CHEST

Effects of CPAP on Metabolic Syndrome in Patients With OSA

A Randomized Trial

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BACKGROUND: OSA is associated with metabolic syndrome (MS), but it is unclear whether OSA treatment with CPAP can revert MS.

RESEARCH QUESTION: Does OSA treatment with CPAP per se have effects on the MS reversibility and the associated metabolic, adiposity and vascular parameters?

STUDY DESIGN AND METHODS: The TREATOSA-MS trial is a randomized placebo-controlled trial that enrolled adult patients with a recent diagnosis of MS and moderate or severe OSA (apnea-hypopnea index [AHI], ≥ 15 events/h) to undergo therapeutic CPAP or nasal dilator strips (placebo group) for 6 months. Before and after each intervention, we measured anthropometric variables, BP, glucose, and lipid profile. To control potential-related mechanisms and consequences, we also measured adiposity biomarkers (leptin and adiponectin), body composition, food intake, physical activity, subcutaneous and abdominal fat (visceral and hepatic fat), and endothelial function.

RESULTS: One hundred patients (79% men; mean age, 48 ± 9 years; BMI, 33 ± 4 kg/m^2; AHI, 58 ± 29 events/h) completed the study (n = 50 per group). The mean CPAP adherence was 5.5 ± 1.5 h/night. After 6 months, most patients with OSA randomized to CPAP retained the MS diagnosis, but the rate of MS reversibility was higher than observed in the placebo group (18% vs 4%; OR, 5.27; 95% CI, 1.27-35.86; $P = .04$). In the secondary analysis, CPAP did not promote significant reductions in the individual components of MS, weight, hepatic steatosis, lipid profile, adiponectin, and leptin, but did promote a very modest reduction in visceral fat and improved endothelial function (all analyses were adjusted for baseline values).

INTERPRETATION: Despite the higher rate of MS reversibility after CPAP therapy as compared with placebo, most patients retained this diagnosis. The lack of significant or relevant effects on adiposity biomarkers and depots supports the modest role of OSA in modulating MS.

TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT02295202; URL: www.clinicaltrials.gov

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KEY WORDS: CPAP; metabolic syndrome; metabolism; randomized controlled trial; sleep apnea

ABBREVIATIONS: FMD = flow-mediated dilation; MS = metabolic syndrome; NDS = nasal dilator strip; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue

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Take-home Points

Study Question: Does OSA treatment with CPAP per se have effects on metabolic syndrome (MS) reversibility and its associated metabolic, adiposity, and vascular parameters?

Results: As compared with placebo, 6 months of CPAP therapy was able to promote a modest effect on the rate of MS reversibility (4% vs 18%). This fact may be explained by the lack of significant or relevant effects of CPAP on several MS-related factors including weight, adiponectin, leptin, visceral fat, and hepatic steatosis.

Interpretation: Despite a significant rate of MS reversibility after CPAP therapy, most of the patients maintained the MS diagnosis. The modest effects of CPAP on MS reversibility underscore the need for combined therapy with CPAP, aiming to maximize MS recovery in parallel with improvements in OSA severity and related symptoms.

Metabolic syndrome (MS) is a common clinical condition associated with increased cardiovascular risk.[1,2] Supporting the potential cardiovascular role of MS, a recent cohort showed that MS recovery was associated with 15% fewer cardiovascular events than patients who retained the MS diagnosis.[3]

Among the comorbidities associated with MS, OSA has gained growing interest in the literature. OSA is characterized by recurrent episodes of upper airway obstructions leading to increased negative intrathoracic pressure, intermittent hypoxia, and sleep fragmentation.[4] Moderate to severe forms of OSA are common in association with MS[5] and may contribute to the number of MS criteria, subclinical inflammation, and surrogate markers of atherosclerosis.[5,6] A cohort study comprising 1,853 participants without MS at baseline showed that moderate to severe OSA was associated independently with a 2.5-fold higher rate of MS than that among participants without OSA after a mean follow-up of 6 years.[7] Collectively, these data suggest that OSA may represent an additional risk factor for MS.[8] However, whether OSA treatment per se promotes significant MS reversibility is not clear. Previous evidence addressing the effects of CPAP was limited by one or more of the following issues: (1) exploration of individual components of MS; (2) observational design; (3) no control for the effects of medications, diet, physical activity, or a combination thereof; (4) lack of detailed data on body composition and visceral fat (including hepatic steatosis).[9-13] The conflicting results observed in the aforementioned articles justify specific studies in this important research area.

This clinical trial aimed to evaluate the impact of OSA treatment with CPAP on MS reversibility (primary end point). Moreover, we explored the effect of CPAP treatment on each MS criterion: inflammatory and metabolic biomarkers, body composition, food intake, physical activity, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), hepatic steatosis, and endothelial function. We hypothesized that effective treatment with CPAP would promote a greater chance of MS reversibility than that with placebo.

Study Design and Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. This was a single-center, parallel-group, placebo-controlled trial of patients with recent diagnoses of OSA and MS recruited at the Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil. After baseline data collection, eligible patients were randomized into two groups: those receiving 6 months of therapeutic CPAP treatment and those receiving nasal dilator strips (NDSs; placebo group). NDSs were adopted as a placebo because they are highly acceptable and have no significant effects on respiratory events, but improve daytime sleepiness (suggesting a placebo effect).[14] Assessments were performed before and after treatment according to a modified intention-to-treat analysis (all patients with available data for addressing the primary end point were included for analysis in the assigned group, regardless of adherence). The trial protocol was approved by the local ethics committee (Certificado de apresentação para apreciação ética) Identifier: 33761314.0.0000.0068 and registered with Clinicaltrials.gov [Identifier: NCT02295202]. Written informed consent was obtained from each participant.

Adults with a recent diagnosis of MS were considered for inclusion in the trial. The exclusion criteria were as follows: (1) BMI of > 40 kg/m^2

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(because of potential weight limitations for the CT scan examination), (2) regular use of medications, (3) alcoholism, (4) current smoking, (5) pre-existing diseases other than those related to the study, (6) receiving treatment for OSA, and (7) performing shift work.

Randomization

An independent staff member prepared a randomization list (http://www.randomization.com/) in advance and placed the sequence and group information in sealed opaque envelopes after the allocation concealment principle. The randomization was stratified by BMI in two groups of patients: BMI of < 32 kg/m^2 and BMI of ≥ 32 kg/m^2. This cutoff was based on the average BMI that we observed in our previous study evaluating the frequency of OSA in consecutive patients with MS.[6]

After confirming the eligibility, the envelopes were opened consecutively and patients were assigned randomly (1:1) to receive CPAP therapy or NDSs. Because of the nature of the intervention, the trial intervention could not be masked to some investigators and patients, but several measurements were performed by professionals not involved with the study (such as laboratorial examinations) or by single investigators blinded to group allocation (for flow-mediated dilation [FMD] and CT scan analyses). Monthly visits to the clinic were scheduled for all participants for 6 months to monitor adherence to both treatments. After completing all steps, a CPAP device and appropriate compliance follow-up were offered to patients randomized to the placebo group. In addition, all groups received lifestyle interventions and medications (if necessary) at the end of the 6-month follow-up. Our ethical committee approved this strategy for allowing the appropriate evaluation of our main outcome.

Interventions

The patients who were assigned to receive CPAP treatment used an automated positive airway pressure machine (REMstar Auto A-Flex System One Series 50; Philips Respironics, Inc.). The pressure was set to automatic mode (range, 6-14 cmH_2O) for 1 week, and thereafter, the patients received their own CPAP machine (REMstar Pro C-Flex System One Series 50), for which the 90th pressure percentile was fixed based on data recorded by the automated device. This option followed the results of a previous trial suggesting better impact on BP using fixed vs autoadjusting CPAP.[15] If necessary, the pressure range was increased aiming at the normal apnea-hypopnea index range ($\leq$ 5 events/h). CPAP adherence was measured objectively (Encore Pro 2 Software; Philips Respironics, Inc.) by downloading data from a memory card in the first week and then monthly. Phone calls or extra visits were allowed if necessary.

All patients assigned to placebo group were instructed to use NDSs (Respire Melhor; GSK Ltd.) every night during the follow-up, bringing any unused NDSs to the predefined visits. Adherence was measured as the percentage use (total number of days using NDSs divided by the total number of days between each monthly visit $\times$ 100).

Procedures

First Phase: Screening: The study was announced in various types of media. Patients considered for the trial answered some questions about their medical history and snoring reports and provided results of recent blood tests ($<$ 1 year) over the telephone or through email. Those with preliminary data suggesting the presence of MS and OSA were invited to participate in an initial clinical evaluation. MS was defined according to the National Cholesterol Education Program's Adult Treatment Panel III criteria.[1] At least three of the following criteria needed to be met: (1) waist circumference of $\geq$ 102 cm in men and $\geq$ 88 cm in women, (2) fasting glucose levels of $\geq$ 100 mg/dL, (3) triglyceride levels of $\geq$150 mg/dL, (4) high-density lipoprotein cholesterol of $<$ 40 mg/dL in men and $<$ 50 mg/dL in women, and (5) systolic BP of $\geq$ 130 mm Hg, diastolic BP of $\geq$ 85 mm Hg, or both.

Second Phase: OSA Diagnosis and MS Confirmation: Selected patients from the first phase underwent polysomnography at the sleep laboratory to define the presence of OSA (e-Appendix 1). Those with an apnea-hypopnea index of $\geq$ 15 events/h of sleep were invited to return to the research center and collect new fasting blood samples. Patients with confirmed MS were invited to complete all clinical assessments described below.

Clinical Assessments

A complete description of the clinical assessments can be found in e-Appendixes 1 and 2.[16-34] All patients underwent a detailed clinical and physical examination including body weight; height; waist, hip, and neck circumference measurements; and BP recordings. The assessments were performed in a blinded fashion.

To avoid the potential impact of other interventions on MS, all patients were instructed not to make any lifestyle changes during the follow-up. Dietary intake pattern and physical activity were evaluated by using the short version of the Food Frequency Questionnaire[20] and the long-form International Physical Activity Questionnaire,[21] respectively.

Fasting blood samples were drawn to determine serum glucose, insulin, lipid profile, thyroid-stimulating hormone, high-sensitivity C-reactive protein, alanine aminotransferase, and aspartate aminotransferase and to perform homeostasis model assessment using standard techniques. Serum adiponectin and leptin were measured using enzyme-linked immunosorbent assay. Salivary cortisol was determined by liquid chromatography-tandem mass spectrometry.[34] Body composition was measured by a direct segmental multifrequency bioelectrical impedance analyzer (InBody S10; Biospace Co.).

A single investigator performed all the radiologic measurements. Fat accumulation in the abdominal area, that is, VAT, SAT, and liver fat, was measured by CT scan (Aquilion One; Toshiba Medical Systems). e-Figure 1 provides detailed techniques and representative examples.

Endothelial function was evaluated by measuring FMD in the brachial artery using a high-resolution ultrasound system (Sequoia Echocardiography System, version 6.0; Acuson, Siemens). FMD was expressed as the percent change in brachial artery diameter from baseline after the reactive hyperemia maneuver.[33]

Outcomes

The primary outcome was the MS reversibility rate in patients with OSA after 6 months of CPAP treatment (ie, those who demonstrated fewer than three MS criteria at the end of the follow-up). The secondary outcomes explored the effects of OSA treatment with CPAP for 6 months on each MS criterion as well as inflammatory and metabolic biomarkers, body composition, VAT, SAT, hepatic steatosis, and endothelial function. These outcomes were chosen because they represent clinical relevance for the MS diagnosis (such as individual components of MS) or to explore intermediate mechanisms related to MS pathophysiologic features or its consequences. A detailed description of the study end points is provided in the e-Appendix 1.

Statistical Analysis

Our study design allowed us to test the effects of CPAP on MS reversibility in patients with OSA without any drug intervention, diet intervention, physical activity intervention, or a combination thereof. At the time we designed the protocol, the sample size was based on the results from two investigations, but one of them was retracted. Therefore, we used preliminary results from an observational study showing significant (up to 38%) improvements in components of MS after 2 months of CPAP therapy.[9] By expecting a more conservative impact of CPAP therapy on MS, we estimated that the total sample size (assuming 1:1 randomization) required detecting a 25% reversal

of MS in the CPAP group and a 5% reversal in the placebo group with 80% power at a two-tailed significance level of 5% was 94 patients treated for 6 months.

Statistical analyses were performed using R version 3.6.0 software (R Foundation for Statistical Computing). Data are expressed as the mean ± SD, median (interquartile range), and absolute frequency and relative frequency, when appropriate. To compare the baseline characteristics of the placebo group and the CPAP treatment group, either the Student *t* test or the Mann-Whitney *U* test was used for continuously distributed variables, and the χ^2 test was used for categorical variables.

The treatment's effect was measured as the difference between the final and starting values for all variables. The intragroup differences from the beginning to the end of the study and the treatment effect between groups were evaluated by mixed-model repeated measures or nonparametric analyses of variance, when appropriate. For all continuous variables, intergroup comparisons of the change were adjusted for baseline values (for avoiding regression to the mean effects). ORs for the reversal of MS were calculated using logistic regression. Significance was assessed with a *P* value of $< .5$ (see e-Appendix 2 for details).

Results

Between March 1, 2015, and April 30 2019, a total of 1,406 patients were screened, but 1,303 were excluded for several reasons, as depicted in Figure 1. One-hundred three patients were randomized to the CPAP or placebo group. Three patients in the CPAP group discontinued the study, preventing the availability of data for the primary and secondary outcomes. Therefore, 100 patients (n = 50 in each group) completed the study.

The baseline characteristics of the entire cohort and of the two groups are presented in Table 1. Overall, we included middle-aged White men with severe OSA. The mean use of CPAP treatment was 5.5 ± 1.5 h/night. The placebo group patients used NDSs on 97 ± 4% of the nights studied. A trend for higher BP in the CPAP group was found, but it did not reach statistical significance. Table 2 summarizes the results for baseline, follow-up, changes in lifestyle habits, anthropometry, and sleep parameters. No significant changes were found in food intake or physical activity or in the anthropometric variables between groups. Consistent with our previous findings,[14] NDSs improved daytime sleepiness, but not OSA severity.

As shown in Figure 2A, CPAP therapy significantly increased MS reversibility compared with placebo. No single MS criterion drove this response for patients whose MS diagnosis was reversed (Fig 2B). The MS reversibility was observed mainly in patients with OSA with three MS criteria at baseline (78% in the CPAP group). The mean number of MS components decreased in the CPAP group from 3.7 ± 0.6 at baseline to 3.2 ± 0.9 at 6 months, whereas they remained stable in the placebo group (3.7 ± 0.6 vs 3.8 ± 0.8, respectively; mean difference, –0.42 ± 0.95 and +0.02 ± 0.80, respectively; $P = .014$).

Compared with placebo, CPAP therapy promoted significant decreases in systolic and diastolic BP at follow-up, but these results were not significant after correcting for baseline BP (Table 3). Regardless of MS reversibility, data on the status for each MS criterion (reversal, maintained, and development) after 6 months of CPAP therapy or placebo are illustrated in Figure 3. We observed no differences in the proportion of patients who demonstrated one or more additional MS criteria during the study.

Baseline and follow-up values of and changes in metabolic and inflammatory parameters not included in the MS criteria are summarized in Table 3. After correcting for baseline values, we did not observe significant differences in the glucose or lipid profiles, alanine aminotransferase, aspartate aminotransferase adiponectin, leptin, or salivary cortisol in the two groups. No other significant changes in inflammatory and metabolic biomarkers were found.

Measurements of body composition are summarized in e-Table 1. No significant difference was found in body fat mass, lean mass, or water content between the two groups. No significant differences in SAT (Table 3) or hepatic steatosis (e-Table 2) were observed between the CPAP and placebo groups. Regarding VAT, the placebo group showed a small increase, whereas the CPAP group showed a small decrease. This comparison remained significant after adjustment for baseline values (Table 3).

Finally, patients who had received CPAP treatment showed a trend toward increasing FMD, whereas those in the placebo group showed significant impairment in the FMD (Table 3). The between-group difference in the change in the FMD was significant.

Discussion

The present randomized study evaluated the impact of OSA treatment on MS, taking into account potential related factors such as food intake, physical activity, and markers of adiposity. Consistent with our hypothesis, this placebo-controlled study showed that 6 months of CPAP treatment in patients with moderate to severe

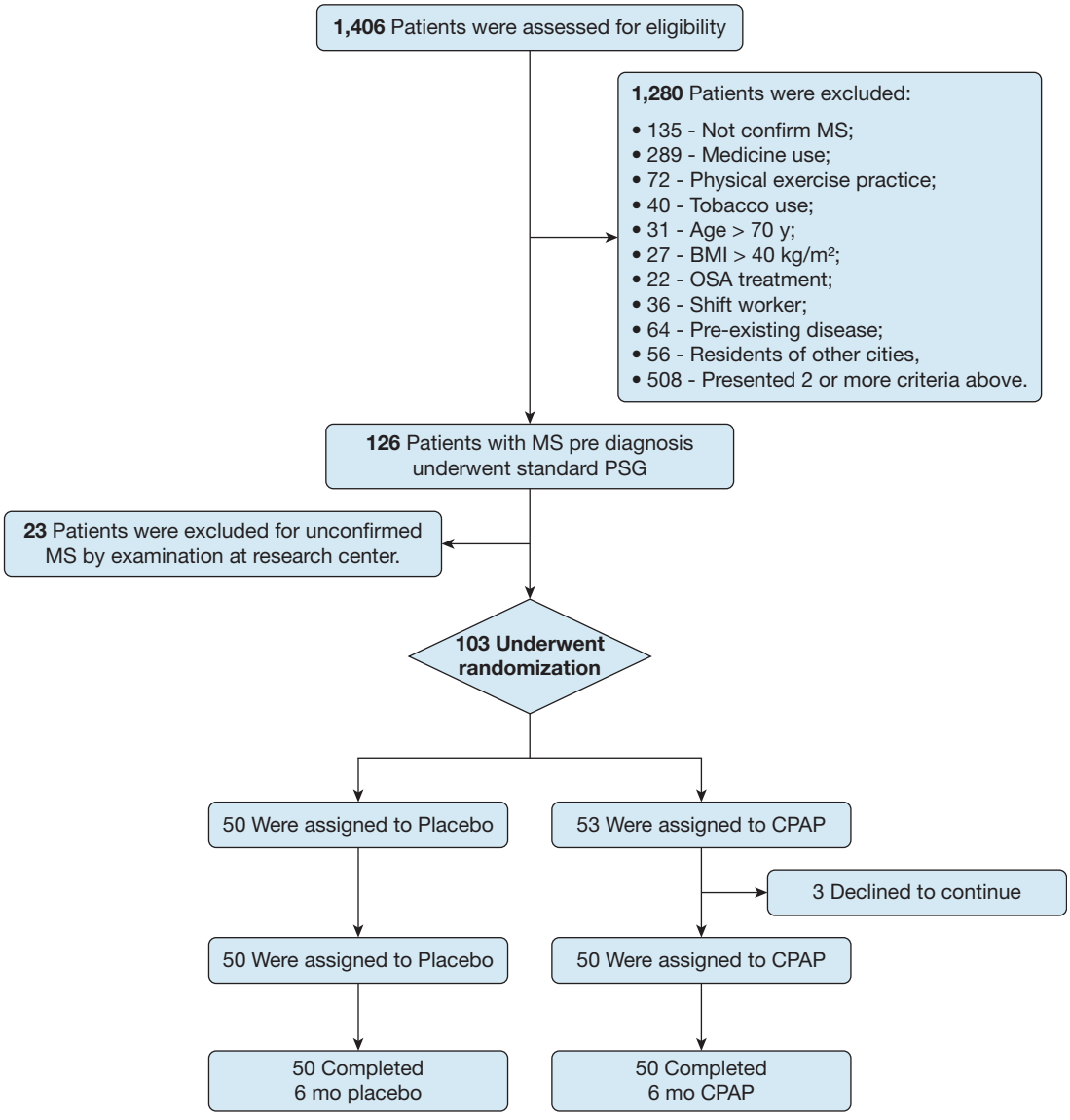

Figure 1 – *Study flowchart showing screening, enrollment, and follow-up of patients. MS = metabolic syndrome; PSG = polysomnography.*

OSA increased the chance of MS diagnosis reversal as compared with placebo. No single MS criterion drove the MS reversibility. However, our secondary analysis underscored that the impact of CPAP therapy is modest. Compared with placebo, CPAP treatment showed no significant effects on diet, physical activity, BMI, leptin, adiponectin, SAT, or hepatic steatosis. A very small (potentially without clinical relevance) reduction in VAT was observed after CPAP. Collectively, our results suggest that the benefits of CPAP therapy in reversing MS are modest.

The primary end point showed that for approximately every five patients with OSA treated with CPAP, the MS diagnosis of one of them was reversed. This result is modest, but considering that no adjuvant therapy was recommended or prescribed during the trial (to evaluate the impact of OSA treatment per se), it may be relevant. Previous investigations evaluating other single therapies for reversing MS diagnosis showed similar results. Stewart et al[35] demonstrated that 6 months of aerobic and resistance exercise training resulted in 17.7% MS reversion in patients 55 to 75 years of age. A large, multicenter, randomized controlled trial evaluating the impact of a Mediterranean diet showed 25.2% and 28.2% MS remission after 1 year and 4.8 years of follow-up, respectively.[36,37] Regarding combined therapy, in a prospective, observational study, Jeejeebhoy et al[38] observed a 22% reversal rate of MS in response to a diet

TABLE 1] Baseline Characteristics of All Randomized Patients

Characteristic	All Patients (N = 100)	Placebo Group (n = 50)	CPAP Group (n = 50)	*P* Value
Age, y	48 ± 9	49 ± 10	48 ± 9	.60
Male sex	79 (79)	41 (82)	38 (76)	.62
White race	68 (68)	40 (80)	28 (56)	.01
Weight, kg	95 (86-106)	95 (87-107)	96 (85-106)	.64
BMI, kg/m^2	32.7 (29.6-35.5)	32.0 (29.8-35.0)	33.1 (29.4-35.7)	.84
Neck circumference, cm	43 ± 4	43 ± 3	42 ± 4	.29
Waist circumference, cm	112 (106-117)	111 (107-117)	113 (105-117)	.27
Hip circumference, cm	113 (108-119)	113 (107-118)	112 (109-119)	.83
Smoking history				.59
Never	61 (61)	28 (56)	33 (66)	
Former smoker > 1 y	30 (30)	17 (34)	13 (26)	
Former smoker ≤ 1 y	9 (9)	5 (10)	4 (8)	
Physical activity level				.32
Inactive	14 (14)	9 (18)	5 (10)	
Insufficiently active	34 (34)	14 (28)	20 (40)	
Active	52 (52)	27 (54)	25 (50)	
BP, mm Hg				
Systolic	132 (124-147)	130 (123-141)	138 (126-150)	.05
Diastolic	88 ± 10	86 ± 10	90 ± 10	.06
Heart rate, beats/min	70 (63-80)	71 (66-80)	66 (63-79)	.18
Fasting glucose, ng/dL	100 (94-112)	100 (94-111)	103 (93-113)	.83
HDL cholesterol, mg/dL	35 (31-40)	35 (30-39)	36 (31-42)	.38
Triglycerides, mg/dL	198 (152-259)	216 (162-258)	171 (140-268)	.49
No. of MS criteria	4.0 (3.0-4.0)	4.0 (3.0-4.0)	4.0 (3.0-4.0)	.54
Sleep parameters				
Epworth sleepiness scale score	13.0 (10.0-17.0)	14 (11.0-16.0)	13.0 (9.0-17.8)	.77
Apnea-hypopnea index, events/h	57 (33-82)	49 (33-76)	62 (35-89)	.14
Sleep N1, % TST	5.2 (2.7-9.2)	5.8 (3.1-9.4)	4.5 (2.4-8.7)	.41
Sleep N2, % TST	61.8 ± 13.1	60.0 ± 12.7	63.4 ± 13.3	.19
Sleep N3, % TST	15.5 (9.3-22.9)	15.9 (12.4-22.6)	13.8 (4.9-23.1)	.09
REM sleep, % TST	15.2 ± 6.1	14.8 ± 6.4	15.6 ± 5.9	.52
Mean nocturnal oxygen saturation, %	93 (91-94)	92 (91-94)	93 (91-94)	.49
TST oxygen saturation < 90%, %	6.3 (1.6-31.6)	7.5 (2.0-31.6)	5.5 (1.2-30.1)	.74

Data are presented as No. (%), mean ± SD, or median (interquartile range). HDL = high-density lipoprotein; MS = metabolic syndrome; REM = rapid eye movement; TST = total sleep time.

and aerobic exercise program in 305 patients at 6 months that remained stable until 1 year. However, in our study, the continuous analysis revealed no significant differences in each component of MS. How to explain this apparent inconsistency between dichotomic and continuous data on MS? Because no single criterion drove this response and most patients did not show reversal of the MS diagnosis during the follow-up, it is not improbable to find that the overall effects of CPAP on continuous variables did not reach significance (in contrast to the positive significance on the MS rate). The presence of a control group allows us to argue that this finding may not be attributable to chance. In addition, our main results are not explained by changes in food intake and physical activity because of the lack of differences between the two groups.

Our secondary analysis revealed that CPAP therapy did not promote significant reductions in several metabolic parameters as compared with placebo. In our study, we adjusted all the results for baseline parameters, thereby

TABLE 2] Effect of CPAP vs Placebo on Lifestyle Habits, Anthropometric Variables, and Sleep Parameters

Variable	Placebo Group				CPAP Group				
	Baseline	Follow-up	Delta[a]	*P* Value[b]	Baseline	Follow-up	Delta[a]	*P* Value[b]	*P* Value[c]
Lifestyle habits									
Physical activity level, min/wk	180 (60-369)	190 (83-465)	0.0 (−84.7 to 232.5)	.25	165 (80-375)	188 (53-405)	−20.0 (−87.5 to 153.7)	.84	.35
Dietary intake pattern									
Energy, kcal	2,278 (1,767-3,045)	2,235 (1,678-2,682)	−200.2 (−607.3 to 370.1)	.19	2,029 (1,652-2,574)	2,023 (1,583-2,492)	−83.3 (−348.4 to 362.5)	.55	.69
Carbohydrates, %	53 ± 7	53 ± 7	0.40 ± 7.96	.73	55 ± 7	54 ± 8	−1.0 ± 8.5	.36	.93
Proteins, %	17 (15-19)	17 (15-20)	−0.10 (−1.39 to 2.62)	.61	17 (15-18)	18 (16-21)	0.71 (−0.92 to 3.28)	.14	.54
Fat, %	30 ± 6	29 ± 6	−0.83 ± 6.70	.35	28 ± 6	28 ± 6	−0.19 ± 5.91	.83	.62
Anthropometry									
Weight, kg	95 (87-107)	95 (86-106)	0.18 (−2.00 to 1.76)	.68	96 (85-106)	94 (86-106)	0.43 (−1.80 to 1.90)	.35	.45
BMI, kg/m^2	32.0 (29.8-35.0)	32.2 (30.0-35.3)	0.02 (−0.66 to 0.62)	.88	33.0 (29.4-35.6)	32.4 (29.1-35.7)	0.15 (−0.61 to 0.75)	.65	.57
Neck circumference, cm	43.1 ± 3.4	42.7 ± 3.6	−0.41 ± 1.40	.07	42.3 ± 4.0	41.8 ± 3.4	−0.52 ± 1.83	**.02**	.49
Hip circumference, cm	113 (107-118)	112 (107-120)	0.0 (−1.4 to 1.8)	.78	112 (109-119)	112 (106-118)	−0.08 (−3.5 to 1.4)	.07	.25
Sleep parameters									
Epworth sleepiness scale score	14 (11-16)	11 (6-15)	−1 (−5 to 0)	< **.001**	13 (9-18)	6 (3-8)	−6 (−9 to −3)	< **.001**	< **.001**
Apnea-hypopnea index, events/h	49 (33-76)	51 (32-69)	4.3 (−15.6 to 13.4)	.50	62 (35-89)	5 (2-8)	−48.6 (−76.8 to −33.6)	< **.001**	< **.001**
Arousal index score, events/h	43 (29-71)	44 (31-59)	1.1 (−15.5 to 13.9)	.76	54 (35-88)	19 (11-28)	−36.3 (−55.0 to −17.0)	< **.001**	< **.001**
TST, h	6.5 (5.9-7.2)	6.6 (5.8-7.0)	−0.15 (−0.50 to 0.77)	.96	6.9 (6.3-7.4)	6.4 (6.0-7.2)	−0.40 (−1.30 to 0.40)	**.02**	.69
Sleep efficiency, %	89 (79-95)	89 (81-94)	−1.1 (−6.0 to 4.3)	.45	92 (87-95)	92 (87-96)	0.8 (−3.2 to 3.3)	.94	.08
Sleep N1, % TST	5.8 (3.1-9.4)	6.7 (3.3-16.8)	0.05 (−3.02 to 8.78)	.27	4.5 (2.4-8.7)	4.9 (2.9-8.4)	0.30 (−3.60 to 3.20)	.94	**.006**
Sleep N2, % TST	60.0 ± 12.7	57.7 ± 12.1	−2.2 ± 12.2	.22	63.4 ± 13.3	54.6 ± 9.0	−8.7 ± 14.4	< **.001**	**.04**
Sleep N3, % TST	15.9 (12.4-22.6)	16.8 (10.5-22.6)	−0.4 (−7.6 to 4.0)	.29	13.8 (4.9-23.1)	19.4 (14.3-25.6)	5.4 (−3.3 to 13.2)	**.001**	**.005**
REM sleep, % TST	14.8 ± 6.4	14.7 ± 6.4	−0.07 ± 5.24	.93	15.6 ± 5.9	18.9 ± 5.8	3.2 ± 7.4	< **.001**	< **.001**
Mean nocturnal oxygen saturation, %	92 (91-94)	92 (92-94)	−0.25 (−0.70 to 1.00)	.64	93 (91-94)	95 (94-96)	2.15 (1.20-3.55)	< **.001**	.65
TST oxygen saturation < 90%, %	7.5 (2.0-31.6)	11.5 (1.6-22.8)	0.11 (−8.57 to 5.04)	.90	5.5 (1.2-30.1)	0.03 (0.00-0.58)	−5.6 (−30.41 to −1.25)	< **.001**	< **.001**

Data are presented as the mean ± SD or median (interquartile range). *P* values in boldface indicate statistical significance. REM = rapid eye movement; TST = total sleep time.
[a]Treatment effect estimate (value of the variable at follow-up subtracted from the baseline value). Note: the median of the differences is not necessarily equal to the difference of the medians.
[b]For the comparison between baseline and follow-up in each group.
[c]Comparisons adjusted for baseline values.

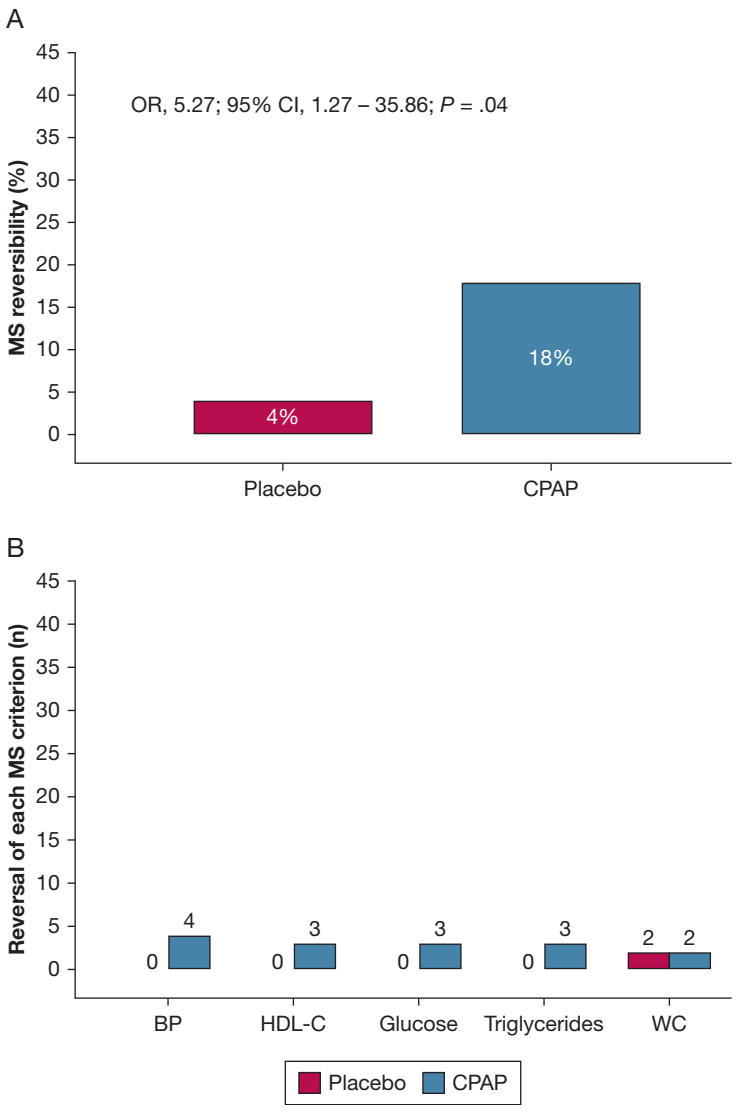

Figure 2 – *A, B, Bar graphs showing the effects of CPAP on MS: primary outcome (OR was calculated using logistic regression) (A) and treatment effect on the reversal of each MS criterion (for those whose MS diagnosis reversed) (B). HDL-C = high-density lipoprotein cholesterol; MS = metabolic syndrome; WC = waist circumference.*

reducing the impact of the regression to the mean statistical effect. The literature addressing the impact of CPAP on glucose, lipid, and other metabolic parameters are inconsistent; most of the evidence is observational or did not control confounders such as diet and physical activity.[38-42] In the present investigation, CPAP did not promote changes in weight, SAT, or hepatic steatosis as compared with the placebo. Although significant, the impact of CPAP on VAT observed in our study was very modest for claiming any clinical relevance or speculation about the potential related mechanisms. A previous meta-analysis from our group pointed to modest weight gain after OSA treatment, but the mean follow-up duration of the enrolled studies was short (approximately 3 months).[43] Moreover, the selected studies were not focused on metabolism or weight, and thus did not control for potential confounders (including food intake and physical activity).[43] The impact of OSA treatment on weight may be influenced by CPAP use: a recent updated meta-analysis addressing the impact of CPAP on BMI showed that using CPAP for $>$ 5 h may mitigate the risk for weight gain in patients with OSA.[44] In our study, the mean use was 5.5 h/night. Therefore, the current investigation adds to the available literature by controlling adiposity parameters, food intake, and physical activity; the lack of significance on these variables may help to explain the modest effects of OSA on MS.

TABLE 3] Effect of CPAP vs Placebo on Metabolic and Inflammatory Profile, Abdominal Fat, and Endothelial Function

Variable	Placebo Group				CPAP Group				
	Baseline	Follow-up	Delta[a]	*P* Value[b]	Baseline	Follow-up	Delta[a]	*P* Value[b]	*P* Value[c]
Variables included in MS criteria									
Waist circumference, cm	111 (107-117)	112 (106-117)	0.2 (−1.3 to 1.3)	.87	113 (105-117)	110 (103-116)	−1.2 (−3.9 to 1.7)	**.03**	.30
BP, mm Hg									
Systolic	130 (123-141)	130 (123-135)	−0.7 (−8.6 to 5.8)	.46	138 (126-150)	128 (119-143)	−7.5 (−13.3 to −0.62)	< **.001**	.18
Diastolic	86 ± 10	85 ± 9	−1 ± 8	.25	90 ± 10	85 ± 11	−5 ± 8	< **.001**	.06
Fasting glucose, ng/dL	100 (94-111)	102 (95-110)	0.0 (−6.7 to 5.0)	.66	103 (93-113)	100 (92-113)	−2.0 (−8.0 to 4.0)	.40	.79
HDL cholesterol, mg/dL	35 (30-39)	34 (31-41)	0.0 (−3.0 to 3.0)	.74	36 (31-42)	38 (31-43)	1.0 (−3.0 to 3.0)	.31	.46
Triglycerides, mg/dL	216 (162-257)	216 (173-251)	2.5 (−19.2 to 37.7)	.82	171 (140-268)	177 (129-223)	−12.0 (−59.0 to −28.0)	.12	.22
Variables not included in MS criteria									
Fasting insulin, mU/L	21.0 (14.0-28.0)	18.0 (14.0-28.0)	−1.0 (−5.5 to 5.0)	.74	17.5 (12.2-23.7)	16.5 (13.0-24.7)	−1.0 (−6.0 to 3.7)	.55	.12
HOMA-IR	5.05 (3.27-8.10)	4.60 (3.60-7.00)	−0.10 (−1.60 to 1.05)	.77	4.30 (3.00-6.40)	4.40 (2.95-5.97)	−0.20 (−1.70 to 0.70)	.56	.23
Cholesterol, mg/dL	203 (186-236)	210 (178-238)	0.0 (−14.2 to 15.5)	.94	212 (185-230)	190 (174-227)	−9.0 (−28.7 to 13.7)	**.007**	.38
Non-HDL cholesterol, mg/dL	165 (150-199)	176 (143-202)	−3.0 (−13.7 to 14.0)	.96	173 (142-193)	155 (138-185)	−7.5 (−26.7 to 9.7)	**.008**	.31
VLDL cholesterol, mg/dL	36 (31-44)	35 (31-44)	0.0 (−3.7 to 4.0)	.55	31 (27-44)	30 (24-36)	−3.0 (−8.0 to 3.0)	**.02**	.16
LDL cholesterol, mg/dL	129 (116-156)	128 (114-159)	−0.5 (−13.7 to 11.7)	.87	134 (111-153)	127 (105-142)	−5.0 (−21.0 to 10.2)	.12	.49
TSH, mUI/L	2.35 (1.52-3.30)	2.10 (1.63-3.08)	0.00 (−0.38 to 0.30)	.16	2.00 (1.63-2.80)	2.25 (1.52-3.10)	0.00 (−0.30 to 0.55)	.32	.26
CRP, mg/dL	0.33 (0.19-0.52)	0.28 (0.18-0.45)	−0.03 (−0.09 to 0.03)	.15	0.30 (0.19-0.53)	0.29 (0.18-0.60)	0.01 (−0.06 to 0.10)	.90	.34
ALT, U/L	14 (7-20)	16 (10-23)	2.0 (−2.0 to 5.7)	**.004**	14 (7-23)	16 (11-23)	0.0 (−4.0 to 5.5)	**.011**	.35
AST, U/L	18 (13-23)	21 (15-24)	2.0 (−2.0 to 5.0)	**.009**	19 (13-23)	20 (16-27)	1.0 (−2.0 to 7.0)	**.004**	.13
Adiponectin, pg/mL	553 (377-988)	665 (412-992)	116 (−217 to 350)	.78	739 (555-1093)	641 (410-1132)	−74 (−330 to 272)	.19	.83
Leptin, pg/mL	146 (95-207)	105 (82-236)	−4.2 (−31.5 to 35.7)	.18	98 (68-213)	102 (62-184)	−1.5 (−33.3 to 22.9)	.76	.86
Salivary cortisol, ng/dL									
7 AM	219 (128-389)	205 (130-396)	6.8 (−202.3 to 206.9)	.69	200 (127-307)	191 (145-378)	30.9 (−96.0 to 152.3)	.74	.42
4 PM	87 (50-120)	72 (31-105)	−6.4 (−63.1 to 45.9)	.16	60 (44-107)	64 (44-92)	3.8 (−35.1 to 30.5)	.85	.39
11 PM	34 (24-66)	33 (24-51)	−0.5 (−21.6 to 13.9)	.42	26 (24-62)	29 (24-45)	0.0 (−17.2 to 13.4)	.51	.20
Abdominal fat									
VAT, cm^2	250.0 (204.0-325.0)	260.0 (204.0-320.0)	4.0 (−13.0 to 19.0)	.33	260.0 (187.5-298.7)	251.5 (187.5-292.0)	−6.0 (−24.2 to 14.0)	.33	**.02**
SAT, cm^2	230.2 ± 83.9	227.4 ± 81.7	−2.7 ± 20.4	.40	213.5 ± 88.1	209.9 ± 91.8	−3.5 ± 25.5	.29	.79
Endothelial function									
FMD, %	3.47 ± 4.86	1.80 ± 4.99	−1.78 ± 5.59	**.03**	1.69 ± 3.69	3.14 ± 4.23	1.60 ± 5.67	.06	**.04**

Data are expressed as the mean ± SD or median (interquartile range). *P* values in boldface indicate statistical significance. ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; FMD = flow-mediated dilation; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment-insulin resistance index; LDL = low-density lipoprotein; MS = metabolic syndrome; SAT = subcutaneous adipose tissue; TSH = thyroid-stimulating hormone; VAT = visceral adipose tissue; VLDL = very low-density lipoprotein.

[a]Treatment effect estimate (value of the variable at follow-up subtracted from the baseline value). Note: median of the differences is not necessarily equal to the difference of the medians.

[b]For the comparison between baseline and follow-up in each group.

[c]Comparisons adjusted for baseline values.

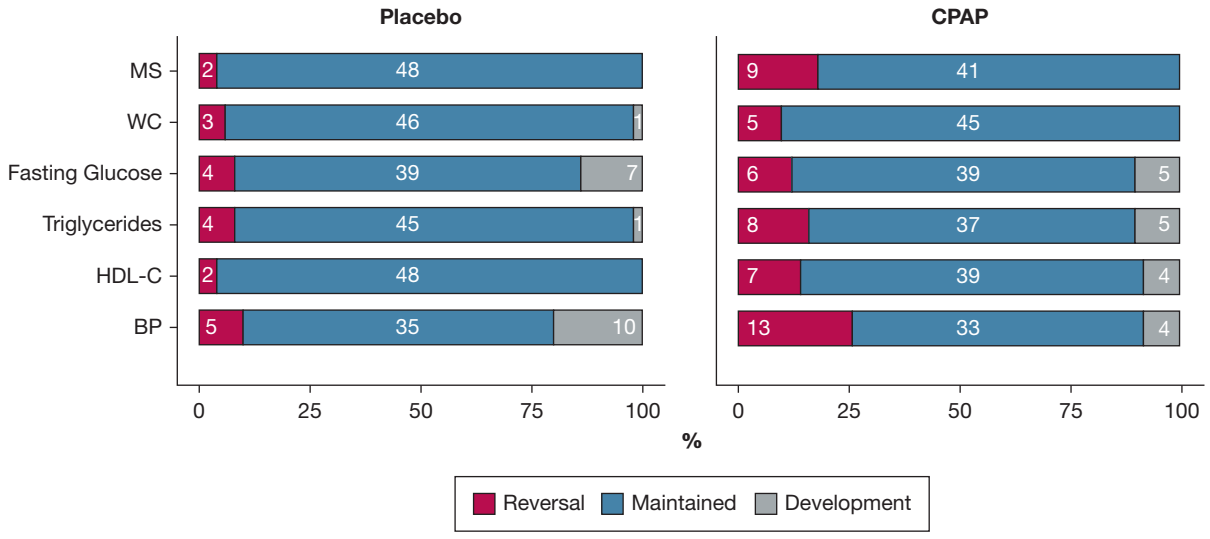

Figure 3 – *Bar graphs showing treatment effect on status of MS and each of its components. Each bar represents the number of people whose diagnosis reversed, whose diagnosis was maintained, or who demonstrated additional components of MS. HDL-C = high-density lipoprotein cholesterol; MS = metabolic syndrome; WC = waist circumference.*

Despite the strengths, our study has limitations. First, it was performed by a single center, with a relatively small sample for carrying out subanalyses. Second, although our study evaluated the relative impact of OSA on MS, the results may not be extrapolated to patients receiving pharmacologic treatment for MS. By concept, patients receiving antihypertensive treatment, glucose, and lipid-lowering therapies do not reverse the related MS criteria.[1] Third, despite our standard randomization procedure, we found (by chance) differences in the frequency of White patients randomized to CPAP or placebo. Although this finding may be relevant, detailed genetic analysis of the Brazilian population revealed substantial genetic admixture.[45] Fourth, the follow-up of patients was relatively short (6 months), which may have influenced the lack of significant reductions in the individual components of MS. However, not allowing patients with MS to alter their diet or physical activity for longer periods may present significant ethical issues. Fifth, we used CT scans for VAT and hepatic steatosis analyses. We chose CT imaging because an ongoing substudy is evaluating epicardial adipose tissue and coronary angiotomography. A recent randomized study devoted to the analysis of intrahepatic triglyceride levels as measured by proton-magnetic resonance spectroscopy showed no effects of CPAP.[46] Of note, the use of sham CPAP at 4 cm H_2O in the control group promoted a significant change in OSA severity (from 33.50/h at baseline to 10.88/h at 6 months).[46] Finally, this was a nonblinded study. Although sham CPAP clearly is preferable as a placebo, this strategy may cause some impact on several studied parameters and some discomfort by using ineffective pressure. A previous randomized crossover trial showed that despite the lack of full disclosure about the presence of sham CPAP, patients revealed a clear preference for active CPAP. After disclosing the presence of placebo, 73% believe they would have been unblinded had they known at the start of the trial.[47]

Interpretation

In conclusion, the TREATOSA-MS trial showed that 6 months of CPAP therapy in patients with OSA promoted a higher chance of MS reversal as compared with placebo. However, most of patients retained the MS diagnosis, despite the expected improvements in sleep. These results underscore the need for combined therapy with CPAP, aiming to maximize MS recovery in parallel with improvements in OSA severity and daytime sleepiness. Supporting this statement, a previous trial in patients with obesity and OSA showed in one of the secondary outcomes that combining effective weight loss with CPAP resulted in more impact on BP reduction than each strategy.[48]

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Author contributions: S. Q. C. G. and L. F. D. are the guarantors of this article and take responsibility for the content of the manuscript, including the data and analysis. S. Q. C. G. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S. Q. C. G. and L. F. D. wrote the initial manuscript draft with input from all authors. All authors contributed substantially to the concept and design of the study, acquisition of the data, data analysis, interpretation of the data, or a combination thereof. All authors reviewed the manuscript critically for important intellectual content and approved the final manuscript.

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Additional information: The e-Appendixes, e-Figure, and e-Tables are available online under "Supplementary Data."

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