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Tele-Pulmonary Rehabilitation and Mediterranean-like Lifestyle, Adjunctively to Continuous Positive Airway Pressure in Obstructive Sleep Apnea Patients: Effects in Fitness and Oxidative Indicators

Vasileios T. Stavrou [1,2,†], Eirini Papayianni [1,†], Kyriaki Astara [3,*,†], George D. Vavougios [4], Meropi D. Kontogianni [5], Alexandra Bargiota [6], Chaido Pastaka [7], Zoe Daniil [1,7] and Konstantinos I. Gourgoulianis [1,7]

1 Laboratory of Cardio-Pulmonary Testing and Pulmonary Rehabilitation, Respiratory Medicine Department, Medical School, University of Thessaly, 41110 Larissa, Greece; vasileiosstavrou@hotmail.com (V.T.S.); eirinipapayianni@gmail.com (E.P.)
2 ONISILOS MSCA COFUND, Medical School, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus
3 Department of Neurology, 417 Army Equity Fund Hospital (NIMTS), 11521 Athens, Greece
4 Department of Neurology, Medical School, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus
5 Department of Nutrition and Dietetics, Harokopio University of Athens, 70 El. Venizelou Street, 17671 Athens, Greece
6 Department of Endocrinology and Metabolic Diseases, Larissa University Hospital, University of Thessaly, 41110 Larissa, Greece
7 Laboratory of Sleep Disorders, Respiratory Medicine Department, Medical School, University of Thessaly, 41110 Larissa, Greece
* Correspondence: kyriakiastara@gmail.com
† These authors contributed equally to this work.

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Abstract: Obstructive sleep apnea (OSA), often overlooked by clinicians, may lead to negative outcomes if left untreated. In this study, we examined the efficacy and efficiency of a 12-week unsupervised tele-rehabilitation program in OSA patients and focused on the potential changes in their fitness indicators and oxidative status. Forty OSA patients were allocated into two groups: the CPAP-group (AHI 52.0 ± 31.5 events/h; age, 49.7 ± 9.4 years; BMI, 32.1 ± 7.6 kg/m^2; control group) versus the non-CPAPgroup (AHI 38.2 ± 21.5 events/h; age, 49.3 ± 10.7 years; BMI, 32.3 ± 5.1 kg/m^2; intervention group; personalized recommendations for nutrition—based on the Mediterranean diet—and exercise programs). Measurements included anthropometric characteristics and body composition through whole-body bioelectrical impedance analysis. In addition, participants underwent blood sampling for reactive oxygen metabolites' levels (d-ROM), plasma antioxidant capacity (PAT), and Lipoprotein (a) (Lp(a)), as well as a 6 min walk test (6MWT). Statistically significant differences were detected in both groups (CPAPgroup versus non-CPAPgroup) after 12 weeks between Lp(a) (−32.2 ± 25.5%, p = 0.021 versus −17.7 ± 16.3%, p = 0.034) and 6MWT (16.6 ± 9.3%, p < 0.001 versus 7.5 ± 6.6%, p = 0.002). ΔNRO2 (oxygen saturation difference between nadir during sleep and resting awake) was significantly associated with d-ROMs levels (p = 0.045), resting mean arterial pressure (p = 0.024), and chest circumference in maximal inhalation and exhalation (Δchest, p < 0.001). To conclude, lifestyle interventions with unsupervised tele-exercise-rehabilitation pulmonary programs and Mediterranean-like diet may serve as adjunctive-to-CPAP therapeutic elements.

Keywords: obstructive sleep apnea; CPAP; rehabilitation; physical activity; oxidative stress

1. Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep [1]. The Apnea–Hypopnea Index (AHI) is utilized to assess the severity of OSA, along with Oxygen-Desaturation Index

(ODI) and oxygen saturation (SpO_2) variability (e.g., nadir SpO_2) [2], and their severity has been associated with several comorbidity phenotypes [3]. These parameters are suggestive of a major pathophysiologic sequence of recurrent apneic episodes, namely intermittent hypoxia, prompted by endothelial dysfunction and the production of reactive oxygen species (ROS) [4], which lead to chronic clinical consequences, like arterial hypertension and increased cardiovascular risk. Oxidative stress is a fundamental orchestrator of OSA, driving efforts towards identifying possible biomarkers for predicting the severity and the comorbidity risk in OSA patients [5]. The gold standard of OSA treatment is continuous positive airway pressure (CPAP), which aims to improve airway patency, resulting in better oxygenation and ventilation. However, adherence to CPAP may be alarmingly limited in the long term [6]. Hence, adjunctive therapeutic modalities are sought to improve compliance. In fact, several studies have suggested that physical activity enhanced CPAP adherence both short term [7] and long term [8].

In terms of lifestyle interventions, the Mediterranean diet has been included in some research studies adjunctively, in order to improve both oxidative stress and OSA severity. Dai et al. indicated that the Mediterranean diet reduced oxidative stress and further reduced the cardiovascular risk [9], while Georgoulis et al. suggested that such dietary modification further improved AHI and sleep architecture in OSA patients, along with CPAP and weight loss [10]. When the Mediterranean diet was combined with exercise, the results showed that anthropometric changes combined with improved oxygenation parameters reinforced AHI reduction and sleep architecture improvement [11].

Exercise has been examined thoroughly for its multiple benefits in OSA patients. It has been established that exercise improves antioxidant activity and keeps ROS in balance [12]. Furthermore, physical activity confers protection from OSA's cardiometabolic consequences; conversely, OSA impairs exercise capacity regardless of age [13,14]. OSA-related impairments mainly affect aerobic capacity and are correlated with its severity [15]. Hence, fitness indicators could serve as additional predictive factors not only for OSA severity, but also for estimating the potentially therapeutic effect of exercise in OSA.

This could come into great usage when implementing rehabilitation programs, which in the post-COVID-19 era, tend to be incorporated into telemedicine approaches [16]. Some studies from our team have also integrated tele-exercise and unsupervised rehabilitation programs in several groups of patients, demonstrating beneficial results in sleep health, antioxidant activity, and anthropometric parameters [17]. With exercise being the core of pulmonary rehabilitation, it is vital to incorporate it in OSA patients, as it is capable of ameliorating its acute and chronic multisystemic detrimental effects [18].

Another crucial factor in integrating multifaceted therapeutic plans is nutritional status. It has been well established that the Mediterranean diet is fundamental in overall well-being and achieving longevity [19]. It has been associated with lowering cardiovascular disease incidence, a detrimental consequence of OSAS [20].

Therefore, the purpose of our study was to examine the efficacy and efficiency of unsupervised tele-rehabilitation program, along with a dietary pattern based on the Mediterranean diet, in OSA patients. We focused on the potential changes in their fitness indicators and oxidative status, while nutritional status was associated through the adherence to the Mediterranean dietary pattern.

2. Materials and Methods

2.1. Participants

A total of 40 consecutive, newly diagnosed adults with OSA were included in our study (Figure 1). Subjects were recruited consecutively between May 2022 and September 2022 and were allocated into two groups: $CPAP_{group}$ (control group) versus non-$CPAP_{group}$ (intervention group) using block randomization (Table 1). All patients allocated to the non-CPAP group received no CPAP treatment (delayed therapy) and were given 12 weeks of unsupervised lifestyle rehabilitation with personalized recommendations for (a) increased adherence to the Mediterranean diet combined with energy restriction for those who were overweight or obese (Supplementary Tables S1 and S2) [19] and (b) an exercise program (according to their fitness test) to improve the patients' cardiometabolic profile (Table 2).

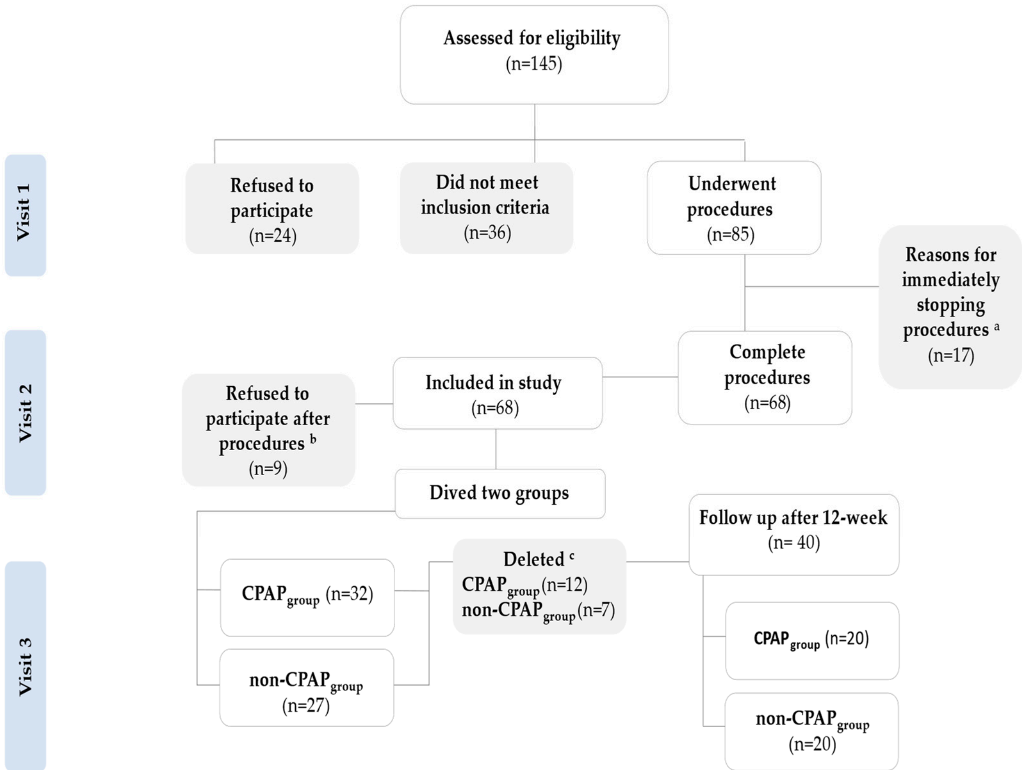

Figure 1. Flow study diagram. Visit 1 = data collected, visit 2 = recommendations for exercise and nutrition; visit 3 = follow up after 12-week intervention; a = reasons resulting in interruption were dizziness, headache, discomfort feeling, and increased systolic (>200 mmHg) and diastolic blood pressure (>100 mmHg); b = reasons resulting in interruption was "not enough time", and c = were excluded for not responding to calls. Procedures refer to measurements, like anthropometric characteristics, sleep quality, Mediterranean-like diet assessment, and physical fitness tests.

Table 1. Polysomnography results between groups. Data are expressed as percent, mean ± standard deviation. Abbreviations: N = non rapid eye movement stage; REM = rapid eye movement; ΔNRO_2 = oxygen saturation difference between nadir during sleep and resting awake.

		Total	$CPAP_{group}$	non-$CPAP_{group}$	*p* Value
Apnea Hypopnea Index	events/h	45.1 ± 24.1	52.0 ± 31.5	38.2 ± 21.5	0.114
Apnea	events/h	15.8 ± 17.5	20.6 ± 12.3	11.0 ± 18.8	0.117
Hypopnea	events/h	29.3 ± 15.0	31.3 ± 14.7	27.2 ± 15.3	0.392
N1	%	3.4 ± 1.6	3.7 ± 1.7	3.2 ± 1.5	0.388
N2	%	58.4 ± 10.5	59.6 ± 9.2	57.1 ± 11.8	0.454
N3	%	10.0 ± 6.3	9.6 ± 4.9	10.4 ± 7.5	0.690
REM	%	11.9 ± 5.8	12.0 ± 4.8	11.7 ± 6.8	0.880
Sleep duration	min	273.3 ± 56.0	272.5 ± 28.4	274.2 ± 75.1	0.925
Desaturation Index		46.1 ± 29.8	52.4 ± 33.0	39.8 ± 25.3	0.185
Nadir oxygen saturation	%	63.6 ± 16.8	60.2 ± 18.7	67.1 ± 15.0	0.183
Average oxygen saturation	%	87.1 ± 7.4	86.4 ± 7.2	87.7 ± 7.7	0.586
Oxygen saturation < 90%	mim	32.7 ± 47.3	45.1 ± 59.2	20.2 ± 27.5	0.754
ΔNRO_2	%	20.6 ± 14.0	37.0 ± 28.5	30.1 ± 25.1	0.176

Table 2. Recommended exercise program for patients with OSAS.

Warm-up and cool-down	15% of each session	Routine exercises
Aerobic exercises	60% of each session	Intermittent outdoor walking
Strength exercise	15% of each session	Multi-joint exercise (large muscle mass)
Mobility-Flexibility	10% of each session	Static or dynamic routine exercises

Inclusion criteria were the following:

- Age and body composition limitations:
  - ages between 18 and 65 years
  - body mass index < 40 kg/m^2 [21]
- Sleep Criteria:
  - Apnea Hypopnea Index ≥ 20 events per hour and sleep duration during polysomnography study > 250 min [22]
- Contraindications for six-minute walking test (6MWT) as described elsewhere [23,24]
- Comorbidities:
  - No relevant comorbidities (e.g., mental illness, musculoskeletal disability, cardiorespiratory diseases etc.)
  - no abnormal pulmonary function test [25]
  - no previous SARS-CoV-2 infection [26]
- Access to new technologies and internet
- Physical Characteristics:
  - no daily physical strain due to working ≥3 h per day
  - no weekly exercise ≥100 min per week with ≥60% of heart rate maximum predicted
  - no active self-reported symptoms (chest pain, fatigue, and/or dyspnea)
- Cognitive Assessment:
  - no cognitive impairment, as indicated by Montreal cognitive assessment (MoCA) test score > 25.

The study was approved by the Institutional Review Board/Ethics Committee of the Medical School of the University of Thessaly (approval reference number: 28927/8 July 2020). For further modifications required in our study, a new approval by the Institutional Review Board/Ethics Committee of the Medical School of the University of Thessaly (approval reference number: 2229/13 April 2022) was made. All participants gave written informed consent in accordance with the Declaration of Helsinki and personal data protection according to the European Parliament and Council of the European Union.

2.2. Measurements

2.2.1. Anthropometric Characteristics and Body Composition

Height was measured using the Seca 700 (Seca, Hamburg, Germany). The Seca 201 (Seca, Hamburg, Germany) was used to measure chest circumference at maximal inhalation and exhalation (Δchest), waist–hip ratio, and neck circumference (between approximately the C3 and C4 cervical vertebrae) in the standing position. Body weight and body composition (i.e., muscle mass, percentage of body fat, visceral fat, lean body mass and total body water) were assessed using whole-body bioelectrical impedance analysis (MC-980, Tanita, Arlington Heights, IL, USA) [27]. Body surface area (BSA) [28] and body mass index (BMI) were calculated according to the following formula:

$$\mathrm{BSA} = \sqrt{\frac{\mathrm{Height(cm)} \times \mathrm{Body\ mass(kg)}}{3600}} \text{ and}$$

$$\mathrm{BMI} = \frac{\mathrm{Body\ mass(kg)}}{\mathrm{Height(m)} \times \mathrm{Height(m)}}$$

2.2.2. Biomarkers

Blood sampling at baseline for oxidative stress measurement was performed 30 min before physical fitness tests. Initially, a 10 mL sample was of peripheral venous blood was collected from each patient from 09.00 to 11.00 a.m., having fasted the previous night. Measurements included the determination of reactive oxygen metabolites' levels (d-ROMs test) and the plasma antioxidant capacity (PAT test) (FRAS5, Parma, Italy) to estimate of oxidative burden (d-ROMs test) and quantified water-soluble antioxidant contents within the same plasma sample (PAT), as previously described [23]. Serum of Lipoprotein (a) (Lp(a)) were measured using the Advia Chemistry System assays on Advia 1800 automatic analyzer (Siemens Healthcare Diagnostics Inc., Erlangen, Germany). Serum Lp(a) levels were determined by immunoturbidimetry with the sample's analyte binding to specific anti-Lp(a) antibodies, coated on latex particles, resulting in agglutination of the latex particles. The amount of agglutination was read out optically via sample turbidity and was directly proportional to the amount of Lp(a) in the sample.

2.2.3. Sleep Quality and Daily Sleepiness

All participants answered the self-report questionnaires (a) for sleep quality over a 1-month time interval (Pittsburgh Sleep Quality Index, PSQI), which consists of 19 individual items, creating 7 components that produce one global score [29], and (b) for the daily sleepiness via used Epworth Sleepiness Scale (ESS), which assesses a subjective measure sleepiness scale: from no chance of dozing (score = 0) to high chance of dozing (score = 3) [30].

2.2.4. Mediterranean-like Diet

The assessment of the dietary habits of the volunteers was carried out through a semi-quantitative food consumption frequency questionnaire (FFQ) which has been tested for its validity and repeatability in the assessment of food consumption from its supplement in the Greek population both in normal-weight and in overweight–obese individuals and in both genders [31]. The nutritional information was used to assess in advance the degree of adherence of the volunteers to the dietary pattern of the Mediterranean diet using the Mediterranean diet score index (MedDietScore). This index takes into account the consumption of 11 foods or food groups, namely the consumption of (1) minimally processed cereals, (2) fruits, (3) vegetables, (4) legumes, (5) potatoes, (6) fish, (7) red meat and meat products, (8) poultry, (9) full-fat dairy products, (10) olive oil, and (11) alcohol [32]. Overall, the MedDietScore takes values from 0 to 55, with a higher score indicating better adherence to the Mediterranean diet.

2.2.5. Physical Fitness Test

The handgrip strength test was assessed using an electronic dynamometer (Camry, EH 101, South El Monte, CA, USA), in which three maximal isometric efforts were performed for 5 s with both hands alternately and in random order with 40 s rest between them, and the mean of the best left and right hand trial was recorded, as previously described [33].

The 6 min walk test (6MWT) was used to assess submaximal exercise capacity, and oxygen saturation (SpO_2), heart rate (HR) (Nonin 9590 Onyx Vantage, Plymouth, MN, USA), and blood pressure (BP, Mac, Nagoya, Japan) were recorded at baseline, at the end of the 6MWT and during the first minute of recovery. Mean arterial blood pressure (MAP) was calculated according to equation [34]:

$$\text{MAP} = \frac{\text{Systolic Blood Pressure} + (2 \times \text{Diastolic Blood Pressure})}{3}$$

The total distance covered during the 6MWT was recorded and the predicted distance covered was calculated using the formula [35]:

$$\text{Men} = (7.57 \times \text{Height}_{(\text{cm})}) - (5.02 \times \text{Age}_{(\text{yrs})}) - (1.76 \times \text{Body mass}_{(\text{kg})}) - 309$$

$$\text{Women} = (2.11 \times \text{Height}_{(cm)}) - (2.29 \times \text{Body mass}_{(kg)}) - (5.78 \times \text{Age}_{(yrs)}) + 667$$

The estimated peak oxygen uptake during the 6MWT [36], calculated using the formula:

$$\text{Oxygen uptake (mL·min·kg)} = 4.948 + 0.023 \times \text{distance (m)}$$

The metabolic equivalent (METs) calculated according to the formula: $\text{METs} = \frac{\text{oxygen uptake(mL·min·kg)}}{3.5}$.

The predicted peak oxygen uptake [37] calculated according to the formula:

$$\text{Oxygen uptake predicted (mL·min·kg)} = \frac{(\text{Height(cm)} - \text{Age(yrs)}) \times 20 \text{ for men and} \times 14 \text{ for women}}{\text{Body mass(m)}}$$

2.3. Interventions Nutrition Program

The personalized recommendations for nutrition program, in accordance with the Mediterranean Diet, were:

- High consumption of cereals (and bread), mainly whole meal
- High consumption of seasonal fruits and vegetables
- Daily consumption of milk and dairy products (preferably low-fat)
- Daily consumption of pulses, nuts, and spices instead of salt
- Consumption of eggs, fish, and poultry on a weekly basis
- Low consumption of meat and meat products
- Occasional consumption of sweets
- High ratio of monounsaturated to saturated fatty acids
- Moderate consumption of ethyl alcohol (mainly in the form of wine)

2.4. Interventions Exercise Program

The unsupervised lifestyle rehabilitation exercise program (Table 2) lasted 12 weeks, with each patient participating in 4 training sessions per week, each session lasting 40–90 min, according to Stavrou et al. [17,38,39]. The warm-up and cool-down consisted of routine exercises for 2 sets of 20–30 s and 20 s rest between sets (child's pose/prayer stretch, standing quadriceps stretch, and doorway stretch) at an intensity of 50–60% of maximum heart rate at the end of the 6MWT ($HR_{max\ 6MWT}$). Aerobic exercise consisted of intermittent outdoor walking on a flat and hard surface, away from busy roads, for several hours a day in conditions free of dust and/or high humidity. The intensity of the aerobic exercise was 4 min at 90–120% of $HR_{max\ 6MWT}$ (progressively increasing sets and repetitions over the 12 weeks) and 1 min at 60% of $HR_{max\ 6MWT}$. Each patient monitored their heart rate using a smartphone (Heart Rate Monitor app, Google Commerce Ltd., version. 5.6, Gordon House, Barrow Street, Dublin 4, Ireland) and/or a smartwatch (Xiaomi Mi Smart Band 5, Beijing, China). Strength (multi-joint) and proprioception exercises were performed using functional circuit training and the resistance for each participant was their body weight. Each session consisted of four bodyweight exercises (squats, lunges, push-ups in or out of the wall, and a one-leg balance test with eyes closed), 2–8 sets, 6–12 repetitions, and 1 min rest between sets (progressively increasing sets and repetitions over the 12 weeks). Mobility and flexibility consisted of routine exercises for 2–4 sets, 6–12 repetitions, and 10–30 s for each repetition (stretching to the point of feeling tight or slightly uncomfortable) and 40 s rest between sets (progressively increasing sets and repetitions over the 12 weeks). All exercises were videotaped and included instructions via the digital platform USTEP (Unique Safe Tele Exercise Program, https://ustep.gr/, accessed on 1 May 2022). Adherence to the program was determined via 1 phone call per week, and each call focused on whether the patients were able to follow the instructions, perform them daily, and troubleshooting. Adherence to the treatment of CPAP, in patients of $CPAP_{group}$, was determined via one phone call per week.

All assessments were performed in the Laboratory of Cardio-Pulmonary Testing and Pulmonary Rehabilitation (University of Thessaly), with an environmental temperature at 23 ± 2 °C and humidity 44 ± 2%. The evaluation was made between Monday and Friday and from 09:00 a.m. to 13:00 p.m.

2.5. Statistical Analysis

A power of 85% and confidence interval of 95% were adopted, with an estimated value for a type I error of 5% for the sample size calculation in this study. A value for 36 patients was obtained. However, since this is a novel combined interventional approach, we recruited 40 patients. Normality of data was assessed using the Kolmogorov–Smirnov one-sample test. Data are presented as percentages for qualitative variables, mean ± standard deviation (SD) for parametric variables, and median and 25th and 75th percentiles for non-parametric variables. Independent samples *t*-tests or Mann–Whitney U-tests for parametric and non-parametric variables were used to assess differences between groups ($CPAP_{group}$ versus non-$CPAP_{group}$). Paired *t*-test or Wilcoxon signed-rank test was used to assess within-group differences before and after the 12-week unsupervised lifestyle rehabilitation program period ($CPAP_{group}$) and within-group differences for the non-$CPAP_{group}$. A Tukey post-hoc test was used to locate any differences between means. Correlations between continuous variables were assessed using Spearman's Rho and Pearson's R correlation coefficients for non-parametric and parametric variables, respectively. For all tests, a *p*-value of <0.05 was considered statistically significant. The IBM SPSS 21 statistical package (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3. Results

3.1. Anthropometric Characteristics and Body Composition

In total, 68 participants were enrolled in our study, and 40 of them finished the 12-week intervention. Table 3 shows the analysis of results between groups, before and after the 12-week lifestyle rehabilitation versus the CPAP treatment period. According to Table 3, the differences in anthropometric parameters, neck circumference, and waist-to-hip ratio decreased in both groups. Body composition improved in both groups, but the non-$CPAP_{group}$ had a greater reduction in visceral fat (7.6 ± 8.5 versus 8.9 ± 8.6%) and an increase in muscle mass (14.2 ± 36.9 versus 23.1 ± 48.8%) compared to the $CPAP_{group}$.

3.2. Biomarkers

There were no statistically significant differences between groups in d-ROMs at baseline and after 12 weeks of lifestyle rehabilitation (Table 3). The $CPAP_{group}$ showed differences in plasma antioxidant capacity at 29.6 ± 44.8% after 12 weeks of CPAP treatment ($t_{(19)}$ = 2.250, p = 0.036). The non-$CPAP_{group}$ showed differences in plasma antioxidant capacity after 12 weeks of lifestyle rehabilitation at 28.6 ± 24.9% ($t_{(19)}$ = 4.078, p < 0.001). Lipoprotein (a) levels decreased in both groups after 12 weeks: the $CPAP_{group}$ showed an increase of 32.2 ± 25.5% ($t_{(19)}$ = 2.523, p = 0.021), and the lifestyle rehabilitation group showed an increase of 28.2 ± 16.9% ($t_{(19)}$ = 2.201, p = 0.034).

3.3. Sleep Quality and Daily Sleepiness

Table 3 shows the analysis of results between groups, before and after the 12 weeks of lifestyle rehabilitation versus CPAP treatment. Table 3 shows that sleep quality improved and daytime sleepiness decreased in both groups.

3.4. Mediterranean-like Diet

The results showed differences between the groups at baseline, with the group selected for CPAP treatment having higher scores compared to the lifestyle rehabilitation group (33.1 ± 3.1 versus 30.6 ± 4.7 score, $t_{(46)}$ = 4.263, p = 0.046, Table 3). After the 12 weeks, the CPAP treatment group decreased the score by 4.3 ± 11.7%, and the lifestyle rehabilitation group increased the score by 2.4 ± 17.5%.

Table 3. Results between groups pre- and post-12-week intervention period. Data are expressed as percent, number, mean ± standard deviation. Abbreviations: 6MWT = six-minute walking test; d-ROMs = reactive oxygen metabolites; ESS = Epworth Sleepiness Scale; METs = metabolic equivalent; PAT = plasma antioxidant capacity; PSQI = Pittsburg Sleep Quality Index.

		$\mathbf{CPAP_{group}}$				$\mathbf{noCPAP_{group}}$				***p* Value between Groups**	
		Baseline	**After 12-w**	**% Changes**	***p* Value**	**Baseline**	**After 12-w**	**% Change**	***p* Value**	**Baseline**	**After 12-w**
Age	years	49.7 ± 9.4	-	-	-	49.3 ± 10.7	-	-	-	0.632	
Sex (Female)	n	1	-	-	-	5	-	-	-	-	
Body mass index	kg/m^2	32.1 ± 7.6	31.8 ± 6.8	−2.9 ± 2.1	0.048	32.3 ± 5.1	31.9 ± 4.6	−3.3 ± 6.4	0.054	0.254	0.349
Body surface area	m^2	2.4 ± 0.6	2.4 ± 0.5	−2.9 ± 2.1	0.730	2.4 ± 0.4	2.3 ± 0.4	−3.3 ± 6.4	0.371	0.837	0.098
Lean body mass	%	78.8 ± 6.5	78.6 ± 6.2	−0.9 ± 0.7	0.521	77.8 ± 6.7	77.5 ± 6.1	−1.1 ± 2.2	0.125	0.457	0.572
Total body water	%	50.8 ± 4.9	50.8 ± 4.4	−1.0 ± 0.8	0.932	49.3 ± 4.1	49.5 ± 4.1	1.0 ± 1.6	0.960	0.594	0.648
Body fat	%	31.1 ± 9.3	31.4 ± 8.7	−4.4 ± 4.1	0.638	33.4 ± 9.0	38.0 ± 11.5	10.4 ± 16.3	0.563	0.852	0.732
Muscle mass	kg	34.7 ± 10.6	31.1 ± 4.4	−14.2 ± 36.9	0.568	28.0 ± 5.3	33.7 ± 13.2	23.1 ± 48.8	0.837	0.642	0.328
Visceral fat	score	15.1 ± 5.1	14.8 ± 5.6	−7.6 ± 8.5	0.328	15.1 ± 6.5	14.3 ± 6.1	−8.9 ± 8.6	0.009	0.517	0.218
Neck circumference	cm	42.0 ± 4.0	41.6 ± 4.0	−2.6 ± 3.0	0.635	40.5 ± 4.0	39.9 ± 4.4	−3.0 ± 3.2	0.463	0.680	0.426
Waist hip ratio	m	1.0 ± 0.1	1.0 ± 0.1	−3.2 ± 2.6	0.922	1.0 ± 0.1	1.0 ± 0.1	−7.8 ± 6.5	0.292	0.642	0.583
Δchest	cm	5.2 ± 2.4	5.9 ± 1.9	41.2 ± 23.6	0.317	6.0 ± 1.9	7.2 ± 2.2	30.8 ± 26.6	0.030	0.188	0.178
d-ROMs	U. carr.	351.3 ± 107.4	321.2 ± 97.2	−15.7 ± 12.6	0.453	327.6 ± 97.3	319.8 ± 87.6	−31.2 ± 28.6	0.453	0.810	0.453
PAT	U. cor.	2138.6 ± 563.8	2401.2 ± 235.4	29.6 ± 44.8	0.054	2140.9 ± 375.5	2563.2 ± 483.3	28.6 ± 24.9	<0.001	0.043	0.047
Lipoprotein (a)	mg/dL	14.1 ± 20.8	12.3 ± 20.9	−32.2 ± 25.5	0.021	24.9 ± 22.4	17.7 ± 16.3	−28.2 ± 16.9	0.034	0.682	0.421
PSQI	score	7.7 ± 4.2	7.6 ± 3.3	−36.5 ± 14.8	0.862	8.2 ± 5.2	7.9 ± 5.6	−48.0 ± 79.1	0.654	0.451	0.333
ESS	score	8.3 ± 3.2	7.0 ± 2.7	−39.3 ± 37.4	0.732	8.4 ± 4.4	7.9 ± 4.2	−19.8 ± 34.9	0.742	0.291	0.315
Mediterranean diet	score	33.1 ± 3.1	31.5 ± 3.5	−4.3 ± 11.7	0.077	30.6 ± 4.7	30.8 ± 4.2	2.4 ± 17.5	0.810	0.046	0.345
Handgrip	kg	44.1 ± 7.9	45.1 ± 8.2	2.1 ± 3.9	0.623	39.9 ± 11.1	40.6 ± 10.9	11.7 ± 29.3	0.542	0.433	0.321
6MWT	m	431.2 ± 54.7	519.9 ± 65.1	16.6 ± 9.3	<0.001	474.8 ± 67.4	507.3 ± 72.0	7.5 ± 6.6	0.002	0.031	<0.001
	% of predicted	72.6 ± 10.5	87.4 ± 14.1	16.3 ± 9.4	<0.001	82.0 ± 14.7	87.3 ± 16.1	8.3 ± 7.4	0.007	0.026	0.432
Hear rate $_{resting}$	bpm	73.7 ± 8.7	73.1 ± 6.7	−4.3 ± 5.4	0.218	76.0 ± 9.6	76.8 ± 12.3	10.4 ± 7.2	0.387	0.221	0.119
Mean arterial pressure $_{resting}$	mmHg	95.9 ± 9.0	94.0 ± 6.6	−5.5 ± 3.8	0.322	92.8 ± 5.6	93.8 ± 8.3	5.7 ± 4.1	0.528	0.107	0.096
Hear rate $_{end\text{-}6MWT}$	bpm	108.1 ± 9.4	111.8 ± 8.6	9.0 ± 6.3	0.355	117.6 ± 18.2	124.2 ± 23.2	13.1 ± 7.9	0.426	0.046	0.032
Mean arterial pressure $_{end\text{-}6MWT}$	mmHg	102.3 ± 11.7	100.1 ± 7.2	−6.7 ± 5.3	0.129	99.6 ± 8.9	101.4 ± 6.3	6.3 ± 5.1	0.157	0.432	0.182
Hear rate 1st $_{min\ recovery}$	bpm	86.1 ± 12.1	91.5 ± 10.6	11.5 ± 6.4	0.441	91.2 ± 12.9	96.5 ± 15.0	13.1 ± 9.1	0.080	0.852	0.226
Mean arterial pressure 1st $_{min\ recovery}$	mmHg	95.4 ± 8.9	95.8 ± 5.2	6.7 ± 4.6	0.453	93.8 ± 5.7	96.8 ± 6.6	6.3 ± 4.3	0.242	0.642	0.433
Estimate oxygen uptake	mL·min·kg	14.9 ± 1.3	16.9 ± 1.6	11.8 ± 6.7	<0.001	15.9 ± 1.6	16.6 ± 1.7	5.2 ± 4.7	0.002	0.033	0.099
	% of predicted	29.1 ± 9.5	30.1 ± 10.7	5.0 ± 3.5	0.015	26.0 ± 11.3	26.5 ± 11.4	6.6 ± 11.9	0.324	0.131	0.327
METs		4.2 ± 0.4	4.8 ± 0.4	11.8 ± 6.7	<0.001	4.5 ± 0.4	4.7 ± 0.5	5.2 ± 4.7	0.003	0.035	0.742

3.5. Physical Fitness Test

All parameters of the physical fitness test are shown in Table 3. The handgrip strength test and exercise capacity improved in both groups after 12 weeks of intervention. A stabilization of hemodynamic parameters was observed in both groups after 12 weeks of exercise rehabilitation.

All patients at baseline had statistically significant correlations among ΔNRO2 (oxygen saturation difference between nadir during sleep and resting awake) and Desaturation Index (r = 0.556, $p < 0.001$), resting systolic blood pressure (r = 0. 376, $p = 0.017$) and recovery phase (r = 0.349, $p = 0.027$), mean arterial pressure at rest (r = 0.356, $p = 0.024$), recovery phase (r = 0.323, $p = 0.042$) and d-ROMs values (r = 0.319, $p = 0.045$). At baseline, statistically significant correlations were found between d-ROMs values and 6MWT (r = −0.340, $p = 0.032$), and between resting systolic blood pressure (r = −0.346, $p = 0.029$) and resting mean arterial pressure (r = −0.345, $p = 0.029$). At baseline, there was a statistically significant difference between PAT and resting diastolic blood pressure (r = −0.403, $p = 0.010$) and resting mean arterial pressure (r = −0.354, $p = 0.025$). Δchest showed statistically significant differences with dROMs (r = −0.406, $p = 0.009$), ΔNRO2 (r = −0.557, p <0.001), Desaturation Index (r = −0.469, $p = 0.002$) and 6MWT (r = 0.355, $p = 0.025$).

4. Discussion

Our results have shown a similar influence of combination of exercise and the Mediterranean-like diet with the gold standard of OSAS therapy, in terms of body composition parameters, antioxidant and cardiovascular biomarkers, and sleep quality.

Regarding cardiovascular profile, it should be noted that all participants were classified as obese or overweight, based on their BMI and body fat percentage. It is important to take into account body fat percentage, as BMI is a rough index of energy deposition but is subjected to body build and proportions [37]. Body fat percentage consists of a more accurate indicator and is independently associated with cardiovascular risk [40,41]. In line with body fat percentage follows visceral fat percentage, which has been shown to be cardinal for systemic metabolic derangements [42]. In our study, significant differences were observed in terms of Lp(a) and visceral fat percentage, along with several oxygenation ($ΔNRO_2$ and ODI) parameters after 12 weeks of unsupervised rehabilitation program and dietary modifications. Abnormal high levels of Lp(a), a highly atherogenic lipoprotein associated independently with CVD [43], are found in OSA patients [44]. Concomitantly, increased visceral fat has been found to serve as an additional factor for cardiovascular risk [45]. Although the effect of CPAP alone has been found beneficial for overall lipidemic profile [44], this was the first study to establish an association with Lp(a), too. However, the efficiency of both exercise and the Mediterranean diet in lowering Lp(a) have been well documented [46,47]. Notably, in our patients, baseline levels were within normal range. Similarly, in line with published literature, the percentage of visceral fat was significantly lower and more pronounced in the non-CPAP group, in which lifestyle interventions were implemented [48]. In fact, the non-CPAP group exhibited a better compliance with a Mediterranean-like diet, as mirrored by their significant MedDietScore increase. A fundamental, 10-year, large cohort study and its 20-year prospective approach in estimating incidence of hypertension have highlighted the importance of a Mediterranean-like diet in controlling cardiovascular risk [49,50].

Although non-significant, other parameters of body composition demonstrated a trendline of change like reduction of body fat, as well as an increase in muscle mass and chest diameter. These results could potentially signify that exercise and the Mediterranean diet alone could fundamentally contribute as therapeutic modalities for OSA, by optimizing body composition, which has been incriminated for OSA severity and its complications [51]. By combining these lifestyle interventions, results were significantly comparable in both groups. Concomitantly, oxygenation parameters followed a similar but non-significant trendline of improvement in both groups, in line with published data regarding the effects of CPAP and exercise in OSA [18,52].

The results were also reflected by improvements in physical indices, like 6MWT and estimate oxygen uptake in both groups. Physical exercise included mainly aerobic training. Aerobic capacity is a strong health predictor that represents the potential cardiorespiratory reservoir, which has been associated with the reduction oxidative stress and inflammation markers and is found hindered in OSA [53,54]. This could be partly attributed to autonomic incapability of adapting to exercise, as assessed indirectly by heart rate variability before and after exercise in OSA [55]. Our study showed that exercise offered an amelioration in autonomic dysfunction as well, by exhibiting significant differences in adaptation of HR after recovery, when comparing the two groups. Similar results were exhibited by Yang et al. who incorporated exercise for the same time interval in OSA patients and correlated such improvement of heart rate after recovery with oxygen saturation change [56]. By implementing a holistic program focusing on increasing aerobic capacity, reducing oxidative stress through exercise and proper diet, adjunctively to gold-standard therapy for OSA, patients are benefited with a decrease in OSA severity along with reduced cardiovascular risk.

However, some limitations exist. First, our sample size was relatively small, limiting the power of correlations. Future randomized studies including larger samples and implementing lifestyle interventions could solidify the hypothetical benefits of exercise and the Mediterranean diet in OSA. Furthermore, due to the incorporation of training intervention, ergospirometry would offer a broader analysis of the cardiopulmonary and metabolic profiles of participants. However, due to COVID-19 legislations, the rehabilitation laboratories were not available and, hence, we opted for tele-exercise programs, as tested before [17,39]. In addition, all participants should undergo a repetitive PSG after the end of the interventional program, in order to examine CPAP efficacy and the extent of effectiveness. Sleep was only reassessed through questionnaires. However, this study was not powered to distinguish CPAP and lifestyle changes independently but as auxiliary modalities for an integrating approach against OSA. Further studies could reinforce these preliminary results.

5. Conclusions

To conclude, exercise and the Mediterranean diet may serve as adjunctive-to-CPAP therapeutic elements, ameliorating holistically OSA severity. Particularly, home-based and unsupervised tele-rehabilitation pulmonary programs exhibited similar efficiency to center-based, signifying cost effectiveness and adherence to training plans. Future large-scaled randomized interventional studies could offer more insight into the effect of lifestyle modifications in OSA and relevant disorders.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app14188424/s1. Table S1: Mediterranean diet score index. Score ranges between 0 and 55, with higher scores signifying better adherence to the Mediterranean dietary pattern. Table S2: Macronutrients basis of the Mediterranean diet, in which the personalized diet program was based. Modified from Davis C et al. Definition of the Mediterranean Diet; A Literature Review. *Nutrients*. **2015** [57].

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