, one crossover trial[8] did not find any change, most likely owing to a small sample size and short follow-up period.

As in the study by Coughlin and colleagues,[8] we did not demonstrate an effect on fasting blood glucose, fasting insulin, or insulin resistance with CPAP. However, several uncontrolled studies reported a decrease in insulin resistance.[12,13] The divergence in results among these studies may be due to racial or ethnic differences among the study populations. We previously observed that insulin resistance is dependent on obesity rather than obstructive sleep apnea in Indian patients,[30] unlike the independent relationship reported in Chinese

patients.[7] The response of insulin resistance to CPAP therapy is significantly greater if the BMI (the weight in kilograms divided by the square of the height in meters) is less than 30.[12] The mean BMI of our patients was about 33, which may account for the lack of improvement in insulin resistance. However, we observed a significant decrease in glycated hemoglobin values with CPAP, probably because glycated hemoglobin is a better marker of glucose control over a 3-month intervention period. Both blood glucose and insulin resistance fluctuate on a day-to-day basis and, unlike glycated hemoglobin, do not reflect long-term glucose control. Furthermore, interpretation of the homeostasis model assessment in patients with diabetes is complicated owing to progressive β-cell failure, which causes insulin levels to decrease.

We demonstrated a significant decrease in BMI and abdominal fat, by using CT, in association with CPAP therapy. These findings could be secondary to a decrease in daytime somnolence and a consequent increase in physical activity after CPAP use at night. Although a direct effect of CPAP therapy on fat reduction is debatable, we speculate that CPAP has a favorable effect on leptin levels, which have been shown to be elevated in patients with obstructive sleep apnea[31] and to normalize with CPAP therapy.[32]

Weight loss could also be a mechanism for improvement in components of the metabolic syndrome in this study, as suggested by the correlation of the metabolic syndrome with a change in BMI. However, baseline BMI was not a determinant of response to therapy. Participant subgroups with more severe metabolic derangements at baseline had greater treatment responses, though a significant response was also noted among patients without baseline metabolic abnormalities. As compared with participants in other studies, our patients had more severe metabolic derangements at baseline, which could be one reason for the better response to CPAP therapy, in addition to our relatively large sample size and long treatment period.

Significant improvement in carotid intima–media thickness was observed among the more adherent patients, suggesting a potential role for CPAP therapy in reversing endothelial damage due to obstructive sleep apnea and the metabolic syndrome. The improvement in CIMT is similar to that in a randomized study of 4 months' duration in which the mean duration of compliance was 6 hours.[33] A 3-month period is probably not long enough to see positive effects in the whole study group. CIMT also may not respond in the same way as serum lipid levels, since plaque formation involves a complex synergy of dyslipidemia, inflammation, and endothelial damage.

Clinical implications of our study can be extrapolated from drug trials showing a 15% and 42% reduction in the risk of coronary heart disease and stroke, respectively, with each reduction of 5 mm Hg in blood pressure[34] and a 20% reduction in the risks of both coronary heart disease and stroke with each reduction of 40 mg per deciliter (1.0 mmol per liter) in LDL cholesterol level.[35] We found a reduction in the systolic blood pressure of 3.8 mm Hg and the diastolic blood pressure of 2.4 mm Hg, along with a decrease in LDL cholesterol level of 9.8 mg per deciliter (0.25 mmol per liter), after CPAP therapy. These results suggest a significant clinical benefit that will lead to a reduction in cardiovascular risk.

The implications of our study are strengthened because, as compared with prior studies, it is large and has a long follow-up period, as well as being a placebo-controlled, double-blind, randomized, crossover study. We incorporated a 1-month washout period (chosen for convenience, with no guidelines to follow in this regard), which appeared to be adequate for all study variables except HDL cholesterol. Furthermore, we reported data on the metabolic syndrome, which is a frequent co-occurrence with obstructive sleep apnea and has a synergistic cardiovascular risk.

Our study has several limitations. A longer washout period may be required to ensure no carryover effects. Ambulatory blood-pressure measurements were not performed because of limited access to equipment when the study began. In addition, follow-up polysomnographic data were not collected.

In conclusion, 3 months of CPAP therapy in a group of patients with moderate-to-severe obstructive sleep apnea syndrome was associated with a decrease in both systolic and diastolic blood pressure, lipid levels, glycated hemoglobin levels, BMI, and abdominal fat content. CPAP treatment leads to improved control of elevated blood pressure and a reduction in metabolic abnormalities.

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